7/30/2008

OC IMAGE PACKAGE COVERSHEET

Please IMAGE the attached package associated with an OC-lead document: (1) 30-Day Notice/135-Day Supplement or (2) Manufacturing Site Change Supplement. If a bundled submission and review is involved, only one copy of the IMAGE package is necessary.

Supplement Type:

- [x] 30-Day Notice/135-Day Supplement
- [ ] Manufacturing Site Change Supplement

Bundled Submission and Review?

- [x] Yes (bundled submissions are identical and one set of review memos is involved)
- [ ] No

IMAGE Package Checklist:

- [x] completed IMAGE coversheet
- [x] copy of signed, dated letter
- [x] copy of OC or OIVD (compliance) lead review memo with reviewer and appropriate management signatures for the given review round
- [ ] if applicable, copy of ODE/OIVD consult review memo with reviewer and appropriate management signatures for the given review round
- [x] if applicable, copies of any other supporting information for the given review round (e.g., email from applicant, EIR report)

IMAGE this package for the following PMA supplement(s):

1. P890003/S142
2. P900061/S076
3. P920015/S046
4. P950024/S011
5. P980050/S034

Etc. P010015/S044

P030036/S007

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
9200 Corporate Blvd
Rockville, MD 20850

JUL 17 2008

Stacey Paetschow Wessman, RAS, MS, MBA
Principal Regulatory Affairs Specialist
Medtronic, Inc.
8200 Coral Sea Street NE
Mounds View, MN 55112

Re: P890003/S142 Leads Service Kit and Leads Wrench Kit
P900061/S076 Epicardial Transvene Lead and Related Accessories
P920015/S046 Subcutaneous Defibrillation Lead and Related Accessories
P950024/S011 Capsure EPI Unipolar and Bipolar Leads
P980050/S034 SVC/CS Transvene Lead
P010015/S044 Lead Assembly
P030036/S007 Lead Assembly
Filed: June 17, 2008

Dear Ms. Wessman:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has evaluated your premarket approval application (PMA) 30-day Notice. The 30-day Notice requested moving manufacturing locations within the same facility. The continuous monitoring system is not covered by this notice and should be submitted under a separate supplement.

Based on the information submitted, FDA has determined that submission of a 135-day PMA supplement is not required. Therefore, you may distribute your device, incorporating the change described above, upon receipt of this letter.

If you have questions concerning this letter, please contact Melissa Burns at (240) 276-0268.

Sincerely yours,

FOR

Gladys Rodriguez
Director
Division of Enforcement B
Office of Compliance
Center for Devices and
Radiological Health

July 28, 2008

Memo to Record

From: Laura J. Byrd
PMA Staff

Subject: Bundled Medtronic 30-Day Notice & Amendments – P890003/S142, P900061/S76, P920015/S46, P950024/S11, P980050/S34, P010015/S44, and P030036/S7

Medtronic submitted a bundled 30-Day Notice on June 17, 2008. The PMAs affected include: P890003/S142, P900061/S76, P920015/S46, P950024/S11, P980050/S34, P010015/S44, and P030036/S7. The purpose of this bundled 30-Day Notice was to request moving the controlled environment areas within the same facility. Medtronic designated P920015/S46 as the "Master Submission" for this bundle, which means P920015/S46 had the full submission in it whereas the other PMA supplements listed only had "Refer to File Letters" in them (i.e., referring to the Master Submission where all the information could be found).

On June 27, 2008, FDA received Amendment 1 to P920015/S46 from Medtronic. Amendment 1 included the addition of extra models to be considered affected by the request for moving the controlled environment areas within the same facility. These additional models included the Model 6701 End Pin Cap Accessory and the Model 6996T Tunneling Tool Accessory. Since P920015/S46 was the designated Master Submission, Medtronic only submitted this change to P920015/S46 and did not include the other PMA Supplements which are a part of this bundled submission. PMA Staff did not pick up on this error when the document came through our office.

On July 11, 2008, Medtronic submitted Amendment 2 to P920015/S46 – FDA DMC received the Amendment on July 14, 2008. Amendment 2 was "... to request the removal of the inclusion of the (b)(4) monitoring system included in original 30-day PMA-S (P920015/S046)." Since P920015/S46 was the designated Master Submission, Medtronic only submitted this change to P920015/S46 and did not include the other PMA Supplements which are a part of this bundled submission. However, this time PMA Staff did pick up on the fact that the other affected PMA Supplements were not addressed for this change.

PMA Staff contacted Medtronic (Stacey Paetschow Wessman) via e-mail on July 15 and 16, 2008 (see attached) explaining the need that all Supplements be addressed for the change requested in P920015/S46 A2. In addition, I also mentioned the error in not requesting the additional models in all the PMA Supplements when P920015/S46 Amendment 1 was submitted. In the July 16, 2008, e-mail I indicated that Medtronic should not only state removal of the (b)(4) monitoring system, but also include the additional models so that all PMA Supplements in the bundle were addressed. In addition, I indicated that the receipt date of the request to remove the (b)(4)

Part 1 - Page 3

(b)(4) monitoring system (and add the additional models) would be the date when FDA DMC received all Amendments in this bundle. The additional Amendments (P890003/S142 A1, P900061/S76 A1, P950024/S11 A1, P980050/S34 A1, P010015/S44 A1, and P030036/S7 A1) were received on July 17, 2008. Note that these Amendment 1's only addressed the removal of the (b)(4) monitoring system and not the additional models.

Since the Office of Compliance had no further issues, they issued a "submission of a 135-day PMA supplement is not required" letter to Medtronic on July 17, 2008. Since the bundled Amendment requesting the removal of the (b)(4) monitoring system was already addressed in the Office of Compliance's letter, this bundled Amendment did not alter their decision or the letter.

On July 24, 2008, FDA received Amendment 2's to P890003/S142, P900061/S76, P950024/S11, P980050/S34, P010015/S44, and P030036/S7. These Amendment 2's are the request for the additional models (Model 6701 End Pin Cap Accessory and Model 6996T Tunneling Tool Accessory) that were absent from the initial request for adding the additional models under P920015/S46 A1 back in June 2008. These Amendments have no impact on the Office of Compliance letter that was issued and faxed on July 17, 2008.

Note that Melissa Burn's review memo addresses the models that are included in this 30-day notice change.

Laura Byrd
7/28/2008

Part 1 - Page 4

Byrd, Laura

From: Byrd, Laura
Sent: Wednesday, July 16, 2008 2:13 PM
To: 'Wessman, Stacey P.'
Subject: RE: Bundled 30-Day Notice Amendment

Hi Stacey.

The Supplement for P900061 is S76.

However, in researching this matter, I discovered that when you added the additional models on June 26th (received June 27th) you also only did it to P920015/S46. So, in addition to the request to withdraw of the (b)(4) monitoring system from the 30-Day Notice for all PMAs in this bundled submission (dated 7/11/2008, received 7/14/2008), you also need to state the additional models that are considered under this 30-Day Notice for all these PMAs.

We have deleted the Amendment for the withdrawal of the (b)(4) monitoring system from P920015/S46 as it should not have been logged in since it wasn't a complete submission to the entire bundle. When the other letters are received we will log them all in together on the date of receipt of the complete submission to the entire bundle. Note: Please use the same letter date of July 11, 2008 for the additional letters you are sending in. The remaining PMAs can be listed on one letter. We just need enough copies to cover all PMAs and at least one additional copy for our data archiving system.

Thanks.
Laura

From: Wessman, Stacey P. [mailto:(b)(6)
Sent: Tuesday, July 15, 2008 5:09 PM
To: Byrd, Laura
Subject: RE: Bundled 30-Day Notice Amendment

Hi Laura
The original submission also included a supplement for P900061-can you please tell me what the number is?
Thanks
Stacey

From: Byrd, Laura [mailto:(b)(6)
Sent: Tuesday, July 15, 2008 2:25 PM
To: Wessman, Stacey P.
Subject: Bundled 30-Day Notice Amendment

Hi Stacey,
We received P920015/S46 A2 on July 14, 2008. It is for removal of the (b)(4) monitoring system change from the current bundled 30-Day Notice.

However, there are 5 other PMAs associated with this change (P890003/S142, P950024/S11, P980050/S34, P010015/S44, and P030036/S7). All these should have amendments associated with them for withdrawal of this feature, but we didn't received anything for them. Please send them in.

Thanks.

Part 1 - Page 5

Laura J. Byrd
Program Operation Staff/PMA
FDA/CDRH/ODE
(b) (6)
(b)(6)

[CONFIDENTIALITY AND PRIVACY NOTICE] Information transmitted by this email is proprietary to Medtronic and is intended for use only by the individual or entity to which it is addressed, and may contain information that is private, privileged, confidential or exempt from disclosure under applicable law. If you are not the intended recipient or it appears that this mail has been forwarded to you without proper authority, you are notified that any use or dissemination of this information in any manner is strictly prohibited. In such cases, please delete this mail from your records. To view this notice in other languages you can either select the following link or manually copy and paste the link into the address bar of a web browser: http://emaildisclaimer.medtronic.com

REVIEW MEMORANDUM

30-DAY NOTICE

DATE: 15 July 2008

TO: The Record

THRU: William MacFarland, Acting Branch Chief, CNDB, DOEB, OC, CDRH

WCM initials 7-24-2008 date

FROM: Melissa Burns, Biomedical Engineer, CNDB, DOEB, OC, CDRH, HFZ-341

SUBJECT: 30-Day Notice
Received: 19 JUL 2008
OC Track: CTS

Applicant: Medtronic, Inc.
8200 Coral Sea Street, MS MVS11
Mounds View, MN 55112
FEI: 2182208

Manufacturing Facility: Medtronic, Inc.
7000 Central Ave N.E. Rd.
149, KM. 56.3
Minneapolis, MN 55432-3576
FEI: 2182208

DEVICES:
P920015/S046 Subcutaneous Defibrillation Lead and Related Accessories
P890003/S142 Leads Service Kit and Leads Wrench Kit
P900061/S076 Epicardial Transvene Lead and Related Accessories
P950024/S011 Capsure EPI Unipolar and Bipolar Leads
P980050/S034 SVC/CS Transvene Lead
P010015/S044 Lead Assembly
P030036/S007 Lead Assembly

OC RECOMMENDATION: 30 Day Approved, No 135 Day Supplement Needed

BACKGROUND:

This application from Medtronic, Inc is a request for a 30-Day Notice review in accordance with 21 CFR 814.39. This application provides notification of moving of the Controlled Environmental Area (CEA) used in manufacture of various lead models and components. The first phase of the CEA move, involving only the model 6937 lead, was reviewed and approved under prior submission P920015/S042 on April 30, 2008.

Medtronic leads are designed for use with a compatible IPG or an ICD as part of a cardiac system. Leads are intended for delivering therapies and/or sensing in the atrium and/or ventricle of the heart.

This change is being implemented due to an upgrade in the manufacturing facility. This change applies to the following model numbers:

PMA Number	Model Numbers	Description
P890003	5873C	Leads Service Kit
	5873W	Leads Wrench Kit
P900061	6721	Epicardial Transvene Lead
	5426	Cable Header
	5460	Ace Header
	6920	Upsizing Sleeve for HV Lead DF-1
	6925	Upsizing Sleeve
P920015	6996SQ	Subcutaneous Defibrillation Lead
	6996S	Subcutaneous Defibrillation
	6726	Y Adaptor
	6707	Downsizing Adaptor
	6725	IS-1 Port Pin Plug
	6944	Lead Assembly
	6947	Lead Assembly
	6701	End Pin Cap Accessory Kit
	6996T	Tunneling Tool Accessory
P950024	4965	CapSure EPI Unipolar Lead
	4968	CapSure EPI Bipolar Lead
P980050	6937A	SVC/CS Transvene Lead
P010015	4194	Lead Assembly
P030036	3830	Lead Assembly

CORRESPONDENCE HISTORY:

Burns, Melissa. "Follow-up Questions P920015/S046, et. al." E-mail to Stacey Paetschow Wessman. July 9, 2008.

Paetschow Wessman, Stacey. "RE: Follow-up Questions P920015/S042." E-mail with Attachments to Melissa Burns. April 24, 2008.

Burns. Melissa and Stacey Paetschow Wessman. Telephone Conversation. July 10, 2008.

Paetschow Wessman, Stacey. "RE: Follow-up Questions P920015/S046, et. al.." E-mail to Melissa Burns. July 10, 2008.

Paetschow Wessman, Stacey. "RE: Follow-up Questions P920015/S046, et. al.." E-mail with Attachment to Melissa Burns. July 11, 2008.

FIRM CONTACT:

Stacey Paetschow Wessman, RAS, MS, MBA
Principal Regulatory Affairs Specialist
Medtronic, Inc.
8200 Coral Sea Street, MS MVS11
Mounds View, MN 55112
Phone: 763-526-2378
Fax: 651-367-0603
E-mail: stacey.p.wessman@medtronic.com

COMPLIANCE REVIEW:

The firm is transferring manufacturing for various leads from the existing Controlled Environment Area (CEA) to a newly constructed CEA within the Medtronic Rice Creek facility. In the original facility layout, there are four CEA areas. The revitalization product consolidated all CEAs into a single location (termed CEA #2). Products and related manufacturing equipment were moved in two phases. Prior 30-day notice P920015/S042 covered Phase I of the move, which impacted only the Model 6937 lead. This submission covers Phase II of the move, which involves all remaining equipment for the above listed products as well as a (b) (6)(4) monitoring system for the new CEA.

The Heating, Ventilation and Air Conditioning (HVAC), room environmental conditions, and gas supplies are equivalent in the new CEA #2 to the existing requirements. Room and surface finishes in the new CEA are the same as the existing, with the exception of a different floor type, ESD tiling rather than seamless linoleum. A new de-ionized (DI) water system has also been installed to support the new CEA; however, the monitoring of the water system remains the same as for the previous system.

The firm originally included qualification of a (b) (6)(4) temperature, humidity, pressure, and (b) (6)(4) monitoring system as part of this 30-day notice; however, during the review cycle it was determined that qualification activities had not been completed for the system (see Questions to firm, below), and the firm sent Amendment 2 to remove this part of the submission from consideration. The firm will submit an additional supplement for the (b) (6)(4) monitoring system at a later time. Room monitoring will continue per the existing Medtronic procedures, as were submitted for Phase 1 under P920015/S042.

All equipment used in the manufacturing of the above listed products will remain the same and has been relocated to the new CEA #2. No product or process changes will result from the move. The Ethylene Oxide (EO) sterilization equipment will not be moved and is not impacted by relocation to the new CEA. The firm provided documentation for:

Part 1 - Page 9

- Facility Qualification (FQ), which includes both:

  Design Qualification (DQ). Drawings and descriptions of how requirements and specification of CEA are to be met. Includes installation plan, and

  Installation Qualification (IQ). Ensures equipment is installed in accordance with design specifications and user and manufacturing requirements. Also verifies that system documentation is available to support operation and maintenance.

  The firm provided the following FQ documents as part of the Submission. Note that BL0018102, BL0017930 and BL0017931 were completed for Phase 1, and included in this submission for completeness:

  - (b)(4) / *Rice Creek Central CEA #2 Facility Qualification Report.* All acceptance criteria were met. Qualification activities included inspections and testing of electrical, plumbing, gas systems, HEPA, major equipment not covered in separate qualification plans, etc.
  - (b)(4) *Rice Creek Central CEA #2 Purified Water System Modifications Installation/Operational Qualification Plan.*
  - (b)(4) *Rice Creek Central CEA #2 Purified Water System Modifications Installation/Operational Qualification Report.* All acceptance criteria were met. Utilities to support the purified water system were verified and chemical and biological testing of the purified water system was performed to ensure that the water meets all requirements.
  - Various equipment installation qualifications.

- Operational Qualification (OQ). Documented verification that facility or utility operate as intended through all anticipated ranges.

  The firm provided the following OQ documents as part of the Submission:

  - (b)(4) *Rice Creek Central CEA #2 Phase 2 Performance Qualification Report.* Room environmental conditions met all acceptance criteria. Microbial counts met acceptance criteria.

- Performance Qualification (PQ). Documented verification that utility, environment, and support systems produce required output.

  The firm provided the following PQ documents as part of the Submission:

  - (b)(4) *Rice Creek Central CEA #2 Phase 2 Performance Qualification Report.* Room environmental conditions met all acceptance criteria. Two lots of product were built in CEA #2 with 100% yield (acceptance criteria was 95% yield minimum).

The firm also completed a Risk Assessment as part of the move process. The firm provided (b)(4) *Rice Creek Central CEA #2 Risk Assesment: Phase 2.* All risks were found acceptable based on successful completion of qualification activities as documented in the submission.

The following questions were forwarded to the firm by e-mail on 09 July 2008 and the firm provided responses via e-mail on 10 July 2008 with follow-up clarifications by e-mail and phone on 10 July 2008:

1) During the installation and operational qualification for the (b)(4) system (Attachments 2 & 3 of the submission), test incidents were recorded (reference pg. 57 of 60 in Attachment 2 and pg. 51 of 54 in Attachment 3). In both instances, the problem was related to issues that required resolution by (b)(4) The summary reports indicated that Medtronic needed to resolve the issues and repeat testing as required. Please provide documentation that these issues have been resolved and all required testing completed.

   Response Review. Upon reviewing the qualification data related to this question, the firm determined that the required resolutions would take longer than anticipated. As such, the firm sent an amendment removing the (b)(4) from the 30-day notice and indicating that the firm will file an additional supplement for this change once all issues have been resolved.

   The firm was asked during a phone call on 10 July 2008 to indicate what manual monitoring is used. The firm clarified that they will continue with the same manual monitoring process that was in-use in the prior CEA and in Phase 1 of the CEA #2 move. The firm's response is adequate.

2) In Attachment 2 to the Facility Qualification Report (Attachment 6 of the submission), sheets 2 and 3 (b)(4) Air Sampler units that were past the calibration due date (due date (b)(4)). Please provide evidence that these units met all functional requirements..

   Response Review. The firm clarified that the testing for Attachment 6 was performed on (b)(4) as dated on the data sheets. The firm further indicated that the testing on the date was for a separate qualification activity, and all calibrated instruments for that qualification were within their due dates. These facts were confirmed in the submission. The firm's response is adequate.

3) In the (b)(4) Installation Qualification (Attachment 30 to the submission), the oven temperature profile failed to meet the acceptance criteria (b)(4) The report indicates that the specifications required for products processed in this oven do not exceed (b)(4) and therefore the results are acceptable. Please indicate how oven temperature is monitored as

part of regular production and how you will ensure that qualification of any future processes that utilize this oven will consider the possible (b)(4) temperature variation.

Response Review. The firm indicated that oven temperature is monitored via (b)(4) is verified to be within acceptable limits by the operator as part of the manufacturing process. The firm further indicated that all new activities that would require use of the (b)(4) would be subject to full process qualification activities specific to the product being manufactured. The firm's response is adequate.

4) Several of the Installation Qualification Reports (e.g., Attachments 40 and 42) indicate that equipment called out in the plan could not be located and was replaced with functionally equivalent equipment. Was this equivalent equipment relocated from the prior CEA location, or is it equipment new to the production process? Also, please provide an explanation for why some equipment could not be located.

Response Review. The firm clarified that some equipment could not be located due to removal from service, etc. Any equipment called for by the manufacturing process documentation was used as required. The firm was further asked to clarify whether any new equipment was put into service in CEA #2 as part of the move process. The firm provided clarification by e-mail on 10 July 2008 that no new equipment was added and all equipment required by the manufacturing process was located and installed per the installation qualification requirements. The firm's response is adequate.

DECISION:

The Office of Compliance signed off on the letter to the manufacturer indicating that the submission of a 135-day PMA supplement is not required and that they may distribute the device incorporating the changes as requested in this supplement. The firm removed the (b)(4) from the submission and will submit this change under a separate supplement at a later date.

SUMMARY:

A copy of the 30-Day Notice Checklist, e-mail information from the firm, and a copy of the letter to the manufacturer are attached.

7/24/2008

Melissa B. Burns

12

Prepared: MBurns: 07/15/08
Reviewed: BMacFarland:
Final:

CC: HFZ-340 (c/f)
HFZ-341 (f/f)

OC Track: CTS

30-Day Notice Checklist

Name of Firm: Medtronic, Inc.

Address of Firm: 8200 Coral Sea Street, MS MVS11
Mounds View, MN 55112

Submissions Number: P920015/S042, P890003/S142, P900061/S076, P950024/S011, P980050/S034, P010015/S044, P030036/S007

Device: Medtronic Leads – Various Models

Type of Change: Manufacturing

Section I By day 5, determine if 30-Day notice is appropriate, If not, why?

If any items below are checked, this submission does not qualify as 30-Day Notice.

1. manufacturing/sterilization site change _____
2. design or performance specification change _____
3. material specification change_____
4. device operating software change_____
5. labeling changes_____

Section II Does the notice contain the following: (Check appropriate answer)

1. Description of change	YES √	NO	NA
2. Reason for change	YES √	NO	NA
3. Rationale for implementation via 30-Day notice	YES √	NO	NA
4. Statement that completed design validation demonstrates that the manufacturing change can be made without significantly changing final device operation. (Reconfirm that the 30-Day Notice is the appropriate submission route.)	YES	NO	NA √
5. A summary or description of procedures for change control including identification, documentation, validation, review and approval of manufacturing changes covered by the notice.	YES √	NO	NA
6. Describe documentation change controls necessary for modifying manufacturing or quality control instructions. (21 CFR 820.40)	YES √	NO	NA

Continued on next page

30-Day Notice Checklist, continued

7. If verification is used instead of process validation, the rationale for using verification in accordance with 21 CFR 820.1(a)(3) should be included.	YES	NO	NA √
8. If changed procedures are validated, summarize the procedures for monitoring and controlling process parameters (21 CFR 820.75(b). For new equipment, process validation should include installation qualification, operator qualifications, and software validation of any software driven equipment.	YES √	NO	NA
9. If changed procedures are to be routinely verified by sampling and independent measurement, summarize statistical rational for the sampling method. (21 CFR 820.250)	YES	NO	NA √
10. If manufacturing change involves changes in components or raw material, a statement describing the evaluation of new suppliers, and a description the type and extent of control to be exercised over the component or raw material. (21 CFR 820.50)	YES	NO	NA √
11. If change involves use of a new contractor for manufacturing or quality control testing, a statement describing procedures and criteria for evaluation of that contractor. (21 CFR 820.50)	YES	NO	NA √
12. Statement of conformity	YES √	NO	NA

Note: On a case by case bases the engineering change order (ECO) record may be requested from the firm if it will assist in bringing clarification to the 30-Day Notice.

OC IMAGE PACKAGE COVERSHEET

Please IMAGE the attached package associated with an OC-lead document: (1) 30-Day Notice/135-Day Supplement or (2) Manufacturing Site Change Supplement. If a bundled submission and review is involved, only one copy of the IMAGE package is necessary.

Supplement Type:

- [x] 30-Day Notice/135-Day Supplement
- [ ] Manufacturing Site Change Supplement

Bundled Submission and Review?

- [ ] Yes (bundled submissions are identical and one set of review memos is involved)
- [x] No

IMAGE Package Checklist:

- [x] completed IMAGE coversheet
- [x] copy of signed, dated letter
- [x] copy of OC or OIVD (compliance) lead review memo with reviewer and appropriate management signatures for the given review round
- [ ] if applicable, copy of ODE/OIVD consult review memo with reviewer and appropriate management signatures for the given review round
- [ ] if applicable, copies of any other supporting information for the given review round (e.g., email from applicant, EIR report)

IMAGE this package for the following PMA supplement(s):

1. P 920015/S045
2. _____
3. _____
4. _____
5. _____

Etc.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
9200 Corporate Blvd
Rockville, MD 20850

JUL 11 2008

Ms. Stacey Paetschow Wessman
Principal Regulatory Affairs Specialist
Medtronic, Inc.
8200 Coral Sea St., MS MV S11
Mounds View, MN 55112

Re: P920015/S045 Sprint Quattro Secure Lead Model 6935
Filed: June 13, 2008
Amended: June 27, 2008

Dear Ms. Wessman:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) 30-day Notice. The submission requested a change in the plasma treatment process for the lead silicone tubing. We have determined a detailed review of the data supporting the change must be performed. Therefore, your 30-day Notice has been converted to a 135-Day PMA Supplement.

The following deficiencies were identified during the review of the 30-day Notice. Because of the lack of this information, review of the PMA cannot continue and, accordingly, we have listed the following deficiencies which require the responses as indicated:

1. Medtronic's rationale for this 30-day Notice is that the change to combined (b)(4) will improve manufacturability. The existing process utilizes both (b)(4) and (b)(4). Please provide a more detailed explanation on how the combined (b)(4) improves manufacturability. Also, please verify that the (b)(4) treatment of the outer tubing is unchanged.

2. Attachment 1 of your submission includes a sample size rationale in Table V of Process Qualification/Validation Plan (b)(4) Although some statistical parameters are provided, in the column labeled, (b)(4)" it is not immediately clear how your firm utilized these statistical parameters to derive the sample size used in testing. Please provide information that demonstrates how you calculated the sample sizes identified in Table V. Please show your calculations and identify all parameters. Please identify all assumptions associated with these statistical calculations.

Part 1 - Page 17

3. Please provide test data and other documentation to show that the tensile strength, elongation, and other mechanical/electrical properties of the base tube material are not altered by the proposed (b)(4) process.

4. Please provide a rationale for why the proposed (b)(4) process would not affect the base tube material differently than the current separate (b)(4) processes.

5. In Attachment 3 of the submission, you have provided a very brief Risk Assessment regarding the change to the plasma treatment process for the lead silicone tubing. Please provide a more detailed Risk Assessment as the risks and benefits of this change are not clearly defined in the information presented in the submission. Also, please provide a rationale for why the proposed (b)(4) process would not affect the base tube material differently than the current separate (b)(4) processes.

6. Please provide documentation of any market approved device where the (b)(4) process is used to prime the same base tubing material.

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your PMA application can be completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 515 of the Federal Food, Drug, and Cosmetic Act for determining reasonable assurance of safety and effectiveness of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at: http://www.fda.gov/cdrh/modact/leastburdensome.html.

This letter reflects the current progress of our review of your application. You may not begin commercial distribution of the device as modified by this PMA 135-day supplement until you have received an approval order. Further review of your application and/or any response to this letter may result in additional deficiencies. CDRH will issue an approval order for the 135-day PMA supplement after the requested information has been reviewed and determined to be acceptable.

Because FDA considers the information submitted with the 30-day Notice as meeting the content requirements for PMA supplements, the time spent reviewing the submission as a 30-day Notice will be deducted from the 135 day period.

You may amend the PMA 135-day supplement to provide the above requested information (3 copies), voluntarily withdraw the PMA (3 copies) or request an extension. The required copies

of the amended PMA 135-day supplement should include the FDA reference number to facilitate processing.

One copy should be sent to:

Food and Drug Administration
Office of Compliance
Field Programs Branch (HFZ-306)
2098 Gaither Road
Rockville, Maryland 20850

The remaining **two copies** should be sent to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this letter, please contact Michelle Noonan-Smith, at (240) 276-0120.

Sincerely yours,

for

Gladys Rodriguez
Director
Division of Enforcement B
Office of Compliance
Center for Devices and Radiological Health

REVIEW MEMORANDUM

30-DAY NOTICE

DATE: July 11, 2008

TO: The Record

THRU: William MacFarland, Acting Branch Chief, CNDB, DOEB, OC, CDRH

WJM initials 7-11-2008 date

FROM: Michelle Noonan-Smith, CNDB, DOEB, OC, CDRH, HFZ-341

SUBJECT: 30-Day Notice
Received: June 13, 2008
Amended: June 27, 2008
OC Track: in CTS

Applicant: Medtronic, Inc.
8200 Coral Sea St., MS MV S11
Mounds View, MN 55112
FEI: 2182208

DEVICES: P920015/S045 Sprint Quattro Secure Lead Model 6935

OC RECOMMENDATION: Information Not Adequate – Send Deficiency Letter and Convert to 135-day Supplement

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BACKGROUND:

This application from Medtronic Vascular is a request for a 30-day Notice review in accordance with 21 CFR 814.39. This application requests a change in the plasma treatment process for the lead silicone tubing. The change is being made to improve manufacturability and yields.

Medtronic's Sprint Quattro Secure Lead Model 6935 is intended for long-term use in the right ventricle for patients indicated for implantable cardioverter defibrillators.

FIRM CONTACT:

Ms. Stacey Paetschow Wessman
Principal Regulatory Affairs Specialist
Medtronic, Inc.
8200 Coral Sea St., MS MV S11
Mounds View, MN 55112
763-526-2378/910-538-3821
FAX 651-367-0603
Stacey.p.wessman@medtronic.com

CORRESPONDENCE HISTORY:

COMPLIANCE REVIEW:

The Office of Compliance (OC) received this 30-Day Notice on June 18, 2008, and it was forwarded to CNDB for review on June 18, 2008.

The applicant is requesting a minor change in the plasma treatment process for the lead silicone multi-lumen tubing. Specifically, the applicant states that additional controls on component features were implemented on the 6935 lead (as reported and approved in P920015/S039), including the addition of a lubricity test for the multi-lumen tubing. The lubricity test is to be performed in each of the three small conductor lumens of the multi-lumen tubing and the requirement is that the average of all lumens, measured (b)(4) each, for a minimum of (b)(4) samples of a lot shall be less than (b)(4) As a result of the addition of this lubricity requirement, the applicant states that they will need to implement a minor modification to the plasma treatment process for the multi-lumen tubing to improve component manufacturability and yield.

The applicant states that, currently, the silicone multi-lumen tubing used in the manufacture of these leads is processed at Medtronic's (b)(4) (b)(4) for plasma treatment of the tubing outer diameter using (b)(4) (b)(4) and of the four largest inner lumen walls (conductor lumens) using (b)(4) (b)(4) as outlined in the tables below:

Current Qualified Process Setting (Set Point A)

(b)(4)

(b)(4)

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Current Qualified Process Setting (Set Point B)

(b)(4)

The applicant states that Set Point A are the SATURATION conditions and that Set Point B are the STABILIZATION and TREATMENT conditions.

The change will be to convert to (b)(4) to saturate the tubing for plasma treatment of the four largest inner lumens of the tubing. The ration is (b)(4) to (b)(4) The processing will also include the following:

(b)(4) **Development Process Settings (Set Point A)**

(b)(4)

(b)(4) **Development Process Settings (Set Point B)**

(b)(4)

The applicant provided a table on page 13 of the submission to summarize the testing being performed in order to establish a minimum level of confidence to permit the application of the (b)(4) Plasma Treatment process to build the Tubing – Multilumen,

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Plasma Treated, (b)(4) Silicone. Attachment 1 of the submission contains the test plan and Attachment 2 contains the test report. A review of these documents shows that all testing was passed with no anomalies or issues. The tests performed are as follows:

Characteristics	Test Method	Requirements	Samples size (minimum)	Rationale for sample plan/strategy	Test Result
Dimensional (outside diameter)		Spec of (b)(4) Sec (b)(4)	Not being tested	High and low extreme runs from 5 characterization DWRs were tested and shown to have no effect on OD dimensions (see Characterization Report (b)(4)	Pass
Length	Visual (b)(4)	Spec of (b)(4) Sec (b)(4) minimum length	100% Attribute Data	All sections will be inspected for length. The final length will be noted on ET Form (b)(4) for each section.	Pass
Plasma (b)(4) Treatment	Verified by process variables (b)(4)	Line speed, OD (b)(4) and ID Power; (b)(4) process data from each run will be compared to the characterized window (See Table III)	Variables Data;	(b)(4) is acceptable to show variation of process variables. Nominal conditions in the Characterization runs showed little variability and all key process variables had (b)(4) or greater.	Pass
Lubricity (ID)	U-Test (b)(4)	Spec of M933157A Sec (b)(4)	Plasma treated tubing samples from each section, lumens 2,3 and 4 measured (b)(4) for a total (b)(4) results per section (see	Each section will have (b)(4) data points collected. The mean of the (b)(4) data points will be compared to the specification	Pass

Characteristics	Test Method	Requirements	Samples size (minimum)	Rationale for sample plan/strategy	Test Result
			spec (b)(4) sec(b)(4) for lumen diagram)	Tubing will be sampled as follows(b)(4) samples will be pulled from each end of the section for a total of(b)(4) The(b)(4) sample will come from the middle of the section. Each tubing sample must be a minimum of(b)(4) (b)(4)	
Tensile Strength	ASTM D412	Spec of (b)(4) (b)(4) (b)(4)	Not being tested.	Combined(b)(4) for Characterizations runs was(b)(4)	Pass
Elongation	ASTM D412	Spec of (b)(4) (b)(4) (b)(4)	Not being tested.	Combined(b)(4) for Characterization runs was(b)(4)	Pass
Visual Criteria	Visual – (b)(4) (b)(4)	Ref(b)(4) of spec. (b)(4) (b)(4)	(b)(4) Attribute Data	Per (b)(4) (b)(4) confidence level and a (b)(4) yield level with(b)(4)	Pass
Color	Visual – (b)(4) (b)(4)	Ref(b)(4) of spec. (b)(4) (b)(4)	(b)(4) Attribute Data	Per (b)(4) (b)(4) confidence level and a (b)(4) yield level with(b)(4)	Pass
Yield (%)	Calculated – based on acceptable product that meets Length, lubricity, Visual Criteria and Color	Yield must be greater than (b)(4) Yield will be calculated on the number of finished acceptable quantity in feet divided by the starting quantity. This will be calculated on the total of all	Not Applicable	Not Applicable Rationale for(b)(4) yield target – Process controls are in place to ensure only acceptable product leaves the facility. Examples of the controls are process (b)(4) (b)(4) and the (b)(4) (b)(4) testing. Machine capacity at the(b)(4) yield will be able to satisfy demand for the tubing.	Pass

		(b)(4) runs			
Biocompatibility Testing	ISO 10993	As defined by ISO 10993	As defined by ISO 10993	Although the surfaces affected by the process change are not tissue contacting, when implanted, MEM cytotoxicity, hemolysis test, endotoxin tests were conducted. Testing met requirements as defined by ISO 10993. Testing was performed to ensure that the material biocompatibility was not altered.	Pass

The applicant, however, did not provide detailed information regarding their statistical rationale for the sample sizes used in the testing. It is also not clear, from the information provided in the submission, why dimensions, tensile strength, and elongation were not tested as indicated in the above table.

The applicant provided in Attachment 3 a Risk Assessment. This is a one page document with very little detail that states that, "The addition of (b)(4) improves the process efficiency making it easier to maintain a consistent plasma treatment process output. The use of (b)(4) in the carrier (b)(4) is similar to the plasma process used to treat the exterior surfaces of the same multilumen tubing component." The Risk Assessment also states that, "The addition of the (b)(4) does not change or create any new risks to the process or finished product performance. Component qualification has demonstrated the process is able to consistently produce product that meets specification (MECC plan and report (b)(4) Biocompatibility testing has been completed on tubing created using the (b)(4) plasma process as part of qualification. The results confirmed that the resultant material continues to meet the biocompatibility requirements for cytotoxicity, hemolysis, and endotoxins, as expected." It is unclear, from the information presented in the submission, how these conclusions were drawn.

The Office of Compliance (OC) has the following questions/requests for additional information:

1. Medtronic's rationale for this 30-day Notice is that the change to combined (b)(4) will improve manufacturability. The existing process utilizes both (b)(4) (Set Point A) and (b)(4) (Set Point B). Please provide a more detailed explanation on how the combined (b)(4) improves manufacturability.

2. Attachment 1 of your submission includes a sample size rationale in Table V of Process Qualification/Validation Plan - Plasma Treated (b)(4) Although some statistical parameters are provided, in the column labeled, (b)(4) (b)(4) it is not immediately clear how your firm utilized these statistical parameters to derive the sample size used in testing. Please provide information that demonstrates how you calculated the sample sizes identified in Table V. Please show your calculations and identify all parameters. Please identify all assumptions associated with these statistical calculations.

3. Please provide a more detailed explanation as to why dimensions, tensile strength and elongation are not evaluated as part of this change as indicated in Table V.

4. In Attachment 3 of the submission, you have provided a very brief Risk Assessment regarding the change to the plasma treatment process for the lead silicone tubing. Please provide a more detailed Risk Assessment as the risks and benefits of this change are not clearly defined in the information presented in the submission. Also please provide your rationale regarding how this change does not affect the design of the device.

On July 8, 2008, an e-mail was sent to ODE regarding this submission. On July 10, 2008, ODE (Mark Fellman) responded stating that they had some concerns with the information presented in the submission. Their concerns are as follows:

1. Please verify that the (b)(4) plasma treatment of the outer tubing is unchanged.

2. Please provide a rationale for why the proposed (b)(4) process would not affect the base tube material differently than the current separate (b)(4) and (b)(4) processes.

3. Please provide documentation of any market approved device where the (b)(4) process is used to prime the same base tubing material.

4. Please provide test data other documentation to show that the tensile strength, elongation, and other mechanical/electrical properties of the base tube material are not altered by the proposed (b)(4) process.

Since some of ODE's concerns resemble OC's concerns, the following questions/requests for information will be sent to the applicant in a conversion letter:

1. Medtronic's rationale for this 30-day Notice is that the change to combined (b)(4) will improve manufacturability. The existing process utilizes both (b)(4) (Set Point A) and (b)(4) (Set Point B). Please provide a more detailed explanation on how the combined (b)(4) improves manufacturability. Also, please verify that the (b)(4) plasma treatment of the outer tubing is unchanged.

2. Attachment 1 of your submission includes a sample size rationale in Table V of Process Qualification/Validation Plan - Plasma (b)(4) Although some statistical parameters are provided, in the column labeled, (b)(4) it is not immediately clear how your firm utilized these statistical parameters to derive the sample size used in testing. Please provide information that demonstrates how you calculated the sample sizes identified in Table V. Please show your calculations and identify all parameters. Please identify all assumptions associated with these statistical calculations.

3. Please provide test data other documentation to show that the tensile strength, elongation, and other mechanical/electrical properties of the base tube material are not altered by the proposed (b)(4) process.

4. Please provide a rationale for why the proposed (b)(4) process would not affect the base tube material differently than the current separate (b)(4) and (b)(4) processes.

5. In Attachment 3 of the submission, you have provided a very brief Risk Assessment regarding the change to the plasma treatment process for the lead silicone tubing. Please provide a more detailed Risk Assessment as the risks and benefits of this change are not clearly defined in the information presented in the submission. Also, please provide a rationale for why the proposed (b)(4) process would not affect the base tube material differently than the current separate (b)(4) processes.

6. Please provide documentation of any market approved device where the (b)(4) process is used to prime the same base tubing material.

DECISION:

The Office of Compliance signed off on the letter to the manufacturer indicating that the 30-day Notice has been converted to a 135-day Supplement.

SUMMARY:

The 30-Day Notice Checklist, the e-mail from ODE dated July 10, 2008, and a copy of the letter to the manufacturer are attached.

Michelle E. Noonan-Smith

Michelle E. Noonan-Smith

12.

Prepared: MNoonan-Smith: July 10, 2008
Reviewed: WMacFarland:
Final:

CC: HFZ-340 (c/f)
HFZ-341 (f/f)
HFZ-341 (MNoonan-Smith)

OC Track: CTS

30-Day Notice Checklist

Name of Firm: Medtronic Inc.

Address of Firm: 8200 Coral Sea St., MS MV S11
Mounds View, MN 55112

Submissions Number: P920015/S045

Device: Sprint Quattro Secure Lead Model 6935

Type of Change: Change in the plasma treatment process for the lead silicone tubing

Section I By day 5, determine if 30-Day notice is appropriate, If not, why?
_____yes, appropriate_____
If any items below are checked, this submission does not qualify as 30-Day Notice.

1. manufacturing/sterilization site change _____
2. design or performance specification change _____
3. material specification change_____
4. device operating software change_____
5. labeling changes_____

Section II Does the notice contain the following: (Check appropriate answer)

1.	Description of change	YES		
2.	Reason for change	YES		
3.	Rationale for implementation via 30-Day notice	YES		
4.	Statement that completed design validation demonstrates that the manufacturing change can be made without significantly changing final device operation. (Reconfirm that the 30-Day Notice is the appropriate submission route.)	YES		
5.	A summary or description of procedures for change control including identification, documentation, validation, review and approval of manufacturing changes covered by the notice.	YES		
6.	Describe documentation change controls necessary for modifying manufacturing or quality control instructions. (21 CFR 820.40)	YES		

Continued on next page

7.	If verification is used instead of process validation, the rationale for using verification in accordance with 21 CFR 820.1(a)(3) should be included.			N/A
8.	If changed procedures are validated, summarize the procedures for monitoring and controlling process parameters (21 CFR 820.75(b). For new equipment, process validation should include installation qualification, operator qualifications, and software validation of any software driven equipment.	YES		
9.	If changed procedures are to be routinely verified by sampling and independent measurement, summarize statistical rational for the sampling method. (21 CFR 820.250)	YES		
10.	If manufacturing change involves changes in components or raw material, a statement describing the evaluation of new suppliers, and a description the type and extent of control to be exercised over the component or raw material. (21 CFR 820.50)			N/A
11.	If change involves use of a new contractor for manufacturing or quality control testing, a statement describing procedures and criteria for evaluation of that contractor. (21 CFR 820.50)			N/A
12.	Statement of conformity	YES		

Note: On a case by case basis the engineering change order (ECO) record may be requested from the firm if it will assist in bringing clarification to the 30-Day Notice.

Noonan-Smith, Michelle

From: Fellman, Mark
Sent: Thursday, July 10, 2008 10:46 AM
To: Noonan-Smith, Michelle
Cc: MacFarland, William C; Shein, Mitchell J.; Fellman, Mark
Subject: RE: Medtronic P920015/S045

Michelle,
I was able to find and review the submission in Image. Medtronic describes the change as follows:

Original:
(b)(4) plasma treatment of tubing outer diameter
(b)(4) treatment of four largest inner lumens of tubing

Proposed:
(b)(4) for plasma treatment of four largest inner lumens of tubing with some altered settings for
(b)(4) and treatment conditions.

I would generally agree that this is a manufacturing change since the modified method of plasma priming does not involve new substances or affect new areas of the tubing. I suggest a few questions for the company:

1. Please verify that the (b)(4) plasma treatment of the outer tubing is unchanged.
2. Please provide a rationale for why the proposed (b)(4) process would not affect the base tube material differently than the current separate (b)(4) processes.
3. Please provide documentation of any market approved device where the (b)(4) process is used to prime the same base tubing material.
4. Please provide test data other documentation to show that the tensile strength, elongation, and other mechanical/electrical properties of the base tube material are not altered by the proposed (b)(4) process.

Mark Fellman P.E.
Scientific Reviewer
Pacing, Defibrillator and Leads Branch
FDA / CDRH / ODE / DCD
9200 Corporate Blvd HFZ-450 Rm 140D
Rockville, Maryland 20850
Ph: (240) 276-4060
Fx: (240) 276-4002

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From: Noonan-Smith, Michelle
Sent: Thursday, July 10, 2008 8:48 AM
To: Fellman, Mark
Cc: MacFarland, William C
Subject: RE: Medtronic P920015/S045

Hi Mark,

Thank you for getting back to me on this. I just looked in Image and the file is in there, but if you are still unable to access, please let me know and I will send it to you as an attachment. It's a pretty large file. Medtronic did provide their testing plan and a testing report to support the change, but I don't believe that any of the tests they conducted show that the new plasma priming process doesn't degrade the material over time.

I can go ahead and convert this notice to a 135-day. From OC's perspective, there were no issues with the file (except perhaps for sample size rationale, but I'll need Bill's input on that), so if you could formulate some questions for me to ask Medtronic, that would be great. That way I'll know exactly what you need for your review.

Thank you,
Michelle

From: Fellman, Mark
Sent: Wednesday, July 09, 2008 3:11 PM
To: Noonan-Smith, Michelle
Cc: Shein, Mitchell J.; Fellman, Mark; Moynahan, Megan
Subject: RE: Medtronic P920015/S045

Michelle,
My concern with this change is that a change in plasma priming could potentially affect the mechanical integrity and biostability of the insulation material over time. Image2000 said the "submission number is valid but not scanned" so I couldn't look into it further. We would want to understand the differences in the areas of the lead that are primed, differences in the application methods, and a strong rationale or test results to demonstrate that the plasma priming process does not degrade the material integrity in the short or long term. If the coverage is the same and the method is similar, this might be fine but I need to see a little more. (b)(4) (b)(4)
(b)(4) (b)(4)
(b)(4) (b)(4)
(b)(4) (b)(4)

Mark

Mark Fellman P.E.
Scientific Reviewer
Pacing, Defibrillator and Leads Branch
FDA / CDRH / ODE / DCD
9200 Corporate Blvd HFZ-450 Rm 140D
Rockville, Maryland 20850
Ph: (240) 276-4060
Fx: (240) 276-4002

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From: Noonan-Smith, Michelle
Sent: Wednesday, July 09, 2008 7:31 AM
To: Shein, Mitchell J.; Fellman, Mark
Subject: FW: Medtronic P920015/S045

Hello Mitchell and Mark,

I wanted to let you know that I have a very short turnaround with this file. It is due on Friday. My workload has been very heavy and I just started looking at this at the end of last week. Yesterday I realized that ODE might want to review this. Sorry for the short notice!

Thanks!
Michelle

From: Moynahan, Megan
Sent: Tuesday, July 08, 2008 5:22 PM

To: Noonan-Smith, Michelle
Cc: Shein, Mitchell J.; Fellman, Mark
Subject: RE: Medtronic P920015/S045

Hi Michelle,
Thanks for sending it along. Mitchell Shein is the current acting branch chief over the pacing branch while I am in my new position as network leader. I've cc'd him on this, along with Mark Fellman who is the pacing leads "guru" over there. They can help you with your request.

Regards,
Megan

From: Noonan-Smith, Michelle
Sent: Tuesday, July 08, 2008 4:08 PM
To: Moynahan, Megan
Subject: Medtronic P920015/S045

Hi Megan,

I am in the process of reviewing a 30-day Notice for Medtronic's Sprint Quattro Secure Lead Model 6935 and I wanted to check with you to see if this is something that ODE would like to review. Medtronic states that they are implementing a "minor" modification to the plasma treatment process for the multi-lumen tubing as a result of the addition of a lubricity requirement (the subject of P920015/S039 approved on 4/29/08). Currently the silicone multi-lumen tubing used in the manufacture of these leads is processed for plasma treatment of the tubing outer diameter using (b)(4) and of the four largest inner lumen walls (conductor lumens) using (b)(4) The change will be to convert to (b)(4) to (b)(4) the tubing for plasma treatment of the four largest inner lumens of the tubing. As a result of this change, they will be changing some of the qualified process settings for Set Point A (b)(4) and Set Point B (b)(4)

I may not be explaining this very well because I am having a hard time understanding exactly what the change is. The file is in Image if you need to see it to make your determination. Is this something that your branch would like to review? Please let me know and, if so, I can set up an eConsult.

Thank you,
Michelle

LCDR Michelle E. Noonan-Smith, USPHS
FDA/CDRH/OC/Division of Enforcement B
Cardiovascular and Neurological Devices Branch
2094 Gaither Road, HFZ-341
Rockville, MD 20850
(b)(6)
Phone: (240) 276-0288
Fax: (240) 276-0129

OC IMAGE PACKAGE COVERSHEET

Please IMAGE the attached package associated with an OC-lead document: (1) 30-Day Notice/135-Day Supplement or (2) Manufacturing Site Change Supplement. If a bundled submission and review is involved, only one copy of the IMAGE package is necessary.

Supplement Type:

- [x] 30-Day Notice/135-Day Supplement
- [ ] Manufacturing Site Change Supplement

Bundled Submission and Review?

- [ ] Yes (bundled submissions are identical and one set of review memos is involved)
- [x] No

IMAGE Package Checklist:

- [x] completed IMAGE coversheet
- [x] copy of signed, dated letter
- [x] copy of OC or OIVD (compliance) lead review memo with reviewer and appropriate management signatures for the given review round
- [ ] if applicable, copy of ODE/OIVD consult review memo with reviewer and appropriate management signatures for the given review round
- [ ] if applicable, copies of any other supporting information for the given review round (e.g., email from applicant, EIR report)

IMAGE this package for the following PMA supplement(s):

1. P920015/S043
2. _____
3. _____
4. _____
5. _____

Etc.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

MAY 1 2008

Margaret M. DePuydt, P.E., RAC
Medtronic, Inc.
Mounds View Facility South
8200 Coral Sea Street N.E.
Moundsview, Minnesota 55112

Re: P920015/S043
Sprint Leads Model No. 6932, 6942, 6943, and 6945
Sprint Quattro Lead Model No. 6944
Sprint Quattro Secure Lead Model No. 6947
Sprint Fidelis Lead Model No. 6930, 6931, 6948, and 6949
DF-1 Y-Adapter/Extender Kit Model No. 6726
Filed: April 1, 2008

Dear Ms. DePuydt:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has evaluated your premarket approval application (PMA) 30-day Notice. The 30-day Notice requested a change to the cure process at a component supplier.

Based on the information submitted, FDA has determined that submission of a 135-day PMA supplement is not required. Therefore, you may distribute your device, incorporating the change described above, upon receipt of this letter.

If you have questions concerning this letter, please contact Bradley Quinn at (240) 276-0297.

Sincerely yours,

Christy Foreman for

Gladys Rodriguez
Director
Division of Enforcement B
Office of Compliance
Center for Devices and Radiological Health

MEMORANDUM

30-DAY NOTICE

DATE: April 29, 2008

TO: The Record

THRU: Christy L. Foreman, Deputy Director, DOEB, OC, CDRH

initials _____ date _____

FROM: Bradley Quinn, Engineer, CNDB, DOEB, OC, CDRH, HFZ-341

SUBJECT: 30 Day Notice PMA Supplement
Received: 04/01/08

Applicant: Medtronic, Inc.
8200 Coral Sea Street NE
Mounds View, Minnesota 55112

DEVICES: P920015/S043
Sprint Leads Model No. 6932, 6942, 6943, 6945
Sprint Quattro Lead Model No. 6944
Sprint Quattro Secure Lead Model No. 6947
Sprint Fidelis Lead Model No. 6930, 6931, 6948, 6949
DF-1 Y-Adapter/Extender Kit Model No. 6726

OC RECOMMENDATION: 30 Day Approved, No 135 Day Supplement Needed

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BACKGROUND:

This application from Medtronic Inc. is a request for a 30-Day Notice review in accordance with 21 CFR 814.39. This submission requests for a minor change to a supplier post-cure process for the DF-1 connector insulation. The change is being made to improve supplier yield. The change has yet to be implemented.

The DF-1 connector insulation for the Sprint Fidelis models listed in the **DEVICES** section of this memo are produced and post-cured at (b)(4) (b)(4)

Part 1 - Page 36

(b)(4) The Sprint Fidelis models are manufactured as finished devices at Medtronic Puerto Rico Operations Co. (MPROC), Rd. 149, Km. 56.3, Call Box 6001, Villalba, Puerto Rico 00766.

The DF-1 connector insulation is used as a strain relief, part no. 153447007, in Sprint Fidelis models. Part no. 153447007 is single-lumen and has a durometer of (b)(4) The DF-1 connector insulation uses a (b)(4) raw material that is vulcanized after extrusion to complete the curing/cross-linking process. A post-cure is not required for this type of material; however, a post-cure is utilized by (b)(4) (b)(4) to stabilize the mechanical properties of the material. The post-cure process is where a material is placed into a large oven and held at a specified temperature for a specified length of time.

Routine monitoring through the acceptance activities of the incoming components have shown a downward drifting of the elongation specification (b)(4) minimum). In order to prevent an inventory shortage, Medtronic collaborated with (b)(4) (b)(4) in assisting with making minor improvements to the post-cure process. The supplier is changing the time and temperature for the 153447007 post-cure from (b)(4) (b)(4) minutes to (b)(4) (b)(4). This change matches a previous change in the post-cure process in 1997. At that time, a post-cure Design of Experiments (DoE) was completed and included crush testing. Testing at the time was performed on part no. 153435001. In contrast to part no. 153447007, part no. 153435001 is multi-lumen and has a durometer of (b)(4) The firm states that this difference has no impact on the component performance, are of the same chemical family, and have the same requirements for tensile strength, elongation, toughness, and extractables. The single-lumen tubing is used in the connector portion of the lead, located in the device implantation pocket, whereas the multi-lumen tubing is subject to tortuous anatomy. The more difficult load conditions on the tubing and history of acceptable performance of the multi-lumen tubing indicate that the change will have no impact on the function of the tubing. Additionally, tubing already subjected to the proposed post-cure have performed within expectations during the life of the product and the same post-cure is currently employed on the multi-lumen tubing used on the leads of all Sprint Fidelis models.

In addition to the 1997 DoE, Differential Scanning Calorimetry testing was performed on the 153447007 to determine the amount of cure in the old and proposed post-cure conditions. The testing showed no significant difference in the amount of cure between the two post-cure settings. Further testing for the change included ensuring that all mechanical and design specifications were met, which included elongation, tensile, toughness, inner diameter, out diameter, and wall thickness. The post-cure ovens at (b)(4) (b)(4) are calibrated every six months at (b)(4) and (b)(4) This calibration covers the proposed post-cure process. No anomalies were noted during testing and there were no new or increased risks or impact on existing device biocompatibility assessments.

CORRESPONDENCE HISTORY:

None.

FIRM CONTACT:

Margaret M. DePuydt, P.E., RAC
Medtronic Inc.
Mounds View Facility South
8200 Coral Sea Street N.E.
Mounds View, Minnesota 55112
Phone: (763) 526-2382 / (612) 845-7771
Fax: (651) 367-0603
E-mail: margaret.m.depuydt@medtronic.com

COMPLIANCE REVIEW:

The Office of Compliance (OC) received this PMA submission, and was forwarded to CNDB for review, on March 1, 2008.

The application requests for a minor change to a supplier post-cure process for the DF-1 connector insulation. The change is being made to improve supplier yield. The firm performed a DoE in 1997 on a similar part, Differential Scanning Calorimetry testing, elongation, tensile, toughness, inner diameter, out diameter, and wall thickness testing. All results met the respective acceptance criteria. Furthermore, the ovens used for the post-cure are calibrated every six months. No anomalies were noted during testing and there were no new or increased risks or impact on existing device biocompatibility assessments.

Additionally, there have been no field reports or issues related to this change.

The firm provided adequate responses to all of the items suggested by the 30-Day Notice Checklist. They provided a description of the changes, the reasons for the changes, and a summary of testing supporting the change. The firm also provided a statement that they conform to the requirements of the Quality System Regulation regarding change control, validation, and document controls found in 21 CFR 820.

DECISION:

The Office of Compliance signed off on the letter to the manufacturer indicating that the submission of a 135-day PMA supplement is not required and that they may distribute the device incorporating the changes as requested in this supplement.

SUMMARY:

A copy of the 30-Day Notice Checklist and a copy of the final letter to the manufacturer are attached.

Bradley Quinn 4/29/08
Bradley Quinn

4/30/08

Prepared: Bquinn: 4/29/08
Reviewed:
Final:

CC: HFZ-340 (c/f)
HFZ-341 (f/f)

30-Day Notice Checklist

Name of Firm: Medtronic, Inc.
Cardiac Rhythm Disease Management

Address of Firm: 8200 Coral Sea Street NE
Mounds View, Minnesota 55112

Submissions Number: P920015/S043

Device: Sprint Leads Model No. 6932, 6942, 6943, 6945
Sprint Quattro Lead Model No. 6944
Sprint Quattro Secure Lead Model No. 6947
Sprint Fidelis Lead Model No. 6930, 6931, 6948, 6949
DF-1 Y-Adapter/Extender Kit Model No. 6726

Type of Change: Change to the supplier post-cure process

Section I By day 5, determine if 30-Day notice is appropriate, If not, why?

If any items below are checked, this submission does not qualify as 30-Day Notice.

1. manufacturing/sterilization site change _____
2. design or performance specification change _____
3. material specification change_____
4. device operating software change_____
5. labeling changes_____

Section II Does the notice contain the following: (Check appropriate answer)

1. Description of change	YES ☒	NO ☐	NA ☐
2. Reason for change	YES ☒	NO ☐	NA ☐
3. Rationale for implementation via 30-Day notice	YES ☒	NO ☐	NA ☐
4. Statement that completed design validation demonstrates that the manufacturing change can be made without significantly changing final device operation. (Reconfirm that the 30-Day Notice is the appropriate submission route.)	YES ☒	NO ☐	NA ☐

Part 1 - Page 41

5. A summary or description of procedures for change control including identification, documentation, validation, review and approval of manufacturing changes covered by the notice.	YES ☒	NO ☐	NA ☐
6. Describe documentation change controls necessary for modifying manufacturing or quality control instructions. (21 CFR 820.40)	YES ☒	NO ☐	NA ☐

Continued on next page

30-Day Notice Checklist, continued

7. If verification is used instead of process validation, the rationale for using verification in accordance with 21 CFR 820.1(a)(3) should be included.	YES ☐	NO ☐	NA ☒
8. If changed procedures are validated, summarize the procedures for monitoring and controlling process parameters (21 CFR 820.75(b). For new equipment, process validation should include installation qualification, operator qualifications, and software validation of any software driven equipment.	YES ☐	NO ☐	NA ☒
9. If changed procedures are to be routinely verified by sampling and independent measurement, summarize statistical rational for the sampling method. (21 CFR 820.250)	YES ☐	NO ☐	NA ☒
10. If manufacturing change involves changes in components or raw material, a statement describing the evaluation of new suppliers, and a description the type and extent of control to be exercised over the component or raw material. (21 CFR 820.50)	YES ☐	NO ☐	NA ☒
11. If change involves use of a new contractor for manufacturing or quality control testing, a statement describing procedures and criteria for evaluation of that contractor. (21 CFR 820.50)	YES ☐	NO ☐	NA ☒
12. Statement of conformity	YES ☒	NO ☐	NA ☐

Note: On a case by case bases the engineering change order (ECO) record may be requested from the firm if it will assist in bringing clarification to the 30-Day Notice.

OC IMAGE PACKAGE COVERSHEET

Please IMAGE the attached package associated with an OC-lead document: (1) 30-Day Notice/135-Day Supplement or (2) Manufacturing Site Change Supplement. If a bundled submission and review is involved, only one copy of the IMAGE package is necessary.

Supplement Type:

- [x] 30-Day Notice/135-Day Supplement
- [ ] Manufacturing Site Change Supplement

Bundled Submission and Review?

- [ ] Yes (bundled submissions are identical and one set of review memos is involved)
- [x] No

IMAGE Package Checklist:

- [x] completed IMAGE coversheet
- [x] copy of signed, dated letter
- [x] copy of OC or OIVD (compliance) lead review memo with reviewer and appropriate management signatures for the given review round
- [ ] if applicable, copy of ODE/OIVD consult review memo with reviewer and appropriate management signatures for the given review round
- [x] if applicable, copies of any other supporting information for the given review round (e.g., email from applicant, EIR report)

IMAGE this package for the following PMA supplement(s):

1. P 920015/S042
2. _____
3. _____
4. _____
5. _____

Etc.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
9200 Corporate Blvd
Rockville, MD 20850

APR 30 2008

Stacey Paetschow Wessman, RAS, MS, MBA
Principal Regulatory Affairs Specialist
Medtronic, Inc.
8200 Coral Sea Street NE
Mounds View, MN 55112

Re: P920015/S042
Model 6937 Lead (SVC Transvene Lead)
Filed: March 31, 2008

Dear Ms. Wessman:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has evaluated your premarket approval application (PMA) 30-day Notice. The 30-day Notice requested moving manufacturing locations within the same facility.

Based on the information submitted, FDA has determined that submission of a 135-day PMA supplement is not required. Therefore, you may distribute your device, incorporating the change described above, upon receipt of this letter.

If you have questions concerning this letter, please contact Melissa Burns at (240) 276-0268.

Sincerely yours,

Christy Foreman for

Gladys Rodriguez
Director
Division of Enforcement B
Office of Compliance
Center for Devices and Radiological Health

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	3275
RECIPIENT ADDRESS	916513670603
DESTINATION ID	
ST. TIME	04/30 15:44
TIME USE	00'44
PAGES SENT	2
RESULT	OK

Christy L. Foreman
Deputy Director

DIVISION OF ENFORCEMENT B
FDA/CDRH OFFICE OF COMPLIANCE
ROCKVILLE, MD 20850

Facsimile Transmission Sheet
(240) 276-0129 FAX Number
(240) 276-0120 Telephone

To: Stacey Paetschow Wessman, RAC, MS, MBA

FAX Number: 651-367-0603

Subject: P920015/S042

Date: 4/30/2008

Number of pages: 1 + Coversheet

Comments:

REVIEW MEMORANDUM

30-DAY NOTICE

DATE: 28 April 2008

TO: The Record

THRU: Nicole Wolanski, Branch Chief, CNDB, DOEB, OC, CDRH

_____ initials _____ date

FROM: Melissa Burns, Biomedical Engineer, CNDB, DOEB, OC, CDRH, HFZ-341

SUBJECT: 30-Day Notice
Received: 31 MAR 2008
OC Track: CTS

Applicant:	Medtronic, Inc. 8200 Coral Sea Street, MS MVS11 Mounds View, MN 55112 FEI:
Manufacturing Facility:	Medtronic, Inc. 7000 Central Ave N.E. Rd. 149, KM. 56.3 Minneapolis, MN 55432-3576 FEI: 2182208

DEVICES: P920015/S042 SVC Transvene Lead (Model 6937)

OC RECOMMENDATION: 30 Day Approved, No 135 Day Supplement Needed

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BACKGROUND:

This application from Medtronic, Inc is a request for a 30-Day Notice review in accordance with 21 CFR 814.39. This application provides notification of moving of the Controlled Environmental Area (CEA) used in manufacture of the model 6937 lead.

3

Medtronic leads are designed for use with a compatible IPG or an ICD as part of a cardiac system. Leads are intended for delivering therapies and/or sensing in the atrium and/or ventricle of the heart.

This change is being implemented due to an upgrade in the manufacturing facility.

CORRESPONDENCE HISTORY:

Burns, Melissa. "Follow-up Questions P920015/S042." E-mail to Stacey Paetschow Wessman. April 23, 2008.

Paetschow Wessman, Stacey. "RE: Follow-up Questions P920015/S042." E-mail with Attachments to Melissa Burns. April 24, 2008.

Burns. Melissa and Stacey Paetschow Wessman. Telephone Conversations. April 28, 2008.

Paetschow Wessman, Stacey. "First email for operational qual." E-mail with Attachments to Melissa Burns. April 28, 2008.

Paetschow Wessman, Stacey. "Email 2." E-mail with Attachments to Melissa Burns. April 28, 2008.

Paetschow Wessman, Stacey. "Email 3." E-mail with Attachments to Melissa Burns. April 28, 2008.

Paetschow Wessman, Stacey. "Email 4-thanks! Sorry about that." E-mail with Attachments to Melissa Burns. April 28, 2008.

FIRM CONTACT:

Stacey Paetschow Wessman, RAS, MS, MBA
Principal Regulatory Affairs Specialist
Medtronic, Inc.
8200 Coral Sea Street, MS MVS11
Mounds View, MN 55112
Phone: 763-526-2378
Fax: 651-367-0603
E-mail: stacey.p.wessman@medtronic.com

COMPLIANCE REVIEW:

The firm is transferring manufacturing for the Model 6937 SVC Transvene Lead from the existing Controlled Environment Area (CEA) to a newly constructed CEA within the Medtronic Rice Creek facility. Products and related manufacturing equipment are being moved in two phases. This 30-day notice covers Phase I of the move, which impacts the

Model 6937 PMA product. In the existing facility layout, there are four CEA areas, the revitalization product will consolidate all CEAs into a single location (termed CEA #2).

The Heating, Ventilation and Air Conditioning (HVAC), room environmental conditions, and gas supplies are equivalent in the new CEA #2 to the existing requirements. Room monitoring will continue per the existing Medtronic procedures. Room and surface finishes in the new CEA are the same as the existing, with the exception of a different floor type, ESD tiling rather than seamless linoleum. A new de-ionized (DI) water system has also been installed to support the new CEA; however, the monitoring of the water system remains the same as for the previous system.

All equipment used in the manufacturing of the Model 6937 lead will remain the same and will be relocated to the new CEA #2. No product or process changes will result from the move. The Ethylene Oxide (EO) sterilization equipment will not be moved and is not impacted by relocation to the new CEA. The firm provided documentation for:

- Facility Qualification (FQ), which includes both:

  Design Qualification (DQ). Drawings and descriptions of how requirements and specification of CEA are to be met. Includes installation plan, and

  Installation Qualification (IQ). Ensures equipment is installed in accordance with design specifications and user and manufacturing requirements. Also verifies that system documentation is available to support operation and maintenance.

  The firm provided the following FQ documents as part of the Submission:

  - BL0018102, Version 2.0, *Rice Creek Central CEA #2 Facility Qualification Report.* All acceptance criteria were met. Qualification activities included inspections and testing of electrical, plumbing, gas systems, HEPA, major equipment not covered in separate qualification plans, etc.
  - BL0017930, Revision 2.0, *Rice Creek Central CEA #2 Purified Water System Modifications Installation/Operational Qualification Plan.*
  - BL0017931, Revision 2.0, *Rice Creek Central CEA #2 Purified Water System Modifications Installation/Operational Qualification Report.* All acceptance criteria were met. Utilities to support the purified water system were verified and chemical and biological testing of the purified water system was performed to ensure that the water meets all requirements.
  - Various equipment installation qualifications included in BL0018103, BL0018105, BL0018079, BL0018080, JET080303.A01, JET080313.A04, BL0018081, BL0018082, JET080212.A01, JET080312.A02, JET080211.A01, JET080313.A03, JET080218.A01, JET080313.A01, BL0018139, and BL0018232. Equipment met all process and manufacturing requirements.

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- Operational Qualification (OQ). Documented verification that facility or utility operate as intended through all anticipated ranges.

  The firm provided the following OQ documents as part of the Submission:

  - (b) (b)(4), Revision 2.0, *Rice Creek Central CEA #2 Performance Qualification Report.* Room environmental conditions met all acceptance criteria. Microbial counts met acceptance criteria.

- Performance Qualification (PQ). Documented verification that utility, environment, and support systems produce required output.

  The firm provided the following PQ documents as part of the Submission:

  - (b) (b)(4) Revision 2.0, *Rice Creek Central CEA #2 Performance Qualification Plan.*
  - (b) (b)(4), Revision 2.0, *Rice Creek Central CEA #2 Performance Qualification Report.* Room environmental conditions met all acceptance criteria. Two lots of product were built in CEA #2 with 100% yield (acceptance criteria was 95% yield minimum).

The only equipment used in manufacture of the 6937 and not moved as part of Phase 1 is a laser.

The following questions were forwarded to the firm by e-mail on 23 April 2008 and the firm provided responses via e-mail on 24 April 2008:

1) Page 1-9 of your submission indicates that all equipment for the Model 6937 lead manufacturing process is to be moved to the new CEA#2 with the exception of one laser. Please clarify, is this laser used in the 6937 manufacturing process and, if so, how have you modified your process to account for the moving of material between the existing and new CEA?

   Response Review. The firm clarified that the laser is used for the 6937 and other models of leads and was therefore not relocated as part of the Phase 1. The firm updated their process to allow transport of the 6937 sub-assemblies from CEA #1 to CEA #2, as documented in (b) (b)(4), Issue 15, *Transfer Piece Parts*, which was provided with the firm's response. The firm also included reference to (b) (b)(4) from the related subassembly manufacturing document (b) (b)(4) Issue 13, which was also provided. The firm's response is adequate.

2) Attachment 1, pg. 1-105, indicates that (b)(b)(4) filters were not yet installed at the time of the qualification. Please provide qualification results for these filters, or justify why qualification is not required.
   Response Review. The firm clarified that the (b)(b)(4) filters in question are part of the Parts Cleaning area that has not yet been remodeled. These filters

will be qualified during commissioning of the Parts Cleaning room. The firm's response is adequate.

3) Please indicate how you have ensured that the rooms not yet qualified (Development, Silicone Molding, Milling, Parts Cleaning, & Material Expeditor) are appropriately isolated/controlled such that they will not impact the operation of the CEA rooms qualified in Phase 1.

Response Review. The firm indicated that the rooms have been qualified for "as-built" and are isolated from the CEA Leads manufacturing area. No personnel or equipment are in these rooms. These areas will be re-qualified during Phase 2. The firm's response is adequate.

4) Several of the attachments are not completely signed-off (Attachment 1, Attachment 3, Attachment 8). Please confirm that the information submitted is approved and released.

Response Review. The firm clarified that the documents at issue were approved via both electronic and hand signature. In these cases, the electronic document control system manages the electronic signatures (and the first page of the documents shows who approved electronically), and the hand signatures are part of the controlled document such that there is a record of all approvals. The firm's response is adequate.

The firm was also contacted by telephone on 28 April 2008 because Table 4 of the submission indicated that the Operational Qualification (OQ) was contained as (b) (4) (Attachment 2) to the submission, but the document provided was not an Operational Qualification. The firm sent the correct attachment by e-mail on 28 April 2008. The OQ was reviewed (see above) and found adequate.

DECISION:

The Office of Compliance signed off on the letter to the manufacturer indicating that the submission of a 135-day PMA supplement is not required and that they may distribute the device incorporating the changes as requested in this supplement.

SUMMARY:

A copy of the 30-Day Notice Checklist, e-mail information from the firm, and a copy of the letter to the manufacturer are attached.

M. B. Burns 4/28/08 4/30/08

Melissa B. Burns

Part 1- Page 50

Prepared: MBurns: 04/28/08
Reviewed: NWolanski:
Final:

CC: HFZ-340 (c/f)
HFZ-341 (f/f)

OC Track: CTS

30-Day Notice Checklist

Name of Firm: Medtronic, Inc.

Address of Firm: 8200 Coral Sea Street, MS MVS11
Mounds View, MN 55112

Submissions Number: P920015/S042

Device: Medtronic Model 6937 Lead

Type of Change: Manufacturing

Section I By day 5, determine if 30-Day notice is appropriate, If not, why?

If any items below are checked, this submission does not qualify as 30-Day Notice.

1. manufacturing/sterilization site change _____
2. design or performance specification change _____
3. material specification change_____
4. device operating software change_____
5. labeling changes_____

Section II Does the notice contain the following: (Check appropriate answer)

1.	Description of change	YES √	NO	NA
2.	Reason for change	YES √	NO	NA
3.	Rationale for implementation via 30-Day notice	YES √	NO	NA
4.	Statement that completed design validation demonstrates that the manufacturing change can be made without significantly changing final device operation. (Reconfirm that the 30-Day Notice is the appropriate submission route.)	YES	NO	NA √
5.	A summary or description of procedures for change control including identification, documentation, validation, review and approval of manufacturing changes covered by the notice.	YES √	NO	NA
6.	Describe documentation change controls necessary for modifying manufacturing or quality control instructions. (21 CFR 820.40)	YES √	NO	NA

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Continued on next page

30-Day Notice Checklist, continued

7. If verification is used instead of process validation, the rationale for using verification in accordance with 21 CFR 820.1(a)(3) should be included.	YES	NO	NA √
8. If changed procedures are validated, summarize the procedures for monitoring and controlling process parameters (21 CFR 820.75(b). For new equipment, process validation should include installation qualification, operator qualifications, and software validation of any software driven equipment.	YES √	NO	NA
9. If changed procedures are to be routinely verified by sampling and independent measurement, summarize statistical rational for the sampling method. (21 CFR 820.250)	YES	NO	NA √
10. If manufacturing change involves changes in components or raw material, a statement describing the evaluation of new suppliers, and a description the type and extent of control to be exercised over the component or raw material. (21 CFR 820.50)	YES	NO	NA √
11. If change involves use of a new contractor for manufacturing or quality control testing, a statement describing procedures and criteria for evaluation of that contractor. (21 CFR 820.50)	YES	NO	NA √
12. Statement of conformity	YES √	NO	NA

Note: On a case by case bases the engineering change order (ECO) record may be requested from the firm if it will assist in bringing clarification to the 30-Day Notice.

Burns, Melissa 4/24/08

From: Wessman, Stacey P. [stacey.p.wessman@medtronic.com]
Sent: Thursday, April 24, 2008 12:46 PM
To: Burns, Melissa
Cc: Wessman, Stacey P.
Subject: RE: Follow-up Questions P920015/S042
Attachments: 091231-001.doc; 501919-XXX_transfer piece part.doc; Visio-CEA 2.pdf

Hi Melissa

Thank you for your questions. Please see the answers below:

1. Page 1-9 of your submission indicates that all equipment for the Model 6937 lead manufacturing process is to be moved to the new CEA#2 with the exception of one laser. Please clarify, is this laser used in the 6937 manufacturing process and, if so, how have you modified your process to account for the moving of material between the existing and new CEA?

This laser is used for the 6937 process as well as for manufacturing other leads. The process was updated to include the transport of the 6937 sub-assemblies from CEA #1 to CEA #2 per reference document (b) (b)(4) The process (b)(4) (b)(4) is included and the applicable excerpts from (b) (b)(4)

2. Attachment 1, pg. 1-105, indicates that (b)(4) filters were not yet installed at the time of the qualification. Please provide qualification results for these filters, or justify why qualification is not required.

These filters were designated for the Parts Cleaning area which has not been remodeled yet. This area will be remodeled at a later date and qualified at that time.

3. Please indicate how you have ensured that the rooms not yet qualified (Development, Silicone Molding, Milling, Parts Cleaning, & Material Expeditor) are appropriately isolated/controlled such that they will not impact the operation of the CEA rooms qualified in Phase 1.

The other rooms have been qualified for "as-built". This information is included in Attachment 1 of the original submission. No equipment has been moved into these rooms and there is no personnel working in these areas. In addition, the layout of the rooms shows that these rooms are isolated from the main CEA Leads area. Lastly, we are not currently building the 6937 lead in CEA 2 as there is duplicate qualified equipment in CEA 1 to build the 6937.

4. Several of the attachments are not completely signed-off (Attachment 1, Attachment 3, Attachment 8). Please confirm that the information submitted is approved and released.

All documents are approved per Medtronic requirements. The documents you are referring to were approved via hand signature and electronic signature. Therapy Delivery uses an electronic filing system for document approvals. This system is a validated system. However, in order to approve documents, you must be a Medtronic employee- typically in the Cardiac Rhythm Disease Management (CRDM) group. These documents used both hand signature for the non-Medtronic and non-CRDM personnel on the approval list. The first page of the pdf document reflects the electronic signature (name, date and time signed). The second page is the first page of the document (title page) and the third page shows what approvals are needed. This is the page where the hand signatures are located.

Please let us know if you have any additional questions.
Thanks
Stacey

From: Burns, Melissa [mailto:Melissa.Burns@fda.hhs.gov]
Sent: Wednesday, April 23, 2008 3:53 PM
To: Wessman, Stacey P.
Subject: Follow-up Questions P920015/S042

Hello Stacey, Part 1 - Page 54

4/28/2008

I have the following questions regarding P020010/S042, which describes qualification for a new Controlled Environment Area (CEA) at the Rice Creek facility to be used for manufacturing of the Model 6937 lead. Please respond to the following:

1. Page 1-9 of your submission indicates that all equipment for the Model 6937 lead manufacturing process is to be moved to the new CEA#2 with the exception of one laser. Please clarify, is this laser used in the 6937 manufacturing process and, if so, how have you modified your process to account for the moving of material between the existing and new CEA?

2. Attachment 1, pg. 1-105, indicates that [(b)(4)] filters were not yet installed at the time of the qualification. Please provide qualification results for these filters, or justify why qualification is not required.

3. Please indicate how you have ensured that the rooms not yet qualified (Development, Silicone Molding, Milling, Parts Cleaning, & Material Expeditor) are appropriately isolated/controlled such that they will not impact the operation of the CEA rooms qualified in Phase 1.

4. Several of the attachments are not completely signed-off (Attachment 1, Attachment 3, Attachment 8). Please confirm that the information submitted is approved and released.

Please provide responses to the above items by 28Apr2008. If you will have difficulty providing information in this timeframe, please let me know. Failure to receive adequate responses to the above items may result in conversion to a 135-day supplement. Please contact me if you have any questions.

Regards,

Melissa Burns, MS
LCDR, US Public Health Service
Regulatory Operations Officer
FDA/Center for Devices and Radiological Health
Office of Compliance, Division of Enforcement B
melissa.burns@fda.hhs.gov
Phone: (240) 276-0268
Fax: (240) 276-0129

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CONTROL

DESCRIPTION OF AND REASON FOR CHANGE	INITIAL/ EMPLOYEE NO./ DATE	
	QUALITY ENGINEER	MFG. ENGINEER
Issue 15 Op 10- Added "If product has not been completed through final QA inspection, no QA acceptance trace record check is required. Proceed to next step, ," in Detail Procedure 1. Admin. Change: Reformat		

DISTRIBUTION INFORMATION

COST CENTER	b(4) b(4)						
QTY							
NOTIFY							

Part 1- Page 56

SUMMARY

List of Operations

OP. NUMBER/ TITLE OF OPERATION	REFERENCE DOCUMENT
010	
(b)(4) (b)(4)	N/A

Part 1 - Page 57

DETAIL

OP. NUMBER:	010
OP. TITLE:	(b)(4) (b)(4)
REFERENCE DOCUMENTS:	N/A

QTY	MEDTRONIC NUMBER	MATERIALS AND EQUIPMENT REQUIRED
AR	N.A.	(b)(4) (b)(4)
1	N.A	
AR	N.A.	
1	N.A.	
AR	141598-001	

DETAILED PROCEDURE:

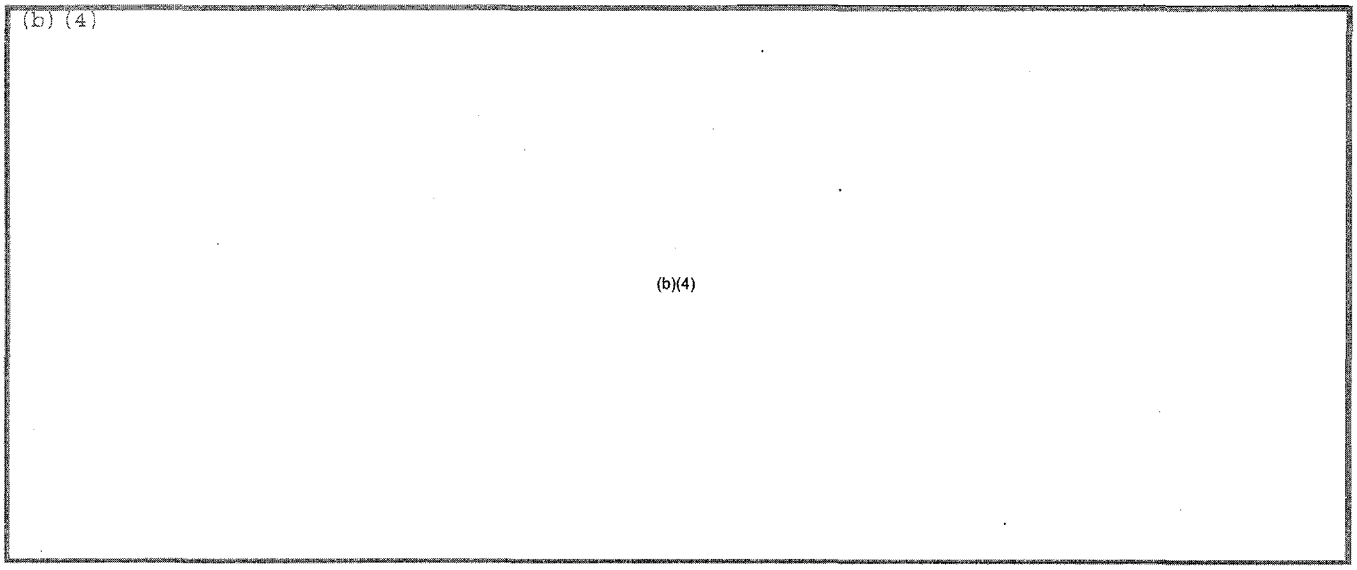
(b)(4) (b)(4)

1.
2.
3.
4.
5.
6.
7.

MEDTRONIC CONFIDENTIAL

This document is electronically controlled.

FIGURE 1



8. End of operation.

Part 1 - Page 59

ASSEMBLE DEFIB. SUBASSY

501919-XXX

DATE	ISS	PAGE	OP
13 Mar 08	13	1	010

QTY	MEDTRONIC NUMBER	MATERIALS AND EQUIPMENT REQUIRED
AR	153030-064	(b) (4)
1	114601-001	
1	153406-001	
1	136331-001	
AR	168169-XXX	
1	N.A.	
1	N.A.	
1	N.A.	
1	N/A	
1	N.A.	(b)(4)
1	061011	
AR	087796	
1	091728-002	
AR	091231-001	
AR	091417-001	
1	N.A.	
AR	N.A.	
1	N.A.	
AR	141598-001	

DETAILED PROCEDURE:

(b) (4)

(b)(4)

ASSEMBLE DEFIB. SUBASSY

(b)(4)

DATE	ISS	PAGE	OP
06 Dec 99	(b)(4)	2	(b)(4)

(b)(4)

(b)(4)

(b) (4)

(b)(4)

Part 1 - Page 62

(b)(4)

(b)(4)

Part 1 - Page 63

ASSEMBLE DEFIB. SUBASSY 501919-XXX

DATE	ISS	PAGE	OP
13 Mar 08	4	5	010

(b) (4)

(b)(4)

-MANUFACTURING DOCUMENT-
DETAIL

INSPECT LASER WELD

501919-XXX

DATE	ISS	PAGE	OP
13 Mar 08	6	1	040

QTY	MEDTRONIC NUMBER	MATERIALS AND EQUIPMENT REQUIRED
1	N.A.	(b) (4)
AR	168504-001	
AR	N.A.	
AR	091231-001	
AR	091417-001	
1	N.A.	
AR	N.A.	
1	N.A.	
AR	141598-001	

(b)(4)

DETAILED PROCEDURE:

(b) (4)

(b)(4)

(b) (4)

(b)(4)

FIGURE 1

ACCEPTABLE CRITERIA

(b)(4)

(b)(4)

INSPECT LASER WELD

501919-XXX

DATE	ISS	PAGE	OP
13 Mar 08	5	3	040

(b) (4)

(b)(4)

(b) (4)

(b)(4)

4/28/08

Medtronic

Therapy Delivery Systems

Electronic File System (TDS EFS)

File Name	Version	Author(s)
BL0018104	2.0	Mike Tumure (Gerbig)

Title: Rice Creek Central CEA #2 Operational Qualification Report

APPROVALS

Signed By	Meaning of Signature	Date/Time (US Central Time)
(b) (6) (b)(6)		

Medtronic

Rice Creek Central Revitalization Project

Rice Creek Central CEA #2 Operational Qualification Report

BL0018104
Revision 2.0

March 21, 2008

Prepared By:

(b)(6)	(b)(6)

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Document Approvals

(b) (6)

(b)(6)

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1. Revision History

Revision	Description of Change
2.0	Initial Release

2. Objective

The purpose of this Operational Qualification report is to confirm that the Operational Qualification (OQ) requirements and acceptance criteria for the remodeled CEA #2 at Medtronic Rice Creek Central in Fridley, MN, USA have been successfully met. Successful completion of these validation requirements provides assurance that the system is operating in conformance with design and owner specifications, and meets current Good Manufacturing Practices (cGMP), regulatory, and quality obligations.

All acceptance criteria established in the OQ Plan (b) (4) have been met, and the CEA #2 is considered qualified "at rest".

3. Scope

This OQ report confirms the qualification requirements and acceptance criteria for the remodeled CEA #2 and associated areas located at the Rice Creek Central Building, 7000 Central Avenue Northeast, Fridley, MN, USA. This plan includes the following rooms and systems:

CEA #2 ISO 7 CEA Leads Build Area (or Leads Manufacturing), Gowning Room, and Material Out

This OQ report confirms the successful completion of the CEA #2 OQ plan requirements and acceptance criteria. The CEA #2 OQ has been executed and results compiled in accordance with the OQ plan.

All validation work has been performed as defined in the approved plan. All documentation required for the plans is contained in this report, or the storage location identified. Any deviation or variation observed during the execution of the plan has been documented with resolution and approval.

4. Background

(B)(4)

5. Systems Description

[(b)(4)] and associated rooms are approximately [(b)(4)] square feet of Controlled Environment Area (CEA). Existing air handling equipment provides conditioned air to a terminal [(b)(4)] [(b)(4)]

The rooms included in this report are the CEA Leads Build Area (or Leads Manufacturing), Gowning Room, and Material Out. All other rooms will be qualified at a later date.

6. Acronyms and Definitions

Pertinent terms and acronyms are defined in the OQ Plan [(b)(4)]

7. References

References are defined in the OQ Plan [(b)(4)] In addition, the Facility Qualification Report has been completed. Please reference [(b)(4)] Rice Creek Central CEA #2 Facility Qualification Report, Version 2.0.

8. Acceptance Criteria

The acceptance criteria for the OQ report are listed in each attachment of Section 11 of the OQ Plan, [(b)(4)]

The results have been recorded per the OQ Plan and any additional information is attached. One deviation was noted during OQ execution and is listed in Section 10.3.

This OQ report includes the OQ phase of qualification for main CEA #2 Leads Build Area, Gowning Room and Material Out. Any additional CEA #2 area to be qualified in the future will have a separate OQ/PQ plan and report.

9. Schedule

Operational Qualification of the CEA #2 was completed in March 2008.

10. OQ Test Plan Attachments

10.1 Signature Verification Form (Attachment #1)

All persons involved with the execution of this Operational Qualification Plan have completed a line of the Signature Verification Form Attachment #1.

10.2 Test Instrument Data Form (Attachment #2)

All test instruments used during plan execution are listed on the Test Instrument Data Sheet, Attachment #2 of the Installation Qualification document, including the

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manufacturer, model number, serial number, date of calibration and calibration due date. Copies of NIST traceable calibration certificates for each test instrument are included in Attachment #2.

10.3 Protocol (Plan) Deviation Report Form (Attachment #3)

One deviation was noted during OQ execution. DRF #1 notes that the humidity readings taken on March 10, 2008 were below the required minimum of [(b)(4)] at some locations. The lowest reading was [(b)(4)] This discrepancy was resolved by resetting the room humidity setpoint in the building automation system back to [(b)(4)] from [(b)(4)] where it had been mistakenly set. Readings were retaken on March 13, 2008 after the setpoint was returned to [(b)(4)] and all readings were in tolerance.

No other deviations were observed during OQ plan execution.

10.4 Room Pressure Differentials-At Rest (Attachment #4)

Room Pressure Differentials and Airflows were measured on [(b)(4)] as specified in the OQ Plan. Test results are included in Attachment #4.

All airflows and pressure differentials met the acceptance criteria contained in the OQ plan of at least [(b)(4)] to any adjacent less clean area.

10.5 Room ISO 14644 Particle Counts-At Rest (Attachment #5)

Room particle counts were taken in the [(B)(4)] as specified in the OQ Plan and met the acceptance criteria as specified. [(B)(4)] with three consecutive readings taken at each sample location.

[(B)(4)]

All rooms met the acceptance criteria. A summary of the results is found on the next page.

0.5 Micron / ft³ Summary

ROOM	REQUIRED HIGHEST AVERAGE AT A LOCATION:	MEASURED HIGHEST AVERAGE AT A LOCATION:
[(B)(4)]	[(B)(4)]	[(B)(4)]
[(B)(4)]	[(B)(4)]	[(B)(4)]

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ROOM	REQUIRED HIGHEST AVERAGE AT A LOCATION:	MEASURED HIGHEST AVERAGE AT A LOCATION:
(B)(4)	(B)(4)	3368

10.6 Room Temperature and Humidity-At Rest (Attachment #6)

(B)(4)

Room Temperature and Relative Humidity At Rest

ROOM	AVERAGE TEMP °F:	LOWEST TEMP °F:	HIGHEST TEMP °F:	AVERAGE RH %:	LOWEST RH %:	HIGHEST RH%:
(b)(4)						

(b)(4)

10.7 Room Microbial Testing-At Rest (Attachment #7)

Room air and surface microbial counts were taken in (B)(4) as specified in the OQ Plan and met the acceptance criteria as specified. Each room was sampled one time, with one reading taken at each sample location for air and selected work surfaces for contact.

Attachment #7 documents the results of this testing. Biotest RCS Plus microbial air samplers were used to sample volumes of (b)(4) of air on a grid pattern established in conformance with ISO 14644-1 Class 7 cleanliness levels. Contact plates were used to sample work surfaces present at the time of testing. Data sheets and drawings indicating the location of each sample are included in Attachment #7.

All rooms met the acceptance criteria. Below is a summary of the results.

Room Viable Counts/ ft³ Summary

ROOM	REQUIRED HIGHEST AVERAGE AT A LOCATION:	MEASURED HIGHEST AVERAGE AT A LOCATION:
[(B)(4)] Air	[(B)(4)]	[(B)(4)]
[(B)(4)] Surface	[(B)(4)]	[(B)(4)]
Material Out	[(B)(4)]	[(B)(4)]
Gown	[(B)(4)]	[(B)(4)]

11. Attachments

Please note some attachments are completed portions of the OQ Plan, [(b) (4)]. Thus, these documents list the plan information in the header portion.

Attachment 1: Signature Verification Form
Attachment 2: Test Data Instrument Form
Attachment 3: Protocol Deviation Report
Attachment 4: Room Pressure Differentials-[(b)(4)]
Attachment 5: Room ISO 14644 Particle Counts-At Rest
Attachment 6: Room Temperature and Humidity-[(b)(4)]
Attachment 7: Room Microbial Testing-[(b)(4)]

ATTACHMENT #1

SIGNATURE VERIFICATION FORM

Designated personnel assigned the responsibility of executing or verifying execution of this protocol will sign, initial and date the corresponding sections in the table below.

Print Name	Signature	Initials	Title	Date
(b)(6)	(b)(6)	WHT	SENIOR VALIDATION SPECIALIST	(b)(4)
		JCB	Certification Technician	(b)(4)

Comments:

Reviewed by: (b)(6) Date: 21 Mar 08

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ATTACHMENT #2

Sheet 1 of 1

TEST INSTRUMENT DATA FORM

Test Instrument	Manufacturer	Model Number	Serial Number	Date of Calibration	Calibration Due Date	Certificate Attached (Y/N)
			(b)(4)			(b)(4)

Comments:

Compiled by: (b)(6) (b)(6)

Reviewed by

Date: (B)(4)

Date:

(b)(4)

(b)(4)

Certificate of Calibration

Manufacturer	(b)(4), (b)(6)
Model Number	
Serial Number	
Instrument Id	(b)(4), (b)(6)
Instrument Type	
Company Name	
Customer Name	
Cal Date	[(B)(4)]
Next Cal Date	[(B)(4)]
(b)(4) *Procedure*	(b)(4) (b)(4)
Cert Number	
Recv In Tolerance	Y
Returned In Tolerance	Y

(b)(4) certifies that at the time of calibration the above listed equipment meets or exceeds all published specifications.

At planned intervals, (b)(4) measurement standards are calibrated to standards traceable to the National Institute of Standards (NIST) or derived from accepted values of physical constants.

Supporting documentation relative to traceability is on file and is available upon request.

The calibration system conforms to ISO/IEC 17025 & ANSI/NCSLZ540-1

(b)(4) Std	Model Number	Instrument Type	(b)(4) Date	(b)(4) Due
(b)(4) (b)(4)		[(B)(4)]	6/29/2007	6/29/2008
			11/28/2006	11/28/2007
			12/8/2006	12/8/2007

Lab Temperature: [(B)4]
Lab Humidity: [(B)4]

Metrologist: (b)(6) (b)(6)

(b)(4) (b)(4)

This certificate shall not be reproduced except in full, without written approval of (b)(b)(4)

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(b)(4)

Certificate of Calibration

Manufacturer	(b)(6), (b)(4)
Model Number	
Serial Number	
Instrument Id	
Instrument Type	
Company Name	
Customer Name	
Cal Date	(b)(4)
Next Cal Date	(b)(4)
(b)(4) *Procedure*	(b)(4)
Cert Number	
Recv In Tolerance	Y

Calibration Notes: Unit and probe calibrated as a system

(b)(4) certifies that at the time of calibration the above listed equipment meets or exceeds all published specifications.

At planned intervals, (b)(4) measurement standards are calibrated to standards traceable to the National Institute of Standards (NIST) or derived from accepted values of physical constants.

Supporting documentation relative to traceability is on file and is available upon request.

(b)(4) Std	Model Number	Instrument Type	Serial Number	(b)(4) Date	(b)(4) Due
(b)(4)		(B)(4)	(b)(4)	(B)(4)	(B)(4)

Lab Temperature (B)(4)

Lab Humidity (B)(4)

Metrologist: (b)(6)

(b)(4)

06/06/2007
09:11:26
Page 1 of 1

This certificate shall not be reproduced except in full, without written approval of (b)(4)

Cert Number 1000058660

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(b)(4)

Certificate of Calibration

(b)(4) Number	: (b)(4)	Date Calibrated	: (b)(4)
Model	: (b)(4)	(b)(4) Due	: (b)(4)
Serial Number	:	Sensor Number	: (b)(4)

This calibration performed by (b)(4) Calibration has been accomplished by size calibration as defined by ASTM F328-97 and JIS B 9921:1997, and performed in compliance with ANSI/NCSL Z540-1. Total uncertainty of this calibration is less than 3.5%, providing an accuracy ratio of 6 to one for channel 1 (50% CE), and 3 to one for other channels (100% CE). The accuracy of the standards and equipment used are traceable to NIST. A record of all work performed is maintained by (b)(4) and performed in accordance with (b)(4) Quality Manual (b)(4). Reproduction of this Certificate except in full is strictly forbidden. (b)(4)

Channel 1	(B)(4)
Channel > 1	(B)(4)

Calibration Performed By (b)(4)

Calibration was under the following controlled conditions :

(B)(4) (B)(4) (B)(4)

Threshold Voltages

(B)(4)
(B)(4)

Calibration Spheres

(B)(4)
(B)(4)
(B)(4)

Calibration Procedure	: (B)(4)	Station	: (B)(4)
Oscilloscope ID	: (B)(4)	(b)(4) Due	: (B)(4)
MCA ID	: (B)(4)	Due	: (B)(4)
FlowMeter ID	: (B)(4)	Due	: (B)(4)
DMM ID	: (B)(4)	Due	: (B)(4)

Signed (b)(6) Title : (b)(4) TECH

Signed Title : Tech

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(b)(4)

Medtronic Calibration Certificate

Date: EN ISO 13485:2003 Certified Certificate #: 125169

Cert No. Q1N 05 03 39709 339

Calibration Performed By:	For (cost center number and location):
MEDTRONIC INC	150046
7000 CENTRAL AVE NE	RICE CREEK CENTRAL
MINNEAPOLIS, MN 55432-3576	FLR1

Equipment Information

Property #:	(b)(4)	Serial Number:	(B)(4)
Description:	(B)(4)		
Manufacturer:	(B)(4)	Date Performed:	(B)(4)
Model Number:	(B)(4)	Performed By:	(b)(6)
Temperature:	(B)(4)	Cal Procedure:	(b)(4) Revision Level: D
Cal. Interval:	(B)(4)	Limiting Condition:	
Cal. Due Date:	(B)(4)	Calibration Result:	PASS

Calibration Notes

Tolerance is ± (B)(4)

	AS LEFT:
(B)(4)	(B)(4)
(B)(4)	(B)(4)
(B)(4)	(B)(4)
(B)(4)	(B)(4)

Test Points (If NONE, all test points are in tolerance)

Seq.	Description	Standard	Tolerance -	Tolerance +	As Found	As Left	Unit
1	(B)(4)	B4	B4	B4			
2	(B)(4)	B4	B4	B4			

Standards Used To Calibrate Equipment

Property Number	Model Number	Description	Cal. Date	Cal. Due Date
(b)(4)	B4	B4	B4	B4
	B4	B4	B4	B4

TRACEABILITY INFORMATION:

Traceability is to National Institute of Standards and Technology (NIST) or an equivalent organization outside of the United States.

Some measurements are traceable and derived from accepted values of natural phenomena or having been derived by the ratio type of self-calibration techniques or accepted industry practice.

END OF REPORT

Medtronic Calibration Certificate

Date: 1/25/2008 | **EN ISO 13485:2003 Certified** Cert No. Q1N 05 03 39709 339 | **Certificate #:** 128847

Calibration Performed By:	For (cost center number and location):
MEDTRONIC INC	150046
7000 CENTRAL AVE NE	RICE CREEK CENTRAL
MINNEAPOLIS, MN 55432-3576	B268

Equipment Information

Property #:	(b)(4)	Serial Number:	(B)(4)
Description:	(B)(4)		
Manufacturer:	(B)(4)	Date Performed:	(B)(4)
Model Number	(B)(4)	Performed By:	(b) (6)
Temperature:	(B)(4)	Cal Procedure:	(b)(4) Revision Level: D
Cal. Interval:	(B)(4)	Limiting Condition:	
Cal. Due Date:	(B)(4)	Calibration Result:	**PASS**

Calibration Notes

Unit tested and found to be within tolerance.

(B)(4)
(B)(4)
(B)(4)
(B)(4)

Final
(B)(4)

*User needs to be made aware that the unit requires a battery that has a full charge in order to operate properly. Using a battery at half life or less will effect their readings and not be correct.

Test Points (If NONE, all test points are in tolerance)

Seq.	Description	Standard	Tolerance -	Tolerance +	As Found	As Left	Unit
1	(B)(4)	(B)(4)	(B)(4)	(B)(4)			
2	(B)(4)	(B)(4)	(B)(4)	(B)(4)			

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Medtronic Calibration Certificate

Date: 1/25/2008 | **EN ISO 13485:2003 Certified** Cert No. Q1N 05 03 39709 339 | **Certificate #: 128847**

Standards Used To Calibrate Equipment

Property Number	Model Number	Description	Cal. Date	Cal. Due Date
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)

TRACEABILITY INFORMATION:

Traceability is to National Institute of Standards and Technology (NIST) or an equivalent organization outside of the United States.

Some measurements are traceable and derived from accepted values of natural phenomena or having been derived by the ratio type of self-calibration techniques or accepted industry practice.

END OF REPORT

Medtronic Calibration Certificate

Date: 1/25/2008 | **EN ISO 13485:2003 Certified** Cert No. Q1N 05 03 39709 339 | **Certificate #:** 128863

Calibration Performed By:	For (cost center number and location):
MEDTRONIC INC	150046
7000 CENTRAL AVE NE	RICE CREEK CENTRAL
MINNEAPOLIS, MN 55432-3576	B268 - STERILIZATION SERVICES

Equipment Information

Property #:	(b)(b)(4)	Serial Number:	(B)(4)
Description:	(B)(4)		
Manufacturer:	(B)(4)	Date Performed:	(B)(4)
Model Number:	(B)(4)	Performed By:	(b) (b)(6)
Temperature:	(B)(4)	Cal Procedure:	(B)(4) Revision Level: D
Cal. Interval:	(B)(4)	Limiting Condition:	
Cal. Due Date:	(B)(4)	Calibration Result:	**PASS**

Calibration Notes

Condition Received: Unit out of tolerance.
Condition Returned: Unit adjusted and placed within tolerance.

*User needs to be aware that unit needs to be used with fully charged batteries. Using batteries that are at half life or less will give the user incorrect readings.

Test Points (If NONE, all test points are in tolerance)

Seq.	Description	Standard	Tolerance -	Tolerance +	As Found	As Left	Unit
1	(B)(4)	(B)(4)	(B)(4)	(B)(4)			
2	(B)(4)	(B)(4)	(B)(4)	(B)(4)			

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Medtronic Calibration Certificate

Date: **EN ISO 13485:2003 Certified** **Certificate #: 128863**

Cert No. Q1N 05 03 39709 339

Standards Used To Calibrate Equipment

Property Number	Model Number	Description	Cal. Date	Cal. Due Date
(b)(4)	[redacted]	[redacted]	[redacted]	[redacted]

TRACEABILITY INFORMATION:

Traceability is to National Institute of Standards and Technology (NIST) or an equivalent organization outside of the United States.

Some measurements are traceable and derived from accepted values of natural phenomena or having been derived by the ratio type of self-calibration techniques or accepted industry practice.

END OF REPORT

Medtronic Calibration Certificate

Date: 2/5/2008 | EN ISO 13485:2003 Certified Cert No. Q1N 05 03 39709 339 | Certificate #: 129873

Calibration Performed By:

MEDTRONIC INC
7000 CENTRAL AVE NE
MINNEAPOLIS, MN 55432-3576

For (cost center number and location):

150046
RICE CREEK CENTRAL
B268

Equipment Information

Property #: (b)(4) | Serial Number: [B)(4)]
Description: [B)(4)]
Manufacturer: [B)(4)] | Date Performed: [B)(4)]
Model Number: [B)(4)] | Performed By: (b)(6)
Temperature: [B)(4)] | Cal Procedure: [B)(4)] | Revision Level: D
Cal. Interval: [B)(4)] | Limiting Condition:
Cal. Due Date: [B)(4)] | Calibration Result: [B)(4)]

Calibration Notes

Unit tested and found to be within tolerance.

Final

[B)(4)] [B)(4)]

* Ensure that when using this unit that a fully charged battery in installed. A battery at half life or lower will through off readings.

Test Points (If NONE, all test points are in tolerance)

Seq.	Description	Standard	Tolerance -	Tolerance +	As Found	As Left	Unit
1	[B)(4)]	[B)(4)]	[B)(4)]	[B)(4)]			
2	[B)(4)]	[B)(4)]	[B)(4)]	[B)(4)]			

Standards Used To Calibrate Equipment

Property Number	Model Number	Description	Cal. Date	Cal. Due Date
(b)(4)	[B)(4)]	[B)(4)]	[B)(4)]	[B)(4)]
	[B)(4)]	[B)(4)]	[B)(4)]	[B)(4)]

TRACEABILITY INFORMATION:

Traceability is to National Institute of Standards and Technology (NIST) or an equivalent organization outside of the United States.

Some measurements are traceable and derived from accepted values of natural phenomena or having been derived by the ratio type of self-calibration techniques or accepted industry practice.

END OF REPORT

ATTACHMENT #3

Sheet 1 of 1

PROTOCOL DEVIATION REPORT FORM

(b)(4), (b)(6)

(b)(4), (b)(6)

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ATTACHMENT #4

Sheet 1 of 1

ROOM PRESSURE DIFFERENTIALS AND AIR FLOWS AT REST

ROOM	PRESSURE VS. ROOM	REQUIRED PRESSURE:	MEASURED PRESSURE:	MEETS ACCEPTANCE CRITERIA?	DATE/INITIAL
(b)(4)					

(b)(4)

COMPLETED TEST REPORTS ATTACHED TO THIS SECTION? (Y) N

ROOMS MEET REQUIREMENTS? (Y) N

Compiled by (b)(6) Date: (b)(4)

Reviewed by (b)(6) Date: (b)(4)

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PRESSURE DIFFERENTIALS AND AIRFLOW DIRECTIONS

— AT REST —

(b) (4)

(b)(4)

ATTACHMENT #5

Sheet 1 of 1

ROOM PARTICLE COUNTS – AT REST

PARTICLE COUNT SUMMARY 0.5 MICRONS/CUBIC FOOT

DATE OF TEST: [(b)(4)]

ROOM	ISO CLASS	REQUIRED HIGHEST AVERAGE AT A LOCATION:	MEASURED HIGHEST AVERAGE AT A LOCATION:	MEETS ACCEPTANCE CRITERIA?	DATE/INITIAL
(b) (4) (b)(4)					

COMPLETED TEST REPORTS ATTACHED TO THIS SECTION? (Y) N

DRAWING SHOWING PARTICLE COUNT LOCATIONS ATTACHED TO THIS SECTION? (Y) N

ROOMS MEET REQUIREMENTS? (Y) N

Comments:

Compiled by (b) (6) (b)(6) Date: [(B)(4)]

Reviewed by Date: [(B)(4)]

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PARTICLE COUNT & TEMP, RH LOCATIONS

— AT REST —

(b) (4)

(b)(4)

MEDTRONIC RICE CREEK CENTRAL
7000 CENTRAL AVE. NE
FRIDLEY, MN

ISO 14644-1 CALCULATION FOR CLEANLINESS LEVEL

CLEAN ZONE TESTED: (B)(4)

(b) (4)

(b)(4)

Clean Zone CEA #2 MAIN Meets
ISO 14644-1 CLASS 7
At 0.5 Micron For Data Collected on March 10, 2008

Statistical Classification Criteria

(b) (4)

(b)(4)

Acceptance Criteria

(b) (4)

(b)(4)

Optional Information

(b) (4)

(b)(4)

(b) (4)

(b)(4)

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MEDTRONIC RICE CREEK CAMPUS
7000 CENTRAL AVE. NE
FRIDLEY, MN

RAW DATA AND AVERAGES FOR ISO 14644-1

Clean Zone Tested:	(B)(4)	Sample Locations:	(B)(4)	
Test Mode:	(B)(4)	Particle Size:	(B)(4)	µ

Particle Counts Sampled On: March 10, 2008

Location	Reading 1	Reading 2	Reading 3	Reading 4	Total	Average per ft^3	Average per m^3	Raw Temp	Raw RH
(b)(4)									

(b)(4)

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MEDTRONIC RICE CREEK CAMPUS
7000 CENTRAL AVE. NE
FRIDLEY, MN

ISO 14644-1 CALCULATION FOR CLEANLINESS LEVEL

CLEAN ZONE TESTED: [(B)(4)]

(b) (4)

(b)(4)

Clean Zone [(B)(4)]
ISO 14644-1 CLASS 7
At 0.5 Micron For Data Collected on March 10, 2008

Statistical Classification Criteria

(b) (4)

(b)(4)

Acceptance Criteria

(b) (4)

(b)(4)

Optional Information

(b) (4)

(b)(4)

(b) (4)

(b)(4)

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MEDTRONIC RICE CREEK CAMPUS
7000 CENTRAL AVE. NE
FRIDLEY, MN

RAW DATA AND AVERAGES FOR ISO 14644-1

(b) (4)

(b)(4)

Particle Counts Sampled On March 10, 2008

Location	Reading 1	Reading 2	Reading 3	Reading 4	Total	Average per ft^3	Average per m^3	Raw Temp	Raw RH
(b) (4)									

(b)(4)

Average Temperature (F): (b)(4)

Average Humidity (RH): (b)(4)

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MEDTRONIC RICE CREEK CENTRAL
7000 CENTRAL AVE. NE
FRIDLEY, MN

ISO 14644-1 CALCULATION FOR CLEANLINESS LEVEL

CLEAN ZONE TESTED: [(B)(4)]

(b)(4)

(b)(4)

Clean Zone [(B)(4)]
ISO 14644-1 CLASS 7
At 0.5 Micron For Data Collected on [(B)(4)]

Statistical Classification Criteria

(b)(4)

(b)(4)

Acceptance Criteria

(b)(4)

(b)(4)

Optional Information

(b)(4)

(b)(4)

(b)(4)

(b)(4)

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MEDTRONIC RICE CREEK CENTRAL
7000 CENTRAL AVE. NE
FRIDLEY, MN

RAW DATA AND AVERAGES FOR ISO 14644-1

Clean Zone Tested:	(b)(4)	Sample Locations:	(b)(4)
Test Mode:	At Rest	Particle Size:	

Particle Counts Sampled On March 10, 2008

(b)(4)

(b)(4)

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ATTACHMENT #6

Sheet 1 of 2

ROOM TEMPERATURE AND RELATIVE HUMIDITY EVALUATION AT REST

(b)(4), (b)(6)

(b)(4), (b)(6)

1

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ATTACHMENT #6

Sheet 2 of 2

ROOM TEMPERATURE AND RELATIVE HUMIDITY EVALUATION AT REST

(b)(4), (b)(6)

(b)(4), (b)(6)

PARTICLE COUNT & TEMP, RH LOCATIONS

— AT REST —

(b) (4)

(b)(4)

MEDTRONIC RICE CREEK CAMPUS
7000 CENTRAL AVE. NE
FRIDLEY, MN

RAW DATA AND AVERAGES FOR ISO 14644-1

Clean Zone Tested:	[(B)(4)....]	Sample Locations:	[(B)(4)]
Test Mode:	[(B)(4)]	Particle Size:	[(B)(4)]

Particle Counts Sampled On March 10, 2008

Location	Reading 1	Reading 2	Reading 3	Reading 4	Total	Average per ft³	Average per m³	Raw Temp	Raw RH
(b)(4)									

(b)(4)

Average Temperature (F): [(B)(4)]

Average Humidity (RH): [(B)(4)]

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MEDTRONIC RICE CREEK CAMPUS
7000 CENTRAL AVE. NE
FRIDLEY, MN

RAW DATA AND AVERAGES FOR ISO 14644-1

Clean Zone Tested:	[(B)(4)]	Sample Locations:	[(B)(4)]
Test Mode:	[(B)(4)]	Particle Size:	[(B)(4)]

Particle Counts Sampled On March 10, 2008

Location	Reading 1	Reading 2	Reading 3	Reading 4	Total	Average per ft^3	Average per m^3	Raw Temp	Raw RH
(b)(4)									
				(b)(4)					

Average Temperature (F): [(B)(4)]

Average Humidity (RH): [(B)(4)]

Part 1 - Page 104

MEDTRONIC RICE CREEK CENTRAL
7000 CENTRAL AVE. NE
FRIDLEY, MN

RAW DATA AND AVERAGES FOR ISO 14644-1

Clean Zone Tested:	[(B)(4)]	Sample Locations:	[(B)(4)]
Test Mode:	[(B)(4)]	Particle Size:	[(B)(4)]

Particle Counts Sampled On: March 10, 2008

Location	Reading 1	Reading 2	Reading 3	Reading 4	Total	Average per ft^3	Average per m^3	Raw Temp	Raw RH
(b) (4)									
				(b)(4)					

Average Temperature (F): [(B)(4)]

Average Humidity (RH): [(B)(4)]

Part 1-Page 105

MEDTRONIC RICE CREEK CAMPUS
7000 CENTRAL AVE. NE
FRIDLEY, MN

TEMPERATURE AND HUMIDITY RAW DATA AND AVERAGES

Clean Zone Tested: [(B)(4)] Sample Locations: [(B)(4)]

Test Mode: [(B)(4)]

Temperature and Humidity Sampled On [(B)(4)]

Location	Raw Temp	Raw RH
(b)(4)		
	(b)(4)	

Average Temperature (°F): [(B)(4)]

Average Humidity (RH): [(B)(4)]

Part 1 - Page 196

MEDTRONIC RICE CREEK CAMPUS
7000 CENTRAL AVE. NE
FRIDLEY, MN

TEMPERATURE AND HUMIDITY RAW DATA AND AVERAGES

Clean Zone Tested: [(B)(4)] Sample Locations: [(B)(4)]

Test Mode: [(B)(4)]

Temperature and Humidity Sampled On [(B)(4)]:

Location	Raw Temp	Raw RH
(b)(4)		
	(b)(4)	

Average Temperature (°F): [(B)(4)]

Average Humidity (RH): [(B)(4)]

Part 1 - Page 107

MEDTRONIC RICE CREEK CAMPUS
7000 CENTRAL AVE. NE
FRIDLEY, MN

TEMPERATURE AND HUMIDITY RAW DATA AND AVERAGES

Clean Zone Tested: [(b)(4)] Sample Locations: [(b)(4)]

Test Mode: [(b)(4)]

Temperature and Humidity Sampled On [(b)(4)]

Location	Raw Temp	Raw RH
(b)(4)	(b)(4)	

Average Temperature (°F): [(b)(4)]

Average Humidity (RH): [(b)(4)]

Part 1 - Page 108

ATTACHMENT #7
SUMMARY OF ROOM VIABLE COUNTS - [(B)(4)]

VIABLE COUNT DATA SHEET CFU/CUBIC FOOT

DATE OF TEST [(B)(4)] Sheet 1 of 2

ROOM	REQUIRED HIGHEST AT A LOCATION:	MEASURED HIGHEST AT A LOCATION:	MEETS ACCEPTANCE CRITERIA?	DATE/INITIAL
(b)(4)				

(b)(4)

COMPLETED TEST REPORTS ATTACHED TO THIS SECTION? (Y) N

DRAWING SHOWING VIABLE SAMPLE LOCATIONS ATTACHED TO THIS SECTION? (Y) N

ROOMS MEET REQUIREMENTS? (Y) N

Compiled by: (b)(6) Date: [(B)(4)]

Reviewed by (b)(6) Date: [(B)(4)]

Part 1 - Page 109

ATTACHMENT #7
ROOM VIABLE COUNTS –AT REST

VIABLE COUNT DATA SHEET CFU/CUBIC FOOT

DATE OF TEST: [(B)(4)] Sheet 2 of 2

ROOM	LOCATION ID:	AEROBIC CFU/FT^3	CONTACT CFU/PLATE	COMMENT
[(B)(4)]				

Comments: [(B)(4) (B)(4)]

Compiled by: (b)(6) Date: [(B)(4)]

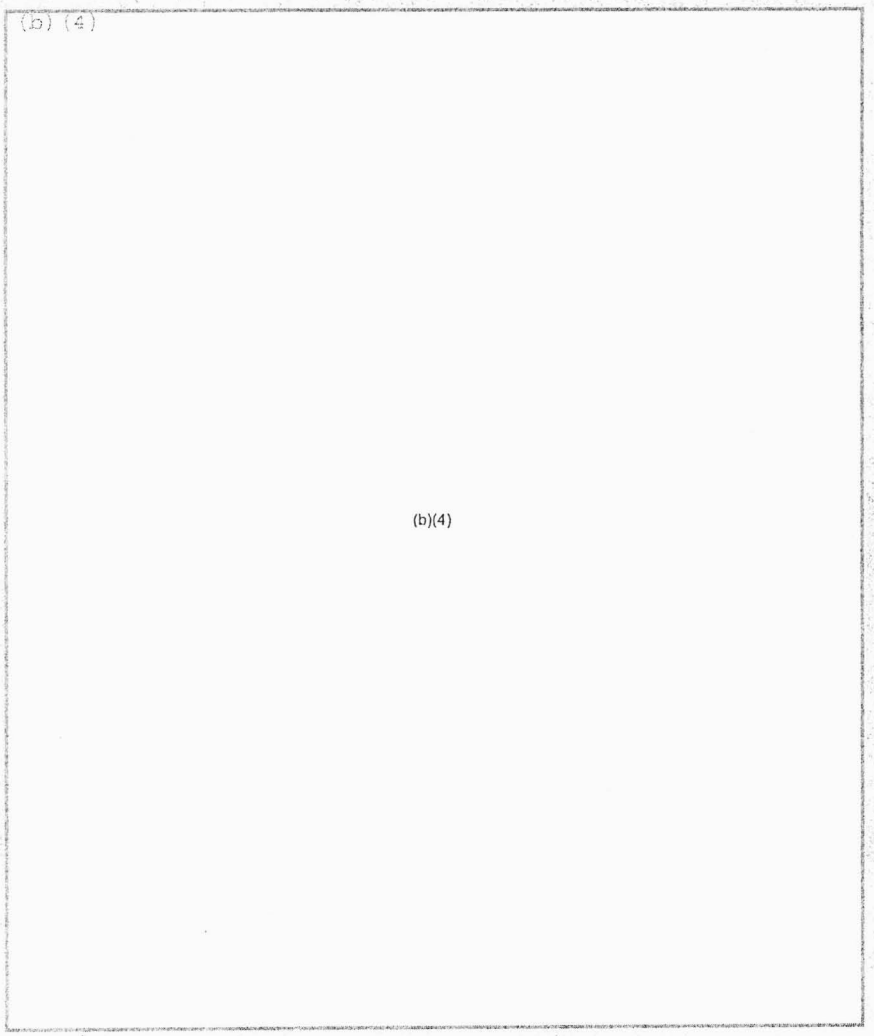
Reviewed by: (b)(6) Date: [(B)(4)]

Part 1 - Page 110

Sampling Plan Number: (b)(4)

Rice Creek CEA 2

(b)(4)



COPY

Use the following prefixes with the site number to denote room:

	LM (Leads Manufacturing)
	GW (Gowning)
	MO (Material Out)

(b)(4)

(b)(4)

(b)(4)

Requestor: (b)(6)

Monitoring Personnel: (b)(6)

Part 1 - Page 111

Viable Surface Results

Result Status: [(B)(4)]

Date out of Incubation: [(B)(4)]

Test Type: [(B)(4)]

Time out of Incubation: [(B)(4)]

Unit of Measure for Limits: [(B)(4)]

Comments: NA = Alert Limit not Required [(b)(4)] [(B)(4)]

EMS No: (b)(4)

Site	Alert Limit	Action Limit	Count (CFU)	CFU/Sq. dm
(b)(4)				

(b)(4)

Performed By: (b)(6) _____ Emp. No: (b)(6) Date: [(B)(4)]

Reviewed By: _____ Emp. No: Date: [(B)(4)]

Part 1 - Page 112

ATTACHMENT #7
SUMMARY OF ROOM VIABLE COUNTS –AT REST

VIABLE COUNT DATA SHEET CFU/CUBIC FOOT

DATE OF TEST [(B)(4)] . Sheet 1 of 2

ROOM	REQUIRED HIGHEST AT A LOCATION:	MEASURED HIGHEST AT A LOCATION:	MEETS ACCEPTANCE CRITERIA?	DATE/INITIAL
(b)(4)				

(b)(4)

COMPLETED TEST REPORTS ATTACHED TO THIS SECTION? (Y) N

DRAWING SHOWING VIABLE SAMPLE LOCATIONS ATTACHED TO THIS SECTION? (Y) N

ROOMS MEET REQUIREMENTS? (Y) N

Compiled by: (b)(6) Date: [(B)(4)]

Reviewed by: (b)(6) Date: [(B)(4)]

Part 1 - Page 113

ATTACHMENT #7
ROOM VIABLE COUNTS –AT REST

VIABLE COUNT DATA SHEET CFU/CUBIC FOOT

DATE OF TEST [(b)(4)] Sheet 2 of 2

ROOM	LOCATION ID:	AEROBIC CFU/FT^3	CONTACT CFU/PLATE	COMMENT
[	(B)(4)]			

Comments: [(B)(4)]

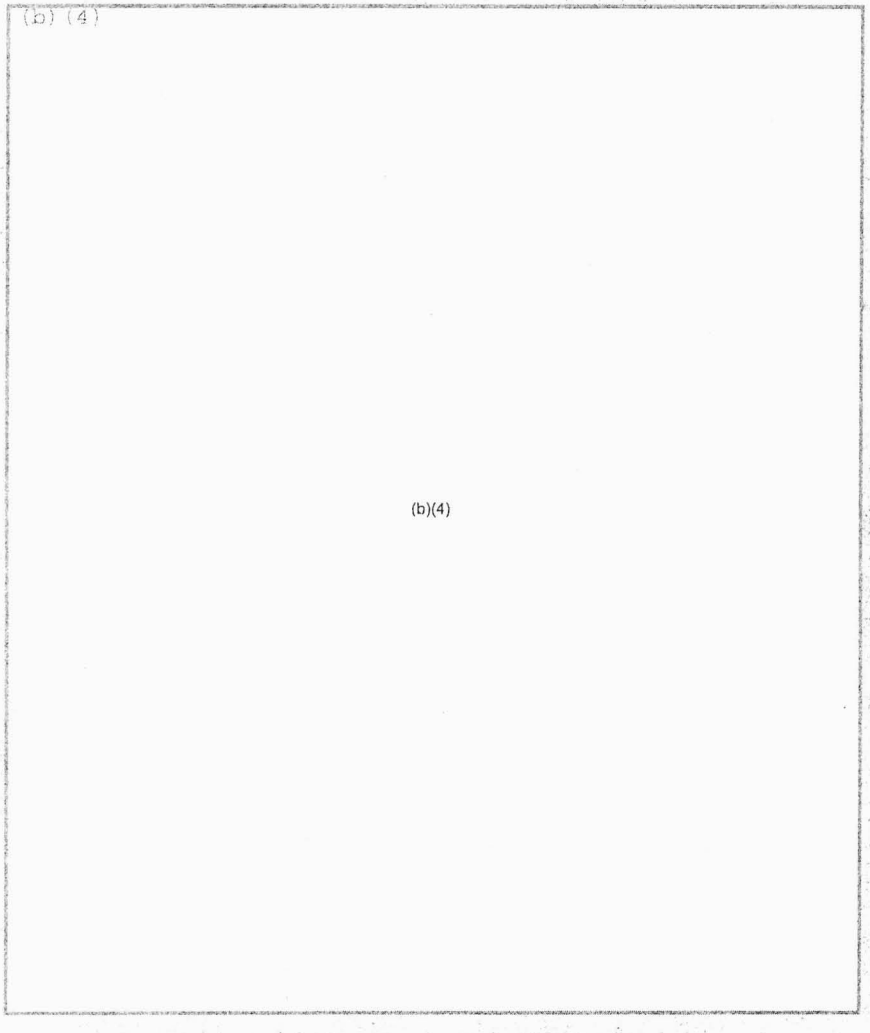
Compiled by: (b)(6) (b)(6) Date [(B)(4)]

Reviewed by Date [(B)(4)]

Part 1 - Page 114

Sampling Plan Number: (b)(4)

Rice Creek CEA 2



COPY

Use the following prefixes with the site number to denote room:

	LM (Leads Manufacturing)
	GW (Gowning)
	MO (Material Out)

Collect one surface sample for each grid square containing an exposed work surface (b)(4)

(b)(4)

Requestor: (b)(6)

Monitoring Personnel: (b)(6)

Part 1 - Page 115

Viable Surface Results

Result Status: [(B)(4)]

Date out of Incubation: [(B)(4)]

Test Type: [(B)(4)]

Time out of Incubation: [(B)(4)]

Unit of Measure for Limits: [(B)(4)]

Comments: NA = Alert Limit not Required (b)(4) [(B)(4)]

EMS No: (b) (4)

Site	Alert Limit	Action Limit	Count (CFU)	CFU/Sq. dm
(b) (4)				
(b)(4)				

Performed By: (b) (6) (b)(6) Emp. No: (b) (6) (b)(6) Date: [(B)(4)]

Reviewed By: Emp. No: Date: [(B)(4)]

Part 1 - Page 116

(b)(4)

Viable Air Results

(b)(4)

Stacey Paetshow Wessman, RAC, MS, MBA
Principal Regulatory Affairs Specialist
Medtronic, Inc.
1015 Gramsie Rd
Shoreview, MN 55126-3082

FEB 6 2008

Re: P920015/S38, Sprint™ and Sprint Fidelis™ Leads
Filed: September 12, 2007
Amended: October 24, 2007

Dear Ms. Wessman:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) 135-day supplement, which requested approval for changing the molding vendor and molding process parameters for the IS-1 connector sleeve component for Sprint Lead Models 6930, 6931, 6945, 6947, 6948, 6949, and 6944. Based upon the information submitted, the PMA 135-day supplement is approved subject to the conditions described within the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device as modified by your PMA 135-day supplement upon receipt of this letter.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the Federal Food, Drug, and Cosmetic Act.

Amendments should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have questions concerning this approval order, please contact Charles Cathlin at (240) 276-0281.

Sincerely yours,

Gladys Rodriguez
Director
Division of Enforcement B
Office of Compliance
Center for Devices and
Radiological Health

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFZ-341	Cathlin	1/24/08			
HFZ 341	Wolf	2/5/08			
340	Foreman	2/6/08			

cc: HFZ-306 (LComella)
HFZ-340 (c/f)
HFZ-341 (CCathlin)
HFZ-401 (Document Mail Center)
HFZ-402 (LFisher)
HFZ-100 (RWalchle)
HFR-CE800 (MIN-DO)
HFZ-450 (DKD)

APPROVAL ORDER FOR A PMA SUPPLEMENT (SA)
Last Modified 12-28-98
NOTE. ENCLOSURE - INCLUDE THE CONDITIONS OF APPROVAL.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

FEB 6 2008

Stacey Paetshow Wessman, RAC, MS, MBA
Principal Regulatory Affairs Specialist
Medtronic, Inc.
1015 Gramsie Rd
Shoreview, MN 55126-3082

Re: P920015/S38, Sprint™ and Sprint Fidelis™ Leads
Filed: September 12, 2007
Amended: October 24, 2007

Dear Ms. Wessman:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) 135-day supplement, which requested approval for changing the molding vendor and molding process parameters for the IS-1 connector sleeve component for Sprint Lead Models 6930, 6931, 6945, 6947, 6948, 6949, and 6944. Based upon the information submitted, the PMA 135-day supplement is approved subject to the conditions described within the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device as modified by your PMA 135-day supplement upon receipt of this letter.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the Federal Food, Drug, and Cosmetic Act.

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Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have questions concerning this approval order, please contact Charles Cathlin at (240) 276-0281.

Sincerely yours,

Christy Foreman for

Gladys Rodriguez
Director
Division of Enforcement B
Office of Compliance
Center for Devices and
Radiological Health

OCT 12 2007

Stacey Paetshow Wessman, RAC, MS, MBA
Principal Regulatory Affairs Specialist
Medtronic, Inc.
1015 Gramsie Rd
Shoreview, MN 55126-3082

Re: P920015/S38, Sprint™ and Sprint Fidelis™ Leads
Filed: September 12, 2007

Dear Ms. Wessman:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) 30-day Notice. The submission requested changes in the molding vendor and molding process parameters for the IS-1 connector sleeve component for Sprint Lead Models 6930, 6931, 6945, 6947, 6948, 6949, and 6944. We have determined a detailed review of the data supporting the change must be performed. Therefore, your 30-day Notice has been converted to a 135-Day PMA Supplement.

The following deficiencies were identified during the review of the 30-day Notice. Because of the lack of this information, review of the PMA cannot continue and, accordingly, we have listed the following deficiencies which require the responses as indicated:

1. Your firm did not adequately address the receiving and acceptance activities that you will implement as a result of the outsourcing of the component in your submission. Please provide procedure(s) addressing the receiving and acceptance activities for the IS-1 connector sleeve components, which are now manufactured by (b)(4). The procedure(s) should include the inspection, testing, and verification of the specifications for received product and the documentation of accepted or rejected product in accordance with 21 CFR 820.80. Your firm should also include the predetermined acceptance levels for the components.

2. Your firm states in the submission that (b)(4) has been a Medtronic certified supplier for (b)(4) years and molds many other lead components, but did not submit purchasing control procedures. Please submit the purchasing control procedure(s) documenting your controls established for (b)(4). The procedures should address the requirements for evaluating and selecting potential suppliers based on their ability to meet specified requirements as required by 21 CFR 820.50.

3. Although your firm provided data verifying that the changes to the molding process produced components within specification, they did not provide information addressing the validation of the changed molding process parameters. Please provide a summary of the validation

of the changed molding process parameters. Please provide a summary of the validation activities for the new molding process parameters to include installation, operation, and performance qualification. Your firm should provide a summary of the procedure(s) for monitoring and controlling the new process parameters as well.

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your PMA application can be completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 515 of the Federal Food, Drug, and Cosmetic Act for determining reasonable assurance of safety and effectiveness of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at:
http://www.fda.gov/cdrh/modact/leastburdensome.html

This letter reflects the current progress of our review of your application. You may not begin commercial distribution of the device as modified by this PMA 135-day supplement until you have received an approval order. Further review of your application and/or any response to this letter may result in additional deficiencies. CDRH will issue an approval order for the 135-day PMA supplement after the requested information has been reviewed and determined to be acceptable.

Because FDA considers the information submitted with the 30-day Notice as meeting the content requirements for PMA supplements, the time spent reviewing the submission as a 30-day Notice will be deducted from the 135 day period.

You may amend the PMA 135-day supplement to provide the above requested information (3 copies), voluntarily withdraw the PMA (3 copies) or request an extension. The required copies of the amended PMA 135-day supplement should include the FDA reference number to facilitate processing.

One copy should be sent to:

Food and Drug Administration

Office of Compliance
Field Programs Branch (HFZ-306)
2098 Gaither Road
Rockville, Maryland 20850

The remaining **two copies** should be sent to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this letter, please contact Charles Cathlin at (240) 276-0281.

Sincerely yours,

Gladys Rodriguez
Director
Division of Enforcement B
Office of Compliance
Center for Devices and
Radiological Health

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFZ-341	Cathlin	10/11/07			
HFZ-341	Webster	10/11/07			

[DO NOT SHOW ON ORIGINAL]

cc: HFZ-306 (LComella)
HFZ-340 (c/f)
HFZ-341 (f/f, CCathlin)
HFZ-402 (LFisher)
HFZ-450 (DCD)
HFR-PA100 (SAN-DO)

N30 30-DAY NOTICE NOT ADEQUATE - SUPPORTING DATA SUBMITTED WITH NOTICE NOW 135-DAY SUPPLEMENT REVIEW NEEDED SIGNIFICANT DEFICIENCIES IDENTIFIED

Last Modified 10-18-01

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

Stacey Paetshow Wessman, RAC, MS, MBA
Principal Regulatory Affairs Specialist
Medtronic, Inc.
1015 Gramsie Rd
Shoreview, MN 55126-3082

OCT 12 2007

Re: P920015/S38, Sprint™ and Sprint Fidelis™ Leads
Filed: September 12, 2007

Dear Ms. Wessman:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) 30-day Notice. The submission requested changes in the molding vendor and molding process parameters for the IS-1 connector sleeve component for Sprint Lead Models 6930, 6931, 6945, 6947, 6948, 6949, and 6944. We have determined a detailed review of the data supporting the change must be performed. Therefore, your 30-day Notice has been converted to a 135-Day PMA Supplement.

The following deficiencies were identified during the review of the 30-day Notice. Because of the lack of this information, review of the PMA cannot continue and, accordingly, we have listed the following deficiencies which require the responses as indicated:

1. Your firm did not adequately address the receiving and acceptance activities that you will implement as a result of the outsourcing of the component in your submission. Please provide procedure(s) addressing the receiving and acceptance activities for the IS-1 connector sleeve components, which are now manufactured by (b)(4) The procedure(s) should include the inspection, testing, and verification of the specifications for received product and the documentation of accepted or rejected product in accordance with 21 CFR 820.80. Your firm should also include the predetermined acceptance levels for the components.

2. Your firm states in the submission that (b)(4) has been a Medtronic certified supplier for (b)(4) years and molds many other lead components, but did not submit purchasing control procedures. Please submit the purchasing control procedure(s) documenting your controls established for (b)(4) The procedures should address the requirements for evaluating and selecting potential suppliers based on their ability to meet specified requirements as required by 21 CFR 820.50.

3. Although your firm provided data verifying that the changes to the molding process produced components within specification, they did not provide information addressing the validation of the changed molding process parameters. Please provide a summary of the validation

of the changed molding process parameters. Please provide a summary of the validation activities for the new molding process parameters to include installation, operation, and performance qualification. Your firm should provide a summary of the procedure(s) for monitoring and controlling the new process parameters as well.

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your PMA application can be completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 515 of the Federal Food, Drug, and Cosmetic Act for determining reasonable assurance of safety and effectiveness of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at:
http://www.fda.gov/cdrh/modact/leastburdensome.html

This letter reflects the current progress of our review of your application. You may not begin commercial distribution of the device as modified by this PMA 135-day supplement until you have received an approval order. Further review of your application and/or any response to this letter may result in additional deficiencies. CDRH will issue an approval order for the 135-day PMA supplement after the requested information has been reviewed and determined to be acceptable.

Because FDA considers the information submitted with the 30-day Notice as meeting the content requirements for PMA supplements, the time spent reviewing the submission as a 30-day Notice will be deducted from the 135 day period.

You may amend the PMA 135-day supplement to provide the above requested information (3 copies), voluntarily withdraw the PMA (3 copies) or request an extension. The required copies of the amended PMA 135-day supplement should include the FDA reference number to facilitate processing.

One copy should be sent to:

Food and Drug Administration

Office of Compliance
Field Programs Branch (HFZ-306)
2098 Gaither Road
Rockville, Maryland 20850

The remaining **two copies** should be sent to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this letter, please contact Charles Cathlin at (240) 276-0281.

Sincerely yours,

Christy Foreman for

Gladys Rodriguez
Director
Division of Enforcement B
Office of Compliance
Center for Devices and
Radiological Health

Ms. Mary Plante
Medtronic, Inc.
Cardiac Rhythm Disease Management
1015 Gramsie Road
Shoreview, MN 55126-3082

JUL 0 3 2007

Re: P920015/S037
Sprint Fidelis Lead Models 6949, 6948, 6931, and 6930
Filed: May 15, 2007
Amended: June 26, 2007

Dear Ms. Plante:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement which qualified for review under the Real-Time Review Program. We have reviewed your application at a teleconference on June 6, 2007.

Your supplement requested approval for design and manufacturing changes to improve the DF-1 leg strength and handling characteristics of Sprint Fidelis leads. Based upon the information submitted, the PMA supplement is approved. You may begin commercial distribution of the device as modified by your PMA supplement in accordance with the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed).

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

CDRH does not evaluate information related to contract liability warranties, however you should be aware that any such warranty statements must be truthful, accurate, and not misleading, and must be consistent with applicable Federal and State laws.

Failure to comply with any postapproval requirement constitutes a ground for withdrawal of approval of a PMA. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

If you have questions concerning this approval order, please contact Mark Fellman at (240) 276-4060.

Sincerely yours,

Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure:
Conditions of Approval for Implantable Defibrillators and Programmers

cc: HFZ-401 (D M C)
HFZ-402 (PMA Staff)
HFZ-306 (Field Programs Branch)
HFZ-450 (D C D)
D.O.

APPROVAL ORDER FOR A PMA SUPPLEMENT (SA)
Last Modified 10-28-04

Prepared by MFellman:ryh:7/2/07

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFZ-450	Fellman	7/2/07			
450	Boam	7/3/07			

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUL 0 3 2007

Ms. Mary Plante
Medtronic, Inc.
Cardiac Rhythm Disease Management
1015 Gramsie Road
Shoreview, MN 55126-3082

Re: P920015/S037
Sprint Fidelis Lead Models 6949, 6948, 6931, and 6930
Filed: May 15, 2007
Amended: June 26, 2007

Dear Ms. Plante:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement which qualified for review under the Real-Time Review Program. We have reviewed your application at a teleconference on June 6, 2007.

Your supplement requested approval for design and manufacturing changes to improve the DF-1 leg strength and handling characteristics of Sprint Fidelis leads. Based upon the information submitted, the PMA supplement is approved. You may begin commercial distribution of the device as modified by your PMA supplement in accordance with the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed).

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

CDRH does not evaluate information related to contract liability warranties, however you should be aware that any such warranty statements must be truthful, accurate, and not misleading, and must be consistent with applicable Federal and State laws.

Failure to comply with any postapproval requirement constitutes a ground for withdrawal of approval of a PMA. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

If you have questions concerning this approval order, please contact Mark Fellman at (240) 276-4060.

Sincerely yours,

for Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure:
Conditions of Approval for Implantable Defibrillators and Programmers

MAY 4 2007

Margaret dePuydt, P.E., R.A.C.
Sr. Regulatory Affairs Specialist
Medtronic, Inc.
1015 Gramsie Road
Shoreview, MN 55126-3082

Re: P920015/R013

Model 6963, 6966, and 6999 leads for the initial Transvene® lead system
Model 6933, 6936, and 6939 leads for Transvene DF-1 system Model 6934 leads for Transvene® Right Ventricular system
Model 6937 Transvene® SVC lead
Model 6707 Lead adaptor
Model 6932, 6942, 6943 and 6945 Sprint™ leads
Model 6944 Sprint™ Quattro™ lead
Model 6947 Sprint™ Quattro Secure™ lead
Model 6996 SQ lead system and 6996T tunneling tool
Model 6725 Pin-Plug Kit
Model 6726 DF-1 Y-Adaptor/Extender Kit
Model 6948, 6949, 6930, and 6931 Sprint Fidelis™ leads

Received: February 15, 2007

Dear Ms. dePuydt:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) Annual Report for the Model 6963, 6966, and 6999 leads for the initial Transvene® lead system; Model 6933, 6936, and 6939 leads for Transvene DF-1 system; Model 6934 leads for Transvene® Right Ventricular system; Model 6937 Transvene® SVC lead; Model 6707 Lead adaptor; Model 6932, 6942, 6943 and 6945 Sprint™ leads; Model 6944 Sprint™ Quattro™ lead; Model 6947 Sprint™ Quattro Secure™ lead; Model 6996 SQ lead system and 6996T tunneling tool; Model 6725 Pin-Plug Kit; Model 6726 DF-1 Y-Adaptor/Extender Kit; and the Model 6948, 6949, 6930, and 6931 Sprint Fidelis™ leads. We have determined that you have met the requirements of 21 CFR 814.82(a)(7). No further information is required at this time.

If you have any questions, please contact Vivianne Holt at (240) 276-4000.

Sincerely yours,

Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

[DO NOT SHOW ON ORIGINAL]

cc:
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ- [ODE Division]
D.O.
[ANNUAL REPORT NO RESPONSE NECESSARY ACKNOWLEDGEMENT LETTER]

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFZ-450	HOLT	5/2/2007	HFZ-402	[illegible]	5-4-2007
HFZ-450	Maynahan	5/3/07			
Z-450	Vickner	5/4/07			
	for BDZ				

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

MAY 4 2007

Margaret dePuydt, P.E., R.A.C.
Sr. Regulatory Affairs Specialist
Medtronic, Inc.
1015 Gramsie Road
Shoreview, MN 55126-3082

Re: P920015/R013

Model 6963, 6966, and 6999 leads for the initial Transvene® lead system
Model 6933, 6936, and 6939 leads for Transvene DF-1 system Model 6934 leads for Transvene® Right Ventricular system
Model 6937 Transvene® SVC lead
Model 6707 Lead adaptor
Model 6932, 6942, 6943 and 6945 Sprint™ leads
Model 6944 Sprint™ Quattro™ lead
Model 6947 Sprint™ Quattro Secure™ lead
Model 6996 SQ lead system and 6996T tunneling tool
Model 6725 Pin-Plug Kit
Model 6726 DF-1 Y-Adaptor/Extender Kit
Model 6948, 6949, 6930, and 6931 Sprint Fidelis™ leads

Received: February 15, 2007

Dear Ms. dePuydt:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) Annual Report for the Model 6963, 6966, and 6999 leads for the initial Transvene® lead system; Model 6933, 6936, and 6939 leads for Transvene DF-1 system; Model 6934 leads for Transvene® Right Ventricular system; Model 6937 Transvene® SVC lead; Model 6707 Lead adaptor; Model 6932, 6942, 6943 and 6945 Sprint™ leads; Model 6944 Sprint™ Quattro™ lead; Model 6947 Sprint™ Quattro Secure™ lead; Model 6996 SQ lead system and 6996T tunneling tool; Model 6725 Pin-Plug Kit; Model 6726 DF-1 Y-Adaptor/Extender Kit; and the Model 6948, 6949, 6930, and 6931 Sprint Fidelis™ leads. We have determined that you have met the requirements of 21 CFR 814.82(a)(7). No further information is required at this time.

If you have any questions, please contact Vivianne Holt at (240) 276-4000.

Sincerely yours,

Donna R. Vochmer

Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

AUG 16 2006

Ms. Michelle Nivala
Regulatory Affairs Specialist
Medtronic, Inc.
Cardiac Rhythm Management
1015 Gramsie Road
Shoreview, MN 55126-3082

Re: P920015/R12
Model 6963, 6966 and 6999 leads for the initial Transvene® lead system, Model 6933, 6936, and 6939 leads for Transvene® DF-1 system; Model 6937 Transvene® SVC lead, Model 6707 lead adaptor; Model 6932 Sprint™ lead, Model 6942 Sprint™, Model 6943 and 6945 Sprint™, Model 6944 Sprint™ Quattro™ lead, Model 6947 Sprint™ Quattro Secure™ lead, Model 6996 SQ lead system and 6996T tunneling tool, Model 6726 DFR-1 YAdaptor/Extender Kit, Model 6949 and 6931 Sprint Fidelis™ leads and Model 6948 and 6930 Sprint Fidelis™ leads
Received: March 6, 2006

Dear Ms. Nivala:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) Annual Report for the Model 6963, 6966 and 6999 leads for the initial Transvene® lead system, Model 6933, 6936, and 6939 leads for Transvene® DF-1 system; Model 6937 Transvene® SVC lead, Model 6707 lead adaptor; Model 6932 Sprint™ lead, Model 6942 Sprint™, Model 6943 and 6945 Sprint™, Model 6944 Sprint™ Quattro™ lead, Model 6947 Sprint™ Quattro Secure™ lead, Model 6996 SQ lead system and 6996T tunneling tool, Model 6726 DFR-1 YAdaptor/Extender Kit, Model 6949 and 6931 Sprint Fidelis™ leads and Model 6948 and 6930 Sprint Fidelis™ leads. We have determined that you have met the requirements of 21 CFR 814.82(a)(7). No further information is required at this time.

If you have any questions, please contact Vivianne Holt at 301-443-8243 x 170.

Sincerely yours,

Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

cc: HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 (DCD)
D.O.

[ANNUAL REPORT NO RESPONSE NECESSARY ACKNOWLEDGEMENT LETTER]

Prepared by:VHolt:att/8/14/06

FILE COPY

3

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFZ 450	Holt	8/14/06						
450	Stein for Moynahan	8/15/06						
HFZ-402	[illegible]	8-16-06						

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG 16 2006

Ms. Michelle Nivala
Regulatory Affairs Specialist
Medtronic, Inc.
Cardiac Rhythm Management
1015 Gramsie Road
Shoreview, MN 55126-3082

Re: P920015/R12
Model 6963, 6966 and 6999 leads for the initial Transvene® lead system, Model 6933, 6936, and 6939 leads for Transvene® DF-1 system; Model 6937 Transvene® SVC lead, Model 6707 lead adaptor; Model 6932 Sprint™ lead, Model 6942 Sprint™, Model 6943 and 6945 Sprint™, Model 6944 Sprint™ Quattro™ lead, Model 6947 Sprint™ Quattro Secure™ lead, Model 6996 SQ lead system and 6996T tunneling tool, Model 6726 DFR-1 YAdaptor/Extender Kit, Model 6949 and 6931 Sprint Fidelis™ leads and Model 6948 and 6930 Sprint Fidelis™ leads
Received: March 6, 2006

Dear Ms. Nivala:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) Annual Report for the Model 6963, 6966 and 6999 leads for the initial Transvene® lead system, Model 6933, 6936, and 6939 leads for Transvene® DF-1 system; Model 6937 Transvene® SVC lead, Model 6707 lead adaptor; Model 6932 Sprint™ lead, Model 6942 Sprint™, Model 6943 and 6945 Sprint™, Model 6944 Sprint™ Quattro™ lead, Model 6947 Sprint™ Quattro Secure™ lead, Model 6996 SQ lead system and 6996T tunneling tool, Model 6726 DFR-1 YAdaptor/Extender Kit, Model 6949 and 6931 Sprint Fidelis™ leads and Model 6948 and 6930 Sprint Fidelis™ leads. We have determined that you have met the requirements of 21 CFR 814.82(a)(7). No further information is required at this time.

If you have any questions, please contact Vivianne Holt at 301-443-8243 x 170.

Sincerely yours,

for Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

JAN 24 2006

Ms. Dianna L. Geck
Sr. Regulatory Affairs Specialist
Cardiac Rhythm Management
Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432

Re: P920015/S034
Model 2091WB Wireless PC Card for use with Model 9986 Desktop/BOSS and Model 2090 CareLink Programmer
Dated: December 6, 2005
Received: December 9, 2005
Amended: December 19, 2005

Dear Ms. Geck:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) acknowledges your December 19, 2005, letter withdrawing the above referenced premarket approval application (PMA) supplement. As requested, this file is now considered closed.

Pursuant to 21 CFR 20.29, a copy of each submission will remain on file with the CDRH. Confidentiality of your PMA application will be maintained in accordance with the provision outlined in 21 CFR sections 814.9, 20.61 and 20.81.

If you decide to resubmit a PMA supplement for this product, a new number will be assigned and the review period will begin again. Please be advised that if there were issues of safety and effectiveness raised by FDA which were not addressed in the submission you withdrew, you should address them in your resubmission.

Questions concerning this withdrawal action should be directed to:

Food and Drug Administration
Center for Devices and Radiological Health
Premarket Approval Section (HFZ-402)
9200 Corporate Blvd.
Rockville, Maryland 20850
(301) 594-2186

Sincerely yours,

Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

cc: HFZ-306 (Field Programs Branch - QSR)
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 [ODE DIVISION]
D.O.
PMA VOLUNTARY WITHDRAWAL ACKNOWLEDGMENT LETTER (WACKVOL)
Modified 02-13-02

Prepared by:JXLee:myb:01/18/06

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450	JXL/BF	1/18/06						
450	Mayer	1/20/06						
450	Zimmerman	1/23/06						
2402	Mellon	1-24-06						

U.S. GPO 1986-169-089

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JAN 24 2006

Ms. Dianna L. Geck
Sr. Regulatory Affairs Specialist
Cardiac Rhythm Management
Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432

Re: P920015/S034
Model 2091WB Wireless PC Card for use with Model 9986 Desktop/BOSS and Model 2090 CareLink Programmer
Dated: December 6, 2005
Received: December 9, 2005
Amended: December 19, 2005

Dear Ms. Geck:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) acknowledges your December 19, 2005, letter withdrawing the above referenced premarket approval application (PMA) supplement. As requested, this file is now considered closed.

Pursuant to 21 CFR 20.29, a copy of each submission will remain on file with the CDRH. Confidentiality of your PMA application will be maintained in accordance with the provision outlined in 21 CFR sections 814.9, 20.61 and 20.81.

If you decide to resubmit a PMA supplement for this product, a new number will be assigned and the review period will begin again. Please be advised that if there were issues of safety and effectiveness raised by FDA which were not addressed in the submission you withdrew, you should address them in your resubmission.

Questions concerning this withdrawal action should be directed to:

Food and Drug Administration
Center for Devices and Radiological Health
Premarket Approval Section (HFZ-402)
9200 Corporate Blvd.
Rockville, Maryland 20850
(301) 594-2186

Sincerely yours,

Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Lyons, Linda

From: Budabin, Steve E.
Sent: Tuesday, October 11, 2005 11:08 AM
To: Lyons, Linda
Subject: RE: P920015/S032

cc:

HFZ-306	(Field Programs Branch - GMP)
HFZ-401	(Document Mail Center)
HFZ-402	(Lisa Fisher)
HFZ-450	(Megan Moynahan)
HFZ-340	(r/f)
HFZ-341	(SBudabin, c/f)
HFR-CE800	(MIN-DO)

Steven E. Budabin, M.S.
Cardiovascular & Neurological
Devices Branch (HFZ-341)
Office of Compliance
Center for Devices and
Radiological Health
240-276-0291
(b)(6) (b)(6)

-----Original Message-----
From: Lyons, Linda
Sent: Tuesday, October 11, 2005 11:03 AM
To: Budabin, Steve E.
Subject: P920015/S032

Hi Steve,

I need the cc list for this PMA.

Thanks.

Linda

4

Part 1 - Page 150

SEP 30 2005

Mary Ellen Best
Principal Regulatory Affairs Specialist
Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, Minnesota 55432-3576

Re: P920015/S032
Filed: September 2, 2005

Dear Ms. Best:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) 30-day Notice. The submission requested approval to change the aeration time following sterilization of the Sprint Fidelis Leads. We have determined a detailed review of the data supporting the change must be performed. Therefore, your 30-day Notice has been converted to a 135-Day PMA Supplement.

The following deficiencies were identified during the review of the 30-day Notice. Because of the lack of this information, review of the PMA cannot continue and, accordingly, we have listed the following deficiencies, which require the responses as indicated:

1. Your submission indicates that the qualification study for the sterilization and aeration activities for the Fidelis Leads was performed at your Rice Creek facility; however, the aeration activities are conducted at the Medtronic Puerto Rico, Inc. (MPRI) facility.

    - Please provide additional information to demonstrate that these two facilities are equivalent.

    - Please explain how environmental contamination controls are equivalent at the MPRI and Rice Creek facility.

2. Your submission indicates that samples are analyzed for sterilant residuals by (b)(4) (b)(4) utilizing the (b)(4) (b)(4) method for the implantable portions of the device. If Medtronic conducts sterilant residual testing in-house, please provide a summary of how the MPRI and Rice Creek facility procedures are equivalent. If the samples are shipped to a contract laboratory for sterilant residual testing, please explain how the samples are shipped.

Part 1 - Page 151

3. Your E-mail of September 28, 2005, appears to contradict the location at which Fidelis Leads are sterilized. You state, "The majority of Fidelis Leads are currently manufactured and sterilized at the Puerto Rico facility" (emphasis added). ..."Since the (b)(4) sterilizers and aeration vessels used at RC and MPRI are equivalent, sterilization and aeration activities representing the MPRI facility are performed at the Rice Creek facility" (emphasis added). Please clarify this discrepancy.

4. Your submission indicates Medtronic screens for residual (b)(4) (b)(4) and (b)(4) (b)(4) Please provide information on any other residual substances tested.

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your PMA application can be completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 515 of the Federal Food, Drug, and Cosmetic Act for determining reasonable assurance of safety and effectiveness of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at: http://www.fda.gov/cdrh/modact/leastburdensome.html

This letter reflects the current progress of our review of your application. You may not begin commercial distribution of the device as modified by this PMA 135-day supplement until you have received an approval order. Further review of your application and/or any response to this letter may result in additional deficiencies. CDRH will issue an approval order for the 135-day PMA supplement after the requested information has been reviewed and determined to be acceptable.

Because FDA considers the information submitted with the 30-day Notice as meeting the content requirements for PMA supplements, the time spent reviewing the submission as a 30-day Notice will be deducted from the 135 day period.

You may amend the PMA 135-day supplement to provide the above requested information (3 copies), voluntarily withdraw the PMA (3 copies) or request an extension. The required copies of the amended PMA 135-day supplement should include the FDA reference number to facilitate processing.

One copy should be sent to:

FILE COPY

Food and Drug Administration
Office of Compliance
Field Programs Branch (HFZ-306)
2098 Gaither Road

2

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFZ-341	Rudolph	9/30/05			
HFZ 340	Rodrigues	9/30/05			

Part 1 - Page 152

One copy should be sent to:

Food and Drug Administration
Office of Compliance
Field Programs Branch (HFZ-306)
2098 Gaither Road
Rockville, Maryland 20850

The remaining **two copies** should be sent to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this letter, please contact Steven E. Budabin, M.S., Consumer Safety Officer at 240-276-0120 or via E-mail at steve.budabin@fda.hhs.gov.

Sincerely yours,

Gladys Rodriguez
Director
Division of Enforcement B
Office of Compliance
Center for Devices and
Radiological Health

FILE COPY

3

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFZ-341	Budabin	9-30-04			

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

SEP 30 2005

Mary Ellen Best
Principal Regulatory Affairs Specialist
Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, Minnesota 55432-3576

Re: P920015/S032
Filed: September 2, 2005

Dear Ms. Best:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) 30-day Notice. The submission requested approval to change the aeration time following sterilization of the Sprint Fidelis Leads. We have determined a detailed review of the data supporting the change must be performed. Therefore, your 30-day Notice has been converted to a 135-Day PMA Supplement.

The following deficiencies were identified during the review of the 30-day Notice. Because of the lack of this information, review of the PMA cannot continue and, accordingly, we have listed the following deficiencies, which require the responses as indicated:

1. Your submission indicates that the qualification study for the sterilization and aeration activities for the Fidelis Leads was performed at your Rice Creek facility; however, the aeration activities are conducted at the Medtronic Puerto Rico, Inc. (MPRI) facility.

    - Please provide additional information to demonstrate that these two facilities are equivalent.

    - Please explain how environmental contamination controls are equivalent at the MPRI and Rice Creek facility.

2. Your submission indicates that samples are analyzed for sterilant residuals by (b)(4) (b)(4) (b)(4) utilizing the (b)(4) (b)(4) method for the implantable portions of the device. If Medtronic conducts sterilant residual testing in-house, please provide a summary of how the MPRI and Rice Creek facility procedures are equivalent. If the samples are shipped to a contract laboratory for sterilant residual testing, please explain how the samples are shipped.

5

Part 1 - Page 154

3. Your E-mail of September 28, 2005, appears to contradict the location at which Fidelis Leads are sterilized. You state, "The majority of Fidelis Leads are currently manufactured and sterilized at the Puerto Rico facility" (emphasis added). ..."Since the (b)(4) sterilizers and aeration vessels used at RC and MPRI are equivalent, sterilization and aeration activities representing the MPRI facility are performed at the Rice Creek facility" (emphasis added). Please clarify this discrepancy.

4. Your submission indicates Medtronic screens for residual (b)(4) (b)(4) and (b)(4) (b)(4) Please provide information on any other residual substances tested.

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your PMA application can be completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 515 of the Federal Food, Drug, and Cosmetic Act for determining reasonable assurance of safety and effectiveness of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at:
http://www.fda.gov/cdrh/modact/leastburdensome.html

This letter reflects the current progress of our review of your application. You may not begin commercial distribution of the device as modified by this PMA 135-day supplement until you have received an approval order. Further review of your application and/or any response to this letter may result in additional deficiencies. CDRH will issue an approval order for the 135-day PMA supplement after the requested information has been reviewed and determined to be acceptable.

Because FDA considers the information submitted with the 30-day Notice as meeting the content requirements for PMA supplements, the time spent reviewing the submission as a 30-day Notice will be deducted from the 135 day period.

You may amend the PMA 135-day supplement to provide the above requested information (3 copies), voluntarily withdraw the PMA (3 copies) or request an extension. The required copies of the amended PMA 135-day supplement should include the FDA reference number to facilitate processing.

One copy should be sent to:

Food and Drug Administration
Office of Compliance
Field Programs Branch (HFZ-306)
2098 Gaither Road

One copy should be sent to:

Food and Drug Administration
Office of Compliance
Field Programs Branch (HFZ-306)
2098 Gaither Road
Rockville, Maryland 20850

The remaining **two copies** should be sent to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this letter, please contact Steven E. Budabin, M.S., Consumer Safety Officer at 240-276-0120 or via E-mail at steve.budabin@fda.hhs.gov.

Sincerely yours,

Gladys Rodriguez

Gladys Rodriguez
Director
Division of Enforcement B
Office of Compliance
Center for Devices and
Radiological Health

JUL - 5 2005

Ms. Mary Ellen Best
Principal Regulatory Affairs Specialist
Cardiac Rhythm Management
Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432

Re: P920015/S31
Sprint™/Sprint Quattro™ Leads
Received: June 17, 2005

Dear Ms. Best:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) acknowledges your letter of June 16, 2005 regarding this premarket approval application (PMA) Supplement and requesting an extension until August 31, 2005 to respond to our January 7, 2005 letter. We agree to your request.

Please be advised that the PMA procedural regulation under 21 CFR 814.44(g) provides that FDA may consider a PMA submission to have been withdrawn voluntarily, that is, by default, if the applicant fails to respond in writing to a written request for an amendment within 180 days after the date FDA issues such a request. **However, the current policy within CDRH has allowed the applicant up to a maximum of 360 days to respond to our letter.**

Any correspondence in response to this letter should be submitted in triplicate in the form of an amendment to the above PMA Supplement submission. If the response includes the information requested in the CDRH deficiency letter, the number of copies specified in that letter should be submitted. All correspondence must include the above PMA Supplement reference number and should be addressed to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions regarding this letter, you may contact Doris Terry at (301) 443-8609 x 160.

Sincerely yours,

Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

cc: HFZ-306 (Field Programs Branch - QSR)
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 (DCD)
D.O.

EXTENSION REQUEST GRANTED FOR ORIGINAL/ SUPPLEMENT

Issued: 6-20-05

Prepared by:DTerry:att/6/23/05

FILE COPY

3

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450	Terry	6/28/05	Z-462	[illegible]	7/5/2005			
450	Mary	6/30/05						
Z-450	Vechner	7/1/05						

SN BDZ

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUL - 5 2005

Ms. Mary Ellen Best
Principal Regulatory Affairs Specialist
Cardiac Rhythm Management
Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432

Re: P920015/S31
Sprint™/Sprint Quattro™ Leads
Received: June 17, 2005

Dear Ms. Best:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) acknowledges your letter of June 16, 2005 regarding this premarket approval application (PMA) Supplement and requesting an extension until August 31, 2005 to respond to our January 7, 2005 letter. We agree to your request.

Please be advised that the PMA procedural regulation under 21 CFR 814.44(g) provides that FDA may consider a PMA submission to have been withdrawn voluntarily, that is, by default, if the applicant fails to respond in writing to a written request for an amendment within 180 days after the date FDA issues such a request. **However, the current policy within CDRH has allowed the applicant up to a maximum of 360 days to respond to our letter.**

Any correspondence in response to this letter should be submitted in triplicate in the form of an amendment to the above PMA Supplement submission. If the response includes the information requested in the CDRH deficiency letter, the number of copies specified in that letter should be submitted. All correspondence must include the above PMA Supplement reference number and should be addressed to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions regarding this letter, you may contact Doris Terry at (301) 443-8609 x 160.

Sincerely yours,

Donna R. Vuchmen

Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Ms. Mary Ellen Best
Principal Regulatory Affairs Specialist
Cardiac Rhythm Management
Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432

Re: P920015/S030
Model 6948 and 6930 Leads
Filed: December 22, 2003
Amended: April 1, 2004

Dear Ms. Best:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for addition of a polyurethane overlay. Based upon the information submitted, the PMA supplement is approved. You may begin commercial distribution of the device as modified by your PMA supplement in accordance with the conditions described below and in the "Conditions of Approval" (enclosed).

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Expiration dating for this device has been established and approved at 2 years. This is to advise you that the protocol used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(7).

CDRH does not evaluate information related to contract liability warranties, however you should be aware that any such warranty statements must be truthful, accurate, and not misleading, and must be consistent with applicable Federal and State laws.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that as soon as possible and before commercial distribution of your device you must submit an amendment to this PMA with copies of all approved labeling in final form. The labeling will not routinely be reviewed by FDA staff when PMA supplement applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have questions concerning this approval order, please contact Kwame Ulmer at (301) 443-8517.

Sincerely yours,

Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

[DO NOT SHOW ON ORIGINAL]

cc: HFZ-306 (Field Programs Branch - QSR)
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 [ODE Division]
HFZ-100 (OST Reviewer - if appropriate __________)
D.O.

APPROVAL ~~APPROVABLE~~ LETTER FOR A PMA SUPPLEMENT (SAD)
Last Modified 01-31-02

Fina;: Linda Bessacque:05/21/04

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFZ 450	ULMER	5/21/04			
HFZ 450	~~Ulmer~~ for Mayrohan	~~5/21/04~~ 6/2			
450	Abel for BDZ	6/3/04			

3

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUN - 8 2004

Ms. Mary Ellen Best
Principal Regulatory Affairs Specialist
Cardiac Rhythm Management
Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432

Re: P920015/S030
Model 6948 and 6930 Leads
Filed: December 22, 2003
Amended: April 1, 2004

Dear Ms. Best:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for addition of a polyurethane overlay. Based upon the information submitted, the PMA supplement is approved. You may begin commercial distribution of the device as modified by your PMA supplement in accordance with the conditions described below and in the "Conditions of Approval" (enclosed).

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Expiration dating for this device has been established and approved at 2 years. This is to advise you that the protocol used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(7).

CDRH does not evaluate information related to contract liability warranties, however you should be aware that any such warranty statements must be truthful, accurate, and not misleading, and must be consistent with applicable Federal and State laws.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that as soon as possible and before commercial distribution of your device you must submit an amendment to this PMA with copies of all approved labeling in final form. The labeling will not routinely be reviewed by FDA staff when PMA supplement applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have questions concerning this approval order, please contact Kwame Ulmer at (301) 443-8517.

Sincerely yours,

for Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

5

JUN - 8

Ms. Mary Ellen Best
Principal Regulatory Affairs Specialist
Cardiac Rhythm Management
Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432

Re: P920015/S029
Model 6949 and 6931 Leads
Filed: November 6, 2003
Amended: April 1, 2004

Dear Ms. Best:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for addition of a polyurethane overlay. Based upon the information submitted, the PMA supplement is approved. You may begin commercial distribution of the device as modified by your PMA supplement in accordance with the conditions described below and in the "Conditions of Approval" (enclosed).

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Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

[DO NOT SHOW ON ORIGINAL]

cc: HFZ-306 (Field Programs Branch - QSR)
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ- [ODE Division]
HFZ-100 (OST Reviewer - if appropriate _____)
D.O.

APPROVAL ~~APPROVABLE~~ LETTER FOR A PMA SUPPLEMENT (SAD)
Last Modified 01-31-02

Final:Linda Bessacque:05/21/04

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFZ 450	ULMER	5/21/04			
HFZ 450	~~[illegible]~~ MOYNAHAN	~~5/21/04~~ 6/2			
450	Ogden	6/7/04			
450	AD/C for ODE	6/3/04			

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUN - 8 2004

Ms. Mary Ellen Best
Principal Regulatory Affairs Specialist
Cardiac Rhythm Management
Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432

Re: P920015/S029
Model 6949 and 6931 Leads
Filed: November 6, 2003
Amended: April 1, 2004

Dear Ms. Best:

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Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

MAR 13

Ms. Mary Ellen Best
Principal Regulatory Affairs Specialist
Cardiac Rhythm Management
Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432

Re: P920015/S029
Model 6949 and 6931 Leads
Filed: November 6, 2003

Dear Ms. Best:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement which requested approval for design changes to current ICD leads and the addition of a polyurethane 80A overlay. We regret to inform you that CDRH has determined that your PMA supplement is not approvable based on the requirements of 21 CFR 814.44(f), which also requires FDA, where practical, to identify measures required to place the PMA supplement in approvable form. Accordingly, to place your PMA supplement in approvable form, you must address the following:

This application was the subject of several pre-IDE discussions and a determination meeting. You have not fully complied with the determination meeting letter dated May 12, 2003. Please address the following:

1. The determination letter dated May 12, 2003, states that 12-week animal data would be provided for the polyurethane lead models; however, you have provided 12-week data on the surface modified endgroup (SME) version of the lead. Please provide the results of animal testing out to 12-weeks on the polyurethane (b)(4) lead models.
2. On page 10 of the Pre-IDE dated February 10, 2003, it states that 8 canines would be implanted with lead Models 6944 and that Model 6947 would serve as the control. However, on page 58 of the Animal Test report, it states that "The electrical data from lead Model 6949 was compared to that collected in the Model 6947 chronic canine study, Reference (P920015/S24)." Please clarify whether the results of the electrical data at 12 weeks were compared to the results of the experiments mentioned in the pre-IDE or if they were compared to an historical control referenced in P920015/S24. If the test results are compared to an historical control please explain in detail the rationale of this decision.

3. On page 86 of Testing Results it states that for pacing thresholds, pacing impedance and R-wave amplitudes, multiple data points were taken for each monitor and that all data points for a particular monitor were averaged. Please clarify if the same number of data points were taken for each electrical parameter. Please indicate if all of them were used for the analysis and if so, the number of points used in the analysis. Because the figures in this report are difficult to read, please also provide the raw data for these figures and the statistical analysis.

Labeling

4. You have omitted the entire section pertaining to clinical study of the submitted lead. However, informing the user that clinical data was not utilized in the approval process constitutes important advice. Therefore please include a statement advising the user that clinical data was not collected in the approval process for this lead.

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your PMA application can be completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 515 of the Federal Food, Drug, and Cosmetic Act for determining reasonable assurance of safety and effectiveness of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at:
http://www.fda.gov/cdrh/modact/leastburdensome.html

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period up to 180 days. As provided by 21 CFR 814.37(c) you may decline to submit a major amendment requested by FDA in which case the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

As provided by 21 CFR 814.44(f), you may amend your PMA supplement as requested above, withdraw the PMA supplement, or consider this letter to be a denial of approval of the PMA supplement under 21 CFR 814.45 and request administrative review. Any request for administrative review either through a hearing or review by an independent advisory committee, under section 515(d)(4) and 515(g) of the Federal Food, Drug, and Cosmetic Act must be submitted in the form of a petition for reconsideration (21 CFR 10.33) and in accordance with the general administrative procedures for submission of documents to the Dockets Management Branch (21 CFR 10.20). Any petition for reconsideration must be submitted to the Food and Drug Administration, Dockets Management Branch (HFA-305), Room 1-23, 12420 Parklawn Drive, Rockville, Maryland 20857, within 30 days of the date you receive this letter. After

reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issues to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

As provided under 21 CFR 814.44(g), FDA will consider this PMA supplement to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA supplement amendment. You may, however, amend the PMA supplement within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA supplement within the 180-day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA supplement and will be assigned a new number. Under these circumstances, any resubmission will be given a new PMA supplement number and will be subject to the requirements of 21 CFR 814.20.

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Food and Drug Administration
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Sincerely yours,

Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

[DO NOT SHOW ON ORIGINAL]

cc: HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 (ODE DIVISION]
HFZ-100 (OST Reviewer - if appropriate _____)
D.O.
SUPPLEMENT NOT APROVABLE
Last Modified 10/16/00

Final: Linda Bessacque:03/05/04

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OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFZ450	ULMER	3/5/04						
450	[illegible]	3/11/04						
450	Vochner	3/19/04						

SMBDZ

U.S. GPO 1986-169-089

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Ms. Mary Ellen Best
Principal Regulatory Affairs Specialist
Cardiac Rhythm Management
Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432

MAR 19 2004

Re: P920015/S029
Model 6949 and 6931 Leads
Filed: November 6, 2003

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3. On page 86 of Testing Results it states that for pacing thresholds, pacing impedance and R-wave amplitudes, multiple data points were taken for each monitor and that all data points for a particular monitor were averaged. Please clarify if the same number of data points were taken for each electrical parameter. Please indicate if all of them were used for the analysis and if so, the number of points used in the analysis. Because the figures in this report are difficult to read, please also provide the raw data for these figures and the statistical analysis.

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Sincerely yours,

Kwame R. Ulmer

Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

MAR 19 2004

Ms. Mary Ellen Best
Principal Regulatory Affairs Specialist
Cardiac Rhythm Management
Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432

Re: P920015/S030
Model 6948 and 6930 Leads
Filed: December 22, 2003

Dear Ms. Best:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement which requested approval for design changes to current ICD leads and the addition of a polyurethane 80A overlay. We regret to inform you that CDRH has determined that your PMA supplement is not approvable based on the requirements of 21 CFR 814.44(f), which also requires FDA, where practical, to identify measures required to place the PMA supplement in approvable form. Accordingly, to place your PMA supplement in approvable form, you must address the following:

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Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

[DO NOT SHOW ON ORIGINAL]

cc: HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 (ODE DIVISION]
HFZ-100 (OST Reviewer - if appropriate _____)
D.O.
SUPPLEMENT NOT APROVABLE
Last Modified 10/16/00

Final: Linda Bessacque:03/05/04
Corrected:03/11/04

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OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
150	mayr	3/18						
Z-450	[illegible]	3/19/04						

a BDZ

U.S. GPO 1986-169-089

21

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Ms. Mary Ellen Best
Principal Regulatory Affairs Specialist
Cardiac Rhythm Management
Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432

MAR 19

Re: P920015/S030
Model 6948 and 6930 Leads
Filed: December 22, 2003

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This application was the subject of several pre-IDE discussions and a determination meeting. You have not fully complied with the determination meeting letter dated May 12, 2003. Please address the following:

1. The determination letter dated May 12, 2003, states that 12-week animal data would be provided for the polyurethane lead models; however, you have provided 12-week data on the surface modified endgroup (SME) version of the lead. Please provide the results of animal testing out to 12-weeks on the polyurethane (b)(4) lead models.
2. On page 10 of the Pre-IDE dated February 10, 2003, it states that 8 canines would be implanted with lead Models 6944 and that Model 6947 would serve as the control. However, on page 58 of the Animal Test report, it states that "The electrical data from lead Model 6949 was compared to that collected in the Model 6947 chronic canine study, Reference (P920015/S24)." Please clarify whether the results of the electrical data at 12 weeks were compared to the results of the experiments mentioned in the pre-IDE or if they were compared to an historical control referenced in P920015/S24. If the test results are compared to an historical control please explain in detail the rationale of this decision.

3. On page 86 of Testing Results it states that for pacing thresholds, pacing impedance and R-wave amplitudes, multiple data points were taken for each monitor and that all data points for a particular monitor were averaged. Please clarify if the same number of data points were taken for each electrical parameter. Please indicate if all of them were used for the analysis and if so, the number of points used in the analysis. Because the figures in this report are difficult to read, please also provide the raw data for these figures and the statistical analysis.

Labeling

4. You have omitted the entire section pertaining to clinical study of the submitted lead. However, informing the user that clinical data was not utilized in the approval process constitutes important advice. Therefore please include a statement advising the user that clinical data was not collected in the approval process for this lead.

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your PMA application can be completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 515 of the Federal Food, Drug, and Cosmetic Act for determining reasonable assurance of safety and effectiveness of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at:
http://www.fda.gov/cdrh/modact/leastburdensome.html

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period up to 180 days. As provided by 21 CFR 814.37(c) you may decline to submit a major amendment requested by FDA in which case the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

As provided by 21 CFR 814.44(f), you may amend your PMA supplement as requested above, withdraw the PMA supplement, or consider this letter to be a denial of approval of the PMA supplement under 21 CFR 814.45 and request administrative review. Any request for administrative review either through a hearing or review by an independent advisory committee, under section 515(d)(4) and 515(g) of the Federal Food, Drug, and Cosmetic Act must be submitted in the form of a petition for reconsideration (21 CFR 10.33) and in accordance with the general administrative procedures for submission of documents to the Dockets Management Branch (21 CFR 10.20). Any petition for reconsideration must be submitted to the Food and Drug Administration, Dockets Management Branch (HFA-305), Room 1-23, 12420 Parklawn Drive, Rockville, Maryland 20857, within 30 days of the date you receive this letter. After

reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issues to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

As provided under 21 CFR 814.44(g), FDA will consider this PMA supplement to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA supplement amendment. You may, however, amend the PMA supplement within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA supplement within the 180-day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA supplement and will be assigned a new number. Under these circumstances, any resubmission will be given a new PMA supplement number and will be subject to the requirements of 21 CFR 814.20.

Information correcting the above deficiencies should be submitted in the form of an amendment. All amendments to the PMA supplement should be submitted in triplicate to the address below and reference the above PMA supplement number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this not-approvable letter, please contact Kwame Ulmer at (301) 443-8517, ext. 166.

Sincerely yours,

Dianne R. Vollmer

Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

21

Ms. Mary Ellen Best
Principal Regulatory Affairs Specialist
Cardiac Rhythm Management
Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432

Re: P920015/S28
Sprint™ Quattro™ Steroid-Eluting Lead Model 6944
Filed: April 28, 2003

Dear Ms. Best:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement which qualified for review under the Real-Time Review Program. We have reviewed your application at a teleconference on June 26, 2003.

Your supplement requested approval for addition of the dexamethasone sodium phosphate (DSP) steroid to the lead tip. Based upon the information submitted, the PMA supplement is approved. You may begin commercial distribution of the device as modified by your PMA supplement in accordance with the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers " (enclosed).

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Expiration dating for this device has been established and approved at two years.

CDRH does not evaluate information related to contract liability warranties, however you should be aware that any such warranty statements must be truthful, accurate, and not misleading, and must be consistent with applicable Federal and State laws.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA supplement submission with copies of all approved labeling in final printed form. The labeling will not routinely be reviewed by FDA staff when PMA applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have questions concerning this approval order, please contact Kwame Ulmer at (301) 443-8517 ext. 166.

Sincerely yours,

Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

[DO NOT SHOW ON ORIGINAL]

cc: HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 [ODE DCD]
HFZ-100 (OST Reviewer - if appropriate)
D.O.

Department of Health & Human Services

Final: MDiallo:mzd4:07/09/03
APPROVAL ORDER FOR A PMA SUPPLEMENT (SA)
Last Modified 02-13-02
NOTE. ENCLOSURE - INCLUDE THE CONDITIONS OF APPROVAL.

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFZ450	OLMER	7/9/03	[illegible]	7/21	
450	[illegible]	7/18/03			
HFZ-450	Donelson	7/18/03			

32

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUL 21 2003

Ms. Mary Ellen Best
Principal Regulatory Affairs Specialist
Cardiac Rhythm Management
Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432

Re: P920015/S28
Sprint™ Quattro™ Steroid-Eluting Lead Model 6944
Filed: April 28, 2003

Dear Ms. Best:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement which qualified for review under the Real-Time Review Program. We have reviewed your application at a teleconference on June 26, 2003.

Your supplement requested approval for addition of the dexamethasone sodium phosphate (DSP) steroid to the lead tip. Based upon the information submitted, the PMA supplement is approved. You may begin commercial distribution of the device as modified by your PMA supplement in accordance with the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers " (enclosed).

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Expiration dating for this device has been established and approved at two years.

CDRH does not evaluate information related to contract liability warranties, however you should be aware that any such warranty statements must be truthful, accurate, and not misleading, and must be consistent with applicable Federal and State laws.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA supplement submission with copies of all approved labeling in final printed form. The labeling will not routinely be reviewed by FDA staff when PMA applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have questions concerning this approval order, please contact Kwame Ulmer at (301) 443-8517 ext. 166.

Sincerely yours,

Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

NOV - 2

Ms. Mary Ellen Best
Senior Product Regulation Manager
Cardiac Rhythm Management
Medtronic, Inc.
7000 Central Avenue N.E.
Minneapolis, MN 55432

Re: P920015/S24
Medtronic® Sprint™ Quattro™ Secure™ Model 6947 Lead
Filed: October 1, 2001

Dear Ms. Best:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement which qualified for review under the Real-Time Review Program. We have reviewed your application at a teleconference on October 24, 2001. A meeting was not necessary to make a decision regarding this supplement.

Your supplement requested approval for the Medtronic® Sprint™ Quattro™ Secure™ Model 6947 Lead. The device, as modified, will be marketed under the trade name Medtronic Sprint Quattro Secure Model 6947 Lead and is indicated for single long-term use in the right ventricle. This lead has application for patients in which arrhythmia management systems are indicated. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the

device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Expiration dating for this device has been established and approved at two years. This is to advise you that the protocol used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(7).

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the Federal Food, Drug, and Cosmetic Act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA supplement submission with copies of all approved labeling in final printed form. The labeling will not routinely be reviewed by FDA staff when PMA applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

If you have questions concerning this approval order, please contact James Lee at (301) 443-8609 ext-168.

Sincerely yours,

James E. Dillard III
Director
Division of Cardiovascular
and Respiratory Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

cc: HFZ-544 (Postmarket Surveillance Branch if appropriate)
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 (DCRD)
HFZ-100 (OST Reviewer - if appropriate)
D.O.

APPROVAL ORDER FOR A PMA SUPPLEMENT (SA)
NOTE. ENCLOSURE - INCLUDE THE CONDITIONS OF APPROVAL.

Prepared by:JLee:att/10/26/01
Revised:JLee:att/11/1/01

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450		11/1/01						
450		11/2						
HFZ402	M. Linden	11/2/01						

U.S. GPO 1986-169-089

(b)(5)

(b)(5)

MEMORANDUM

DATE: SEP 10 2001

TO: The Record

FROM: Kent A. Berthold, Consumer Safety Officer
Cardiovascular and Neurological Devices Branch, DOE III, OC, CDRH
Thru: Christy Foreman, Acting Deputy Director, DOE III CLF 9/10/01

RE: P830061/S032, P850089/S047, P890003/S064, P900061/S045, P920015/S023, P930039/S010, P950024/S004, P980016/S019, and P980050/S007
Medtronic Pacing Leads
Received: July 17, 2001

FIRM: Cardiac Rhythm Management
Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, Minnesota 55432

On July 17, 2001, we received a 30-Day Notice from Cardiac Rhythm Management, Medtronic, Inc. regarding a change in the supplier of polyetherurethane.

COMPLIANCE REVIEW

Our review determined that the applicant had submitted adequate data to demonstrate that the change in the manufacturing process was conducted in accordance with the Quality System Regulation.

ODE REVIEW

The ODE review determined that the firm submitted sufficient information to address safety and effectiveness issues for the change in the manufacturing process. A copy of ODE's review is attached.

CONCLUSION

As a result of the review of the 30-Day Notice by OC/ODE, it was decided that a 135-Day Supplement is not required. A copy of the

25

letter sent to the sponsor is attached.

Kent A. Berthold

\

Attachments:
ODE's review
Letter sent to sponsor

Prep:KABerthold:8-30-01
Reviewed:CForeman:
Final:kab:

Original:
30-Day Notice File

bcc:
HFZ-306 (Comella)
HFZ-340 (Foreman, 3)
HFZ-341 (Berthold, Firm File)
HFZ-402 (Nguyen, Wolanski)
HFZ-450 (Donelson)

Tracking
C:\MY DOCUMENTS\LETTER\30-DAY NOTICE, REVIEW MEMORANDUM, MEDTRONIC

Berthold, Kent A.

From:	Donelson, Jan
Sent:	Tuesday, August 07, 2001 5:14 PM
To:	Foreman, Christy; Berthold, Kent A.
Subject:	P830061/S032, P850089/S047, P890003/S064, P900061/S045, P920015/S023, P930039/S010, P950024/S004, P980016/S019, and P980050/S007

Christy and Kent -

Re: P830061/S032, P850089/S047, P890003/S064, P900061/S045, P920015/S023, P930039/S010, P950024/S004, P980016/S019, and P980050/S007
Medtronic Pacing Leads
Received: July 17, 2001

DCRD has reviewed the above document, as well as your draft letter to the applicant regarding this 30-Day Notice requested an evaluation of the change in the supplier of polyetherurethane. We have no unresolved concerns regarding safety and effectiveness issues.

In addition, we find your letter acceptable for issuance with modification as tracked in the letter on the L drive.

If you have any questions, please contact me at 443-8320 (x158).

Jan Donelson
Assistant Director for Program Operations
Division of Cardiovascular and Respiratory Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
jld@cdrh.fda.gov
(301) 443-8320 Ext. 158

Berthold, Kent A.

From: Donelson, Jan
Sent: Tuesday, August 07, 2001 5:14 PM
To: Foreman, Christy; Berthold, Kent A.
Subject: P830061/S032, P850089/S047, P890003/S064, P900061/S045, P920015/S023, P930039/S010, P950024/S004, P980016/S019, and P980050/S007

Christy and Kent -

Re: P830061/S032, P850089/S047, P890003/S064, P900061/S045, P920015/S023, P930039/S010, P950024/S004, P980016/S019, and P980050/S007
Medtronic Pacing Leads
Received: July 17, 2001

DCRD has reviewed the above document, as well as your draft letter to the applicant regarding this 30-Day Notice requested an evaluation of the change in the supplier of polyetherurethane. We have no unresolved concerns regarding safety and effectiveness issues.

In addition, we find your letter acceptable for issuance with modification as tracked in the letter on the (b)(4)

If you have any questions, please contact me at 443-8320 (b)(5), (b)(6)

Jan Donelson
Assistant Director for Program Operations
Division of Cardiovascular and Respiratory Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
(b)(6)
(301) 443-8320 Ext. 158

28

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG 8 2001

Kristy K. Mollner, RAC
Product Regulation Manager
Cardiac Rhythm Management
Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432

Re: P830061/S032, P850089/S047, P890003/S064, P900061/S045, P920015/S023, P930039/S010, P950024/S004, P980016/S019, and P980050/S007
Medtronic Pacing Leads
Received: July 17, 2001

Dear Ms. Mollner:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has evaluated your premarket approval application (PMA) 30-day Notice. The 30-day Notice requested an evaluation of the change in the supplier of polyetherurethane.

Based on the information submitted, FDA has determined that submission of a 135-day PMA supplement is not required.

If you have questions concerning the letter, please contact the Field Programs Branch at (301) 594-4695 or the PMA Staff at (301) 594-2186.

Sincerely yours,

Thinh Nguyen
Director, Premarket Approval
Application Program
Program Operations Staff
Office of Device Evaluation
Center for Devices and
Radiological Health

Ms. Jacque L. Keller
Product Regulation Manager
Cardiac Rhythm Management
Medtronic, Inc.
7000 Central Avenue N.E.
Minneapolis, MN 55432

JUN 15 2001

Re: P920015/S22
Model 6726 DF-1 Y-Adaptor/Extender Kit
Filed: May 30, 2001

Dear Ms. Keller:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement which qualified for review under the Real-Time Review Program. We have reviewed your application at a teleconference on June 14, 2001. A meeting was not necessary to make a decision regarding this supplement.

Your supplement requested approval for Model 6726 DF-1 Y-Adaptor/Extender Kit. The device is indicated to adapt two DF-1 lead connectors to a single DF-1 compatible connector port and/or will extend the length of a DF-1 lead connector. The Model 6726 has application for patients in which ICD systems are indicated. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval For Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the Federal Food, Drug, and Cosmetic Act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA supplement submission with copies of all approved labeling in final printed form. As part of our reengineering effort, the Office of Device Evaluation is piloting a new process for review of final printed labeling. The labeling will not routinely be reviewed by FDA staff when PMA applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment. Please see the CDRH Pilot for Review of Final Printed Labeling document at http://www.fda.gov/cdrh/pmat/pilotpmat.html for further details.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

We are interested in continuing to improve the Real-Time PMA Program. If you have any suggestions for how we can modify it, please send a facsimile to Bonnie Markovitz at (301) 827-2930 or an electronic message to her at BAM@CDRH.FDA.GOV at CDRH.

If you have questions concerning this approval order, please contact James Lee at (301) 443-8609 ext-168.

Sincerely yours,

James E. Dillard III
Director
Division of Cardiovascular
and Respiratory Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

cc: HFZ-544 (Postmarket Surveillance Branch if appropriate)
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ- [ODE Division]
HFZ-100 (OST Reviewer - if appropriate)
D.O.

APPROVAL ORDER FOR A PMA SUPPLEMENT (SA) Modified 9-24-99
NOTE. ENCLOSURE - INCLUDE THE CONDITIONS

Prepared by:JLee:att/6/14/01

FILE COPY FACTS search 6/15/01 indicates the firm is ACCEPTABLE M. Parker

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450	JLee	6/14	HFZ402	M. Parker	6/15/01			
450	Jerry for Provost	6/14/01						
450	[illegible]	6/14/01						

43

JUN 11 2001

Ms. Jacque L. Keller
Product Regulation Manager
Cardiac Rhythm Management
Medtronic, Inc.
7000 Central Avenue N.E.
Minneapolis, MN 55432

Re: P920015/S021
Model 6996 SQ Lead system and 6996T tunneling tool
Filed: February 5, 2001
Amended: April 11, 2001

Dear Ms. Keller:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for the Model 6996 SQ Lead system and the 6996T tunneling tool. The Model 6996 SQ Lead system is for single, long-term subcutaneous use and is intended for use in patients in which implantable cardioverter defibrillators (ICD) are indicated. The lead is intended for use if a standard ICD system with one or two transvenous leads has not been efficacious in providing acceptable DFT measurements. The Model 6996 SQ lead is intended for use only with the following systems: a Medtronic ICD featuring a connector block with at least two DF-1 connector ports; and a Medtronic right ventricular lead for defibrillating/pacing/sensing. In addition, a third defibrillation lead, such as any Medtronic SVC lead, may be used with a lead adaptor. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval For Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the

labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act. You are reminded that as soon as possible and before commercial distribution of your device you must submit an amendment to this PMA with copies of all approved labeling in final form. As part of our reengineering effort, the Office of Device Evaluation is piloting a new process for review of final printed labeling. The labeling will not routinely be reviewed by FDA staff when PMA supplement applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment. Please see the CDRH Pilot for Review of Final Printed Labeling document at http://www.fda.gov/cdrh/pmat/pilotpmat.html for further details.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

If you have questions concerning this approval order, please contact James Lee at (301) 443-8609 ext-168.

Sincerely yours,

James E. Dillard III
Director
Division of Cardiovascular
and Respiratory Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES

cc: HFZ-300 (Field Programs Branch - QSR)
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 (DCRD)
HFZ-100 (OST Reviewer - if appropriate)
D.O.

APPROVAL ORDER FOR A PMA SUPPLEMENT (SA) Modified 9-24-99
NOTE. ENCLOSURE - INCLUDE THE CONDITIONS OF APPROVAL.

Prepared by:JLee:att/5/15/01

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450	[illegible]	5/15	450	[illegible]	6/8/01			
450	for MVP / Cu	5/31	402	M. [illegible]	6/11/01			
450	Provost	6/6/01						

FACTS search 6/11/01 indicates all facilities acceptable [illegible]

U.S. GPO 1986-169-089

Ms. Jacque L. Keller
Product Regulation Manager
Cardiac Rhythm Management
Medtronic, Inc.
4000 Lexington Avenue North
Shoreview, MN 55126-2983

FEB - 5 2001

Re: P920015/S20
Medtronic Model 6725 Pin-plug Kit
Filed: November 13, 2000

Dear Ms. Keller:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement which qualified for review under the Real-Time Review Program. A meeting was not necessary to make a decision regarding this supplement.

Your supplement requested approval for the Medtronic Model 6725 Pin-plug Kit. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the Federal Food, Drug, and Cosmetic Act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA supplement submission with copies of all approved labeling in final printed form. As part of our reengineering effort, the Office of Device Evaluation is piloting a new process for review of final printed labeling. The labeling will not routinely be reviewed by FDA staff when PMA applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment. Please see the CDRH Pilot for Review of Final Printed Labeling document at http://www.fda.gov/cdrh/pmat/pilotpmat.html for further details.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

We are interested in continuing to improve the Real-Time PMA Program. If you have any suggestions for how we can modify it, please send a facsimile to Bonnie Markovitz at (301) 827-2930 or an electronic message to her at BAM@CDRH.FDA.GOV at CDRH.

If you have questions concerning this approval order, please contact Doris Terry at (301) 443-8609 ext-160.

Sincerely yours,

James E. Dillard III
Director
Division of Cardiovascular and
Respiratory Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

cc: HFZ-544 (Postmarket Surveillance Branch if appropriate)
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 (DCRD)
HFZ-100 (OST Reviewer - if appropriate)
D.O.

APPROVAL ORDER FOR A PMA SUPPLEMENT (SA) Modified 9-24-99
NOTE. ENCLOSURE - INCLUDE THE CONDITIONS OF APPROVAL.

Prepared by:DTerry:att/1/25/01
Final:att/1/25/01

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450		1/24/01	HFZ402	M. Parker	2/5/01			
450		2/5/01						
2-450	S. Rhodes	2/5/01						

FACTS search 2/5/01 indicates firm is ACCEPTABLE M. Parker

U.S. GPO 1986-169-089

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Ms. Jacque L. Keller
Product Regulation Manager
Cardiac Rhythm Management
Medtronic, Inc.
4000 Lexington Avenue North
Shoreview, MN 55126-2983

FEB - 5 2001

Re: P920015/S20
Medtronic Model 6725 Pin-plug Kit
Filed: November 13, 2000

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Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

We are interested in continuing to improve the Real-Time PMA Program. If you have any suggestions for how we can modify it, please send a facsimile to Bonnie Markovitz at (301) 827-2930 or an electronic message to her at BAM@CDRH.FDA.GOV at CDRH.

If you have questions concerning this approval order, please contact Doris Terry at (301) 443-8609 ext-160.

Sincerely yours,

for James E. Dillard III
Director
Division of Cardiovascular and
Respiratory Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

December 22, 2000

MARY ELLEN BEST
MEDTRONIC, INC.
7000 CENTRAL AVENUE, N.E.
MINNEAPOLIS, MN 55432

Dear MS. BEST:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) acknowledges receipt of your PMA AMENDMENT. This PMA AMENDMENT has been assigned the following unique document control number. Failure to reference this assigned number in future correspondence may result in processing delays.

PMA Number: P920015/S017/A004
Dated: 21-DEC-2000
Received: 22-DEC-2000
Device: SPRINT QUATTRO MODEL 6944 LEAD

Any questions concerning this submission should be directed to the undersigned at (301)594-1184. All future correspondence regarding this PMA should be identified with the PMA number assigned above and should be submitted with the required number of copies to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

Sincerely yours,

Janet L. Donelson
Assistant Director for Program Operations
Division of Cardiovascular and
Respiratory Devices

Office of Device Evaluation
Center for Devices and
Radiological Health

DEC 15 '0

Ms. Mary Ellen Best
Regulatory Affairs Manager
Cardiac Rhythm Management
Medtronic, Inc.
7000 Central Ave. N.E.
Minneapolis, MN 55432

Re: P920015/S17
Medtronic® Sprint™ Quattro™ Model 6944 Lead
Filed: June 20, 2000
Amended: July 24, October 26, and November 2, 2000

Dear Ms. Best:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for the Medtronic® Sprint™ Quattro™ Model 6944 Lead. The device, as modified, will be marketed under the trade name Medtronic® Sprint™ Quattro™ Model 6944 Lead and is intended for single long-term use in the right ventricle. This lead has application for patients in which implantable cardioverter defibrillators are indicated. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Expiration dating for this device has been established and approved at two years.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that as soon as possible and before commercial distribution of your device you must submit an amendment to this PMA with copies of all approved labeling in final form. As part of our reengineering effort, the Office of Device Evaluation is piloting a new process for review of final printed labeling. The labeling will not routinely be reviewed by FDA staff when PMA supplement applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment. Please see the CDRH Pilot for Review of Final Printed Labeling document at http://www.fda.gov/cdrh/pmat/pilotpmat.html for further details.

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PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

If you have questions concerning this approval order, please contact Charles S.C. Ho, Ph.D., at (301) 443-8609 X 144.

Sincerely yours,

James E. Dillard III
Director
Division of Cardiovascular and
Respiratory Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Page 3 - Ms. Mary Ellen Best

cc: HFZ-300 (Field Programs Branch - QSR)
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 (DCRD)
D.O.

APPROVAL ORDER FOR A PMA SUPPLEMENT (SA) Modified 9-24-99
NOTE. ENCLOSURE - INCLUDE the Conditions of Approval for Implantable Defibrillators and Programmers.

Prepared by:CHo:att/12/15/00

FILE COPY

GMP profile acceptable per FHOTS database
check on 12/15/00 [illegible]

51

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450	HO	Dec 15 2000	450	[illegible]	12/15			
450	KURTZMAN	12/15/00	2402	[illegible]	12/15/00			
450	[illegible]	12/15/00						

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

DEC 15 2000

Ms. Mary Ellen Best
Regulatory Affairs Manager
Cardiac Rhythm Management
Medtronic, Inc.
7000 Central Ave. N.E.
Minneapolis, MN 55432

Re: P920015/S17
Medtronic® Sprint™ Quattro™ Model 6944 Lead
Filed: June 20, 2000
Amended: July 24, October 26, and November 2, 2000

Dear Ms. Best:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for the Medtronic® Sprint™ Quattro™ Model 6944 Lead. The device, as modified, will be marketed under the trade name Medtronic® Sprint™ Quattro™ Model 6944 Lead and is intended for single long-term use in the right ventricle. This lead has application for patients in which implantable cardioverter defibrillators are indicated. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

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Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

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Sincerely yours,

James E. Dillard III
Director
Division of Cardiovascular and
Respiratory Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Dennis H. Connolly, M.D.
Senior Product Regulation Manager
Tachyarrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432-3576

SEP - 7 2000

Re: P920015/S19
Medtronic Model 6937A SVC/CS Transvene® Lead
Filed: August 29, 2000

Dear Dr. Connolly:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) acknowledges your August 28, 2000, letter withdrawing the referenced premarket approval application (PMA) SUPPLEMENT. As requested, this file is now considered closed.

Pursuant to 21 CFR 20.29, a copy of each submission will remain on file with the Center for Devices and Radiological Health. Confidentiality of your PMA application will be maintained in accordance with the provision outlined in 21 CFR sections 814.9, 20.61 and 20.81.

If you decide to resubmit a PMA SUPPLEMENT for this product, a new number will be assigned and the 180-day period will begin again. Please be advised that if there were issues of safety and effectiveness raised by FDA which were not addressed in the submission you withdrew, you should address them in your resubmission.

Questions concerning this withdrawal action should be directed to:

Food and Drug Administration
Center for Devices and Radiological Health
Premarket Approval Section (HFZ-402)
9200 Corporate Boulevard
Rockville, Maryland 20850
(301) 594-2186

Sincerely yours,

James E. Dillard III
Director
Division of Cardiovascular and
Respiratory Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Page 3 - Dennis H. Connolly, M.D.

cc: HFZ-300 (Potential Export Issue)
HFZ-300 (Field Programs Branch - QSR)
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 (DCRD)
D.O.

PMA VOLUNTARY WITHDRAWAL ACKNOWLEDGMENT LETTER (WACKVOL)
Modified 1-5-97

Prepared by: [redacted]att/9/1/00
Final:att/9/1/00

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFZ 450	WEIZENBAUM	9/1/00						
450	HAWKEY	9/6/00						
HFZ402	M. Park	9/7/00						

56

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

SEP - 7 2000

Dennis H. Connolly, M.D.
Senior Product Regulation Manager
Tachyarrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432-3576

Re: P920015/S19
Medtronic Model 6937A SVC/CS Transvene® Lead
Filed: August 29, 2000

Dear Dr. Connolly:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) acknowledges your August 28, 2000, letter withdrawing the referenced premarket approval application (PMA) SUPPLEMENT. As requested, this file is now considered closed.

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57

Questions concerning this withdrawal action should be directed to:

Food and Drug Administration
Center for Devices and Radiological Health
Premarket Approval Section (HFZ-402)
9200 Corporate Boulevard
Rockville, Maryland 20850
(301) 594-2186

Sincerely yours,

James E. Dillard III
Director
Division of Cardiovascular and
Respiratory Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

August 29, 2000

DENNIS H. CONNOLLY, MD, RAC
MEDTRONIC, INC.
RICE CREEK CENTER
7000 CENTRAL AVE. NE
MINNEAPOLIS, MN 55432

Dear MR. CONNOLLY, MD, RAC:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) acknowledges receipt of your PMA AMENDMENT. This PMA AMENDMENT has been assigned the following unique document control number. Failure to reference this assigned number in future correspondence may result in processing delays.

PMA Number: P920015/S019/A001
Dated: 28-AUG-2000
Received: 29-AUG-2000
Device: SUPERIOR VENA CAVA (SVC)/CORONARY SINUS (CS

Any questions concerning this submission should be directed to the undersigned at (301)594-1184. All future correspondence regarding this PMA should be identified with the PMA number assigned above and should be submitted with the required number of copies to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

Sincerely yours,

Janet L. Donelson
Assistant Director for Program Operations
Division of Cardiovascular and
Respiratory Devices

Office of Device Evaluation
Center for Devices and
Radiological Health

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

June 22, 2000

DENNIS H. CONNOLLY, MD, RAC
MEDTRONIC, INC.
RICE CREEK CENTER
7000 CENTRAL AVE. NE
MINNEAPOLIS, MN 55432

Dear MR. CONNOLLY, MD, RAC:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) acknowledges receipt of your PMA SUPPLEMENT. This PMA SUPPLEMENT has been assigned the following unique document control number. Failure to reference this assigned number in future correspondence may result in processing delays.

PMA Number: P920015/S019
Dated: 21-JUN-2000
Received: 22-JUN-2000
Device: SUPERIOR VENA CAVA (SVC)/CORONARY SINUS (CS

Any questions concerning this submission should be directed to the undersigned at (301)594-1184. All future correspondence regarding this PMA should be identified with the PMA number assigned above and should be submitted with the required number of copies to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

Sincerely yours,

-S-

Janet L. Donelson
Assistant Director for Program Operations
Division of Cardiovascular and
Respiratory Devices

Office of Device Evaluation
Center for Devices and
Radiological Health

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

March 22, 2000

MEDTRONIC, INC.
7000 CENTRAL AVENUE, N.E.
MINNEAPOLIS, MN 55432

Dear Sirs:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) acknowledges receipt of your PMA REPORT. This PMA REPORT has been assigned the following unique document control number. Failure to reference this assigned number in future correspondence may result in processing delays.

PMA Number: P920015/R006
Dated: 21-MAR-2000
Received: 22-MAR-2000
Device: MEDTRONIC(R) TRANSVENE LEAD SYSTEM

Any questions concerning this submission should be directed to the undersigned at (301)594-1184. All future correspondence regarding this PMA should be identified with the PMA number assigned above and should be submitted with the required number of copies to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

Sincerely yours,

Janet L. Donelson
Assistant Director for Program Operations
Division of Cardiovascular,
Respiratory, and Neurological
Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

4

POSTMARKET

INSPECTION

P920015/S-15

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

JUN - 1 1999

DATE:

FROM: PMA Postmarket Coordinator, FPB,
DPO, OC, CDRH, (HFZ-306)

SUBJECT: **POSTMARKET INSPECTION REQUEST**

TO: District Director, SJN-DO, HFR-SE500

NAI 11/24/99

PMA NOs.: P920015/S15

DEVICE NAME: Medtronic Sprint Model 6943 and 6945 Leads

APPLICANT: Medtronic, Inc.
7000 Central Avenue, NE
Minneapolis, MN 55432

MANUFACTURER(s): Medtronic Puerto Rico, Inc. - **CFN# 2182208**
Call Box 6001, Villalba West Industrial Area
State Road 149, Km. 56.3
Villalba, Puerto Rico 00766
(7/28/98 Previous EI)

A Premarket Approval application was approved on **November 23, 1998,** for the above referenced product. In accordance with C.P. 7383.001 Medical Device Premarket Approval and Postmarket Inspections, the postmarket PMA inspection of the manufacturer(s) and/or sterilizer(s) must be scheduled within eight to twelve months following the application approval date which would be between **July and November 1999.**

During the postmarket inspection, emphasis should be placed upon examining any changes the firm may have made in the design, manufacturing process, and/or quality assurance systems relative to the PMA device or the manufacturing process. The postmarket inspection should also confirm that commitments made by the firm at the time the application was approved have been completed or are underway in accordance with those commitments. Attachment B of the Compliance Program provides detailed guidance for conducting the inspection.

Attached is a Notification of Postmarket Inspection Form which should be returned by facsimile to me by July 99, with the planned inspection date. Upon receipt of this form, and approximately 30 days before the expected start date of the inspection, I will send copies of all the cover letters for any PMA Supplements submitted by the firm since this PMA Supplement was approved. Remember, in accordance with C.P. 7383.001 Part II, Page 3, the District must query the CDRH MDR system before initiating a postmarket inspection to determine if MDR reports have been submitted for the PMA approved device.

2

I have attached a PMA Supplement Report although no new supplements have been submitted since S15. Query of the Maude MDR Database resulted in no MDRs for the product code LWS since the last inspection.

Please report the inspectional time to PAC 83001**A** - Medical Device Premarket Approval and Postmarket Inspections - C.P. 7383.001. If the District Decision results in an OAI classification, please forward the EIR to HFZ-306 as stated in the C.P. and mark the coversheet "**PMA POSTMARKET INSPECTION**". In addition, if your District issues a Warning Letter to the firm as a result of the OAI classification, please add HFZ-306 A. Sheapp to the distribution list and forward a copy to this office.

Following the inspection for data tracking purposes, please fill out the requested postmarket inspection data listed on the Notification of Postmarket Inspection Form. Please FAX the completed form to me with a copy of the EIR coversheets with endorsement and FDA 483, if issued.

The following reporting data is provided for your information. If you need any further information, please do not hesitate to contact me.

Product Code: 74 LWS
PAC: 83001**A**
Priority: Routine
Est. Comp. Time: 30 Hours

Contact:

Ann Sheapp
2098 Gaither Road
Rockville, Maryland 20850
Phone: 301-594-4695
FAX: 301-594-4715

Ann L. Sheapp

Attachments

P920015/S15 - Leads - Models 6943 and 6945

10/13/98- PMA recd & assigned to DOE III, Due 10/28/98.
10/21/98- PMA Review recd from DOE III.
11/10/98- GMP Check Memo sent to SJN, Due 11/23/98.
11/12/98- Response to GMP Check recd from SJN.
11/19/98- Clearance & final approval memo sent to ODE.

POSTMARKET

INSPECTION

P830061 /S28

P850089/S39
P890003/S55
P920015/S14
P930039/S6
P950024/S1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

MAR 30 1999

DATE:

FROM: PMA Postmarket Coordinator, FPB,
DPO, OC, CDRH, (HFZ-306)

SUBJECT: **POSTMARKET INSPECTION REQUEST**

TO: Director Director, SJN-DO, HFR-SE500

PMA NUMBERS: P830061/S28
P850089/S39
P890003/S55
P920015/S14
P930039/S6
P950024/S1

DEVICE NAME: CardiVentus Defibrillators and Pacing Leads

APPLICANT: Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432

11/24/99
NAT

MANUFACTURER(S): Medtronic Puerto Rico, Inc. -CFN# 2649622
Villalba West Industrial Area
Road 149, Km. 56.3, Call Box 6001
Villalba, PR 00766
(7/23/98 Previous EI)

A Premarket Approval application was approved on **August 12th, 1998,** for the above referenced products. In accordance with C.P. 7383.001 Medical Device Premarket Approval and Postmarket Inspections, the postmarket PMA inspection of the manufacturer(s) and/or sterilizer(s) must be scheduled within eight to twelve months following the application approval date which would be between **April and August 1999.**

During the postmarket inspection, emphasis should be placed upon examining any changes the firm may have made in the design, manufacturing process, and/or quality assurance systems relative to the PMA devices or the manufacturing process. The postmarket inspection should also confirm that commitments made by the firm at the time these applications were approved have been completed or are underway in accordance with those commitments. Attachment B of the Compliance Program provides detailed guidance for conducting the inspection.

Attached is a Notification of Postmarket Inspection Form which should be returned by facsimile to me by May 12 99, with the planned inspection date. Upon receipt of this form, and approximately 30 days before the expected start date of the inspection, I will send copies of all the cover letters for any PMA Supplements submitted by the firm since these PMA Supplements were approved. Remember, in accordance with C.P. 7383.001 Part II, Page 3, the District must query the CDRH MDR system before initiating a postmarket inspection to determine if MDR reports have been submitted for the PMA approved devices.

2

I have attached six PMA Supplement Summary Reports. Query of the CDRH database resulted in no MDR Summary Reports at this time.

Please report the inspectional time to PAC 83001A - Medical Device Premarket Approval and Postmarket Inspections - C.P. 7383.001. If the District Decision results in an OAI classification, please forward the EIR to HFZ-306 as stated in the C.P. and mark the coversheet "**PMA POSTMARKET INSPECTION**". In addition, if your District issues a Warning Letter to the firm as a result of the OAI classification, please add HFZ-306 A. Sheapp to the distribution list and forward a copy to this office.

Following the inspection for data tracking purposes, please fill out the requested postmarket inspection data listed on the Notification of Postmarket Inspection Form. Please FAX the completed form to me with a copy of the EIR coversheets with endorsement and FDA 483, if issued.

The following reporting data is provided for your information. If you need any further information, please do not hesitate to contact me.

Product Codes: DTB; LWS; DXY 74 Cardiovascular
PAC: 83001A
Priority: Routine
Est. Comp. Time: 30 Hours

Contact: Ann Sheapp
2098 Gaither Road
Rockville, Maryland 20850
Phone: 301-594-4695
FAX: 301-594-4715

Ann Sheapp

Ann L. Sheapp

Attachments

Mr. Robert McNamer
Senior Product Regulation Manager
Cardiac Rhythm Management, MS T276
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432

Re: P920015/S16
Medtronic® Sprint™ Lead Models 6932, 6937, 6942, 6943 and 6945
Filed: August 12, 1999

Dear Mr. McNamer:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for adding a caution label to the Medtronic® Sprint™ Lead Models 6932, 6937, 6942, 6943 and 6945. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may continue production and commercial distribution of the device as modified by your PMA supplement.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the Federal Food, Drug, and Cosmetic Act.

You are reminded that as soon as possible and before commercial distribution of your device you must submit an amendment to this PMA with copies of all approved labeling in final form. As part of our reengineering effort, the Office of Device Evaluation is piloting a new process for review of final printed labeling. The labeling will

not routinely be reviewed by FDA staff when PMA supplement applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment. Please see the CDRH Pilot for Review of Final Printed Labeling document at http://www.fda.gov/cdrh/pmat/pilotpmat.html for further details.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

Under section 519(e) of the act (as amended by the Safe Medical Devices Act in 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of device user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonably likely to have serious adverse consequences.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR § 821.20(b) and the devices that FDA has designated for tracking at 21 CFR § 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705-10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)).

If you have questions concerning this approval order, please contact Doris Terry at (301) 443-8609 ext. 160.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Director
Division of Cardiovascular,
Respiratory and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

cc: HFZ-300 (Field Programs Branch - GMP)
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 [ODE Division]
HFZ-100 (OST Reviewer - if appropriate)
D.O.
APPROVAL ORDER FOR A PMA SUPPLEMENT (SA) Modified 11-19-98
NOTE. ENCLOSURE - INCLUDE THE CONDITIONS OF APPROVAL.

Preparedby:dTerry:myb:09/23/99

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450		9/23/99						
450		9/23						
2462		9/24/99						

U.S. GPO 1986-169-089

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

SEP 24 1999

Mr. Robert McNamer
Senior Product Regulation Manager
Cardiac Rhythm Management, MS T276
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432

Re: P920015/S16
Medtronic® Sprint™ Lead Models 6932, 6937, 6942, 6943 and 6945
Filed: August 12, 1999

Dear Mr. McNamer:

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Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the Federal Food, Drug, and Cosmetic Act.

You are reminded that as soon as possible and before commercial distribution of your device you must submit an amendment to this PMA with copies of all approved labeling in final form. As part of our reengineering effort, the Office of Device Evaluation is piloting a new process for review of final printed labeling. The labeling will

not routinely be reviewed by FDA staff when PMA supplement applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment. Please see the CDRH Pilot for Review of Final Printed Labeling document at http://www.fda.gov/cdrh/pmat/pilotpmat.html for further details.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

Under section 519(e) of the act (as amended by the Safe Medical Devices Act in 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of device user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonably likely to have serious adverse consequences.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR § 821.20(b) and the devices that FDA has designated for tracking at 21 CFR § 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705-10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)).

If you have questions concerning this approval order, please contact Doris Terry at (301) 443-8609 ext. 160.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Director
Division of Cardiovascular,
Respiratory and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

August 15, 1999

ROBERT MC NAMER
MEDTRONIC, INC.
7000 CENTRAL AVENUE, N.E.
MINNEAPOLIS, MN 55432

Dear MR. MC NAMER:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) acknowledges receipt of your PMA SUPPLEMENT. This PMA SUPPLEMENT has been assigned the following unique document control number. Failure to reference this assigned number in future correspondence may result in processing delays.

PMA Number: P920015/S016
Dated: 11-AUG-1999
Received: 12-AUG-1999
Device: MEDTRONIC SPRINT FAMILY OF TRANSVENOUS DEFI

Any questions concerning this submission should be directed to the undersigned at (301)443-8320. All future correspondence regarding this PMA should be identified with the PMA number assigned above and should be submitted with the required number of copies to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

Sincerely yours,

for Janet L. Donelson
Assistant Director for Program Operations
Division of Cardiovascular,
Respiratory, and Neurological
Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

PREMARKET

INSPECTION

P920015/S15

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20850

M E M O R A N D U M

DATE: November 19, 1998

FROM: Field Programs Branch, CDRH, HFZ-306

SUBJECT: **CLEARANCE and FINAL APPROVAL**
PMA P920015/S15

TO: Premarket Approval Coordinator
HFZ-402

Mfr.: Medtronic Puerto Rico Inc.
Villalba West Industrial Area
Villalba, PR 00766

Applicant: Medtronic Inc.
7000 Central Avenue, NE
Minneapolis, MN 55432

(b)(5)

(b)(5)

Product: Sprint Leads Models 6943
and 6945

An inspection of the above referenced manufacturer was accomplished on 7/23/98.

On the basis of the information reviewed, the firm has an acceptable GMP program.

Also, The San Juan District office and OC concurs with the final approval of this PMA Supplement.

This should complete all of the sites awaiting inspection that are currently outstanding concerning this PMA.

Vertleen Covington

cc:
HFZ-306
HFA-224
DOE III
HFR-SE500
#99-3

Same site
This Postmarket Request
(approved 11/23/98) should be
ready within next week

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20850

MEMORANDUM

DATE: November 10, 1998

FROM: Vertleen Covington, Field Programs Branch, DPO
OC/CDRH, HFZ-306, 301-594-4695

SUBJECT: **REQUEST FOR PMA PREAPPROVAL INSPECTION CHECK**
P920015/S15

Mfr.: Medtronic Puerto Rico, Inc.
Villalba West Industrial Area
Villalba, PR 00766

TO: District Director
SJN-DO, HFR-SE500

CFN#: 2649622

Applicant: Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55440

Product: Sprint Leads Models 6943 & 6945

On 7/23/98, your office completed a GMP inspection at the manufacturer site and found this facility to have an acceptable GMP program. GSP, MTL, and PRF were covered during that inspection.

1. Based on the 7/23/98 inspection, could a recommendation of approval be submitted for the above reference PMA.

[X] CONCUR [ ] NOT CONCUR

2. If not, please state the reason (use an additional sheet if necessary).

3. If it is not approvable, will it be re-inspected? [ ] Yes [ ] No

4. If yes, when is the inspection planned? Date: _____

5. If no, please state the reason (use an additional sheet if necessary).

==> **TO RESPOND, PLEASE FAX** (do NOT send via the FDA electronic mail system) **THIS FORM BY CLOSE OF BUSINESS ON 11/23/98, TO VERTLEEN COVINGTON AT 301-594-4715.**

This response must be signed by the District Director or authorized designee.

Date: 11/12/98

Yvonne E. Ayala
District Director or PMA's Coordinator

3

PMA REVIEW

DATE:	October 21, 1998
FROM:	CSO, Cardiovascular and Neurological Devices Branch, HFZ-341, DOE III, OC
THROUGH:	Chief, Cardiovascular Branch and Neurological Devices Branch, HFZ-341, DOE III, OC EWS 10/22/98
TO:	Vertleen J. Covington, PMA Coordinator, Field Programs Branch, HFZ-306, OC
SUBJECT:	Review of PMA P920015/S15, dated September 25, 1998
	Applicant: Medtronic, Inc. 7000 Central Avenue, N.E. Minneapolis, MN 55440
	Mfr. Site: Medtronic Puerto Rico, Inc. Villalba West Industrial Area Villalba, Puerto Rico 00766
	CFN: 2649622
DEVICE:	Sprint Leads Models 6943 and 6945
CVDNB RECOMMEN-DATION:	Clearance

The purpose of this PMA supplement P920016/S15 is to change the current manufacturing site from Medtronic's Minneapolis location to the Medtronic facility in Puerto Rico. The Sprint leads models 6943 and 6945 will be manufactured at the new facility. These are active fixation leads (screw-in), endocardial, steroid-eluting, pacing, sensing, and cardioversion/defibrillation leads which are intended to be used as part of an implantable tachyarrhythmia cardioversion/defibrillation (ICD) system. The models 6943 and 6945 leads consist of silicone multi-lumen tubing that separates two PTFE-coated conductor cables and a tip-conductor coil.

The CVNDB review of the PMA submission indicates from the data provided that it appears that no changes will be made to the existing manufacturing procedures other than the relocation to the new site.

The Puerto Rico facility was last inspected on July 30, 1998, and no FDA 483 was issued. The purpose of this investigation was in response to the firm's PMA supplement to move the Sprint leads models 6932 and 6942 and the CapSureFix, model 6940 active fixation leads from the Minneapolis facility to this same Puerto Rico facility. These devices are also very similar in nature. No deficiencies were found at the facility and it appeared that the installation qualifications and necessary process verifications and validations were adequate. The inspection, therefore, was classified NAI. Since the last inspection was less than three months ago, and the change to another site is similar, plus the devices are very similar, it is the recommendation of the CVNDB that this site be cleared.

Mary Ann Fitzgerald

Reviewed/final:MAFitzgerald:10-21-98

cc:
HFZ-340
HFZ-341

OC Track: 76620

Medtronic

Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432-3576 USA
www.medtronic.com

August 11, 1999

Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Dr.
Rockville MD 20850

Re: **Special PMA Supplement - Changes Being Effected**
P920015

Dear Sir/Madam:

Enclosed is a **Special PMA Supplement** for the Medtronic Sprint family of transvenous defibrillation leads (P920015). The purpose of this special PMA Supplement is to add a caution to the package labels of the following lead models:

6932	6943
6937	6945
6942	

In recent in-house bench testing, it was found that by withdrawing the above listed lead models through a SafeSheath introducer. that damage may occur to the shock coil of the defibrillation lead. Although the SafeSheath brand was the only introducer specifically tested, Medtronic feels the results of the testing are applicable to any introducer that includes a hemostasis valve in its construction. It should be noted that Medtronic has not received any information from the field that any defibrillation leads have been pulled back through a hemostasis valve and been damaged. In good clinical practice, this may never occur, but Medtronic feels responsible to add a caution to our labeling based upon the results of in-house testing.

Furthermore, Medtronic wants to advise users to use a larger introducer size than what is currently recommended on the lead labeling when using an introducer that features a hemostasis valve. This is due to the tight fit of the lead passing through the hemostasis valve. It is not necessary to advise a specifically larger introducer size as even a half size larger introducer size than what the labeling recommends will be sufficient.

The text of the added caution would read:

> CAUTION: Inserting the lead using a lead introducer that features a hemostasis valve may require a larger introducer than the size recommended on the labeling. Do not withdraw the lead through a hemostasis valve to avoid distortion of the coil electrode.

Specific details of each affected lead's name, description, and intended use are provided in **ATTACHMENT A.** Samples of the package labels are provided in **ATTACHMENT B.**

Medtronic intends to implement this revision to the package labeling 30 days after this PMA Supplement has been filed.

This submission is provided in triplicate in accordance with 21 CFR Part 814. This submission contains confidential commercial or trade secret information and Medtronic requests that it be given maximum protection provided by the law. If additional information is required, please contact the undersigned.

Sincerely,
MEDTRONIC, INC.

Robert McNamer

Robert McNamer
Sr. Product Regulation Manager
Cardiac Rhythm Management, MS T276
7000 Central Ave. N.E.
Minneapolis MN 55432

phone: (612) 514-4458
fax: (612) 514-6424

MODEL 6932

Device Name: Medtronic Model 6932 Steroid Eluting, Tripolar, Endocardial, Tined, Ventricular Lead for Pacing, Sensing, Cardioversion, and Defibrillation.

Intended Use: This lead is intended for single, long-term use in the right ventricle.

Device Description: The model 6932 is a steroid eluting, tripolar, endocardial, tined, ventricular lead designed for pacing, sensing, and delivering cardioversion and defibrillation therapies. The distal tip contains a maximum of 1 mg of dexamethasone sodium phosphate. The lead also features tines near the distal tip. The three electrodes of the lead are: tip, ring, and coil.

- The tip electrode connects electrically to the connector pin of the IS-1 bipolar leg of the bifurcation. The IS-1 bipolar leg is the only one that will accept a stylet.
- The ring electrode connects electrically to the connector ring of one IS-1 bipoar leg of the bifurcation.
- The defibrillation coil electrode connects electrically to the connector pin of the DF-1 unipolar leg of the bifurcation. The DF-1 Unipolar leg will not accept a stylet.

Manufacturer: Medtronic, Inc.
Rice Creek Facility
7000 Central Ave. N.E.
Minneapolis MN 55432

- and -

Medtronic, Inc.
Medtronic Puerto Rico, Inc. (MPRI)
Villalba West Industrial Area
Villalba PR, Puerto Rico 00766

MODEL 6937

Device Name: Medtronic Model 6937 Unipolar, Endocardial, Superior Vena Cava Lead

Intended Use: This lead is intended for single, long-term use in the superior vena cava.

Device Description: The model 6937 is a unipolar, endocardial superior vena cava lead is designed for the delivery of cardioversion and defibrillation therapies. Silicone insulation surrounds the low resistance conductor coil and the coil electrode is a platinum alloy. The lead also has a DF-1 connector.

Manufacturer: Medtronic, Inc.
Rice Creek Facility
7000 Central Ave. N.E.
Minneapolis MN 55432

MODEL 6942

Device Name: Medtronic Model 6942 Steroid Eluting, Tined, Ventricular Lead with CapSure® SP Tip. and RV/SVC Electrode Coils

Intended Use: This lead is intended for single, long-term use in the right ventricle.

Device Description: The model 6942 is a steroid eluting, tined, ventricular lead designed for pacing, sensing, and delivering cardioversion and defibrillation therapies. The distal tip contains a maximum of 1 mg of dexamethasone sodium phosphate. The lead features tines near the electrode tip. The three electrodes of the lead are: tip, RV coil and SVC coil.

- The tip electrode connects electrically to the connector pin of the IS-1 bipolar leg of the trifurcation. The IS-1 bipolar leg is the only one that will accept a stylet.
- The RV electrode coil connects electrically to the connector pin of one DF-1 unipolar leg of the trifurcation. The RV electrode coil also connects electrically to the connector ring of the IS-1 bipolar leg of the trifurcation.
- The SVC electrode coil connects electrically to the connector pin of the other DF-1 unipolar leg of the trifurcation.

Manufacturer: Medtronic, Inc.
Rice Creek Facility
7000 Central Ave. N.E.
Minneapolis MN 55432

- and -

Medtronic, Inc.
Medtronic Puerto Rico, Inc. (MPRI)
Villalba West Industrial Area
Villalba PR, Puerto Rico 00766

MODEL 6943

Device Name: Medtronic Model 6943 Steroid Eluting, Screw-in, Ventricular Lead with CapSure® SP Tip, Ring Electrode, and RV Electrode Coil.

Intended Use: This lead is intended for single, long-term use in the right ventricle.

Device Description: The model 6943 is a steroid eluting, screw-in, ventricular lead designed for pacing, sensing, and delivering cardioversion and defibrillation therapies. The distal tip contains a maximum of 1 mg of dexamethasone sodium phosphate. The lead has a helical tip electrode made of platinum alloy that can be actively fixed in the endocardium. The helix can be extended or retracted by rotating the lead connector pin using a fixation tool. The three electrodes of the lead are: helix, ring, and coil.

- The helix electrode connects electrically to the connector pin of the IS-1 bipolar leg of the bifurcation. The IS-1 bipolar leg is the only one that will accept a stylet.
- The ring electrode coil connects electrically to the connector ring of one IS-1 bipolar leg of the bifurcation.
- The defibrillation coil electrode connects electrically to the connector pin of the DF-1 unipolar leg of the bifurcation. The DF-1 unipolar leg will not accept a stylet.

Manufacturer: Medtronic, Inc.
Rice Creek Facility
7000 Central Ave. N.E.
Minneapolis MN 55432

- and -

Medtronic Puerto Rico, Inc. (MPRI)
Villalba West Industrial Area
Villalba PR, Puerto Rico 00766

11

MODEL 6945

Device Name: Medtronic Model 6945 Steroid Eluting, Screw-in, Ventricular Lead with CapSure® SP Tip, and RV/SVC Electrode Coils.

Intended Use: This lead is intended for single, long-term use in the right ventricle.

Device Description: The model 6945 is a steroid eluting, screw-in, ventricular lead designed for pacing, sensing, and delivering cardioversion and defibrilation therapies. The distal tip contains a maximum of 1 mg of dexamethasone sodium phosphate. The lead has a helical tip electrode made of platinum alloy that can be actively fixed in the endocardium. The helix can be extended or retracted by rotating the lead connector pin using a fixation tool. The three electrodes of the lead are: helix, RV coil, and SVC coil.

- The helix electrode connects electrically to the connector pin of the IS-1 bipolar leg of the trifurcation. The IS-1 bipolar leg is the only one that will accept a stylet.
- The RV electrode coil connects electrically to the connector pin of one DF-1 unipolar leg of the trifurcation. The RV electrode coil also connects electrically to the connector ring of the IS-1 bipolar leg of the triifurcation. The DF-1 unipolar leg will not accept a stylet.
- The SVC electrode coil connects electrically to the connector pin of the other DF-1 unipolar leg of the trifurcation.

Manufacturer: Medtronic, Inc.
Rice Creek Facility
7000 Central Ave. N.E.
Minneapolis MN 55432

- and -

Medtronic Puerto Rico, Inc. (MPRI)
Villalba West Industrial Area
Villalba PR, Puerto Rico 00766

PREMARKET

INSPECTION

P830061/528 P920015/514

P850089/539 P930039/56

P890003/555 P950024/51

8/7/98 - PMA review recd from DOE III. Based on the information reviewed in the PMA submission and the most recent GMP inspection, which covered the referenced PMAs, DOE III recommends approval of the PMA submissions.

Clearance & final approval memo issued to ODE.

8/12/98 - EIR recd from SJN. The supplements were approved based on OA's review of the Mfg. Section and the firm's most recent GMP inspection which was Classified NAI. EIR assigned to DOE III for review, due 9-4-98.

8/25/98 - EIR review recd from DOE III. PMA Supplements were approved on 8/12/98 based on the NAI inspection

EXPEDITE - Medtronic P950024/S1

P830061/S18, P850089/S39, P890003/S55, P920015/S14, P930039/S6
Pacing leads

4/20/98- Medtronic sent a copy of the firm's Master Plan for a site change to FPB for review and feedback.

4/21/98- Master Plan assigned to DOE III, due to FPB 5-1-98. (The firm plans to submit the PMA Supplement in the near future).

5/13/98- DOE III Completed their review of the firm's qualification Plans for the site move. The firm will submit the qualification data after the move.
DOE III sent the firm a letter acknowledging the receipt of the submission and to let the firm know that their plans appear to be adequate.

7/22/98- PMA Supplement recd & assigned to DOE III for review. & due 8-5-98.

7/25/98- P930029/S12 initiated an inspection which included coverage of the above referenced PMA Supplements. The EI ended on 7/25/98 And Classified NAI. A recommendation will be forwarded to CDE to complete the Manufacturing Section Review for the above Supplements. (See Memo & recd from S.JN-DO dated 7/27/98 regarding the outcome of the EI).

3

3

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

MAY 13 1998

Ms. Vickie Pearson, RAC
Sr. Product Regulation Manager
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 554332-4000

Dear Ms. Pearson:

Your pre-PMA submission to request approval of a manufacturing site relocation at Medtronic Puerto Rico, Inc. in Villalba, PR, dated April 17, 1998, has been forwarded to our office for response.

We have reviewed your pre-PMA submission. You are correct that all of the equipment must receive installation qualification and your plan appears adequate.

You are incorrect, however, that your manufacturing processes do not need to be re-validated. If it was a process that initially required validation, a re-validation must be performed before distribution of products can occur. Your PMA supplement will need to include an evaluation of which processes will require validation, per 21 CFR 820.75. Your PMA supplement should also include either the plan or the actual procedures for the re-validation.

The San Juan district office will determine the adequacy of the re-validation effort at an establishment inspection at the new facility.

Sincerely yours,

Mary Ann Fitzgerald

Mary Ann Fitzgerald
Consumer Safety Officer
Cardiovascular and Neurological Devices Branch
Division of Enforcement III
Office of Compliance
Center for Devices and Radiological Health

4

Final:MAFitzgerald:5-12-98
Init:KABerthold:5-13-98
Review/comment:KATrautman:5-13-98
Final:MAFitzgerald:5-13-98

cc:
HFZ-306
HFR-SE550 (JBeckwith)
HFZ-340 (3)
HFZ-341 (3)

Track: 74341

Medtronic

Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432-3576 USA
Internet: www.medtronic.com
Telephone: (612) 514-4000

May 21, 1999

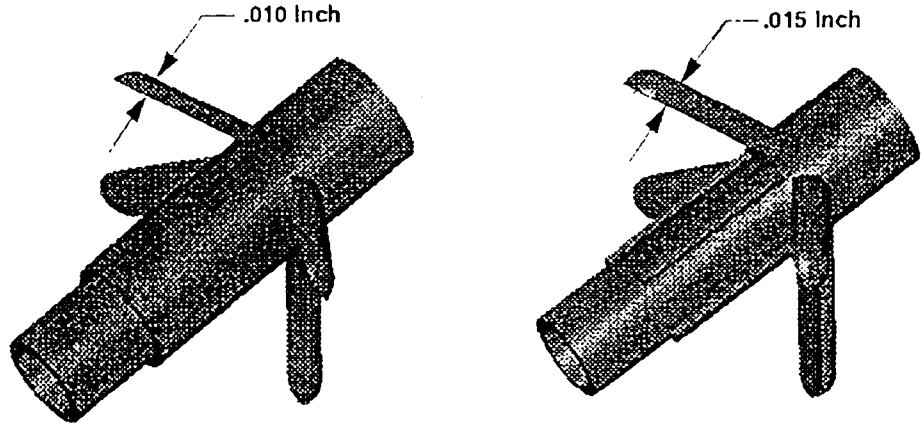
FDA/CDRH/ODE
Document Mail Center HFZ-401
9200 Corporate Boulevard
Rockville, Maryland 20850
FAX (301) 480-4204

RE: **REAL-TIME REVIEW**
PMA Supplement for a tine design change to the Medtronic® CapSure SP Novus Model 4092 (and Vitatron Excellence PS+ Model IMK49B)

- P830061
- Model 4092 (IMK49B), reference P830061/S27, approved 8/27/98

Medtronic requests approval to change the tine design on the Model 4092/IMK 49B to the design on the currently marketed CapSure SP Models 4023 and 4024 (ref. P830061/S10 and S12, approved 8/07/91 and 8/19/91, respectively). The differences in the tine design between the current 4092/IMK 49B and the Model 4023/4024 are demonstrated in the following table.

	Model 4092/IMK 49B	Model 4023/4024
Tine Material	(b)(4)	
Number of Tines	4	4
Tine Thickness	0.015" thick by 0.031" wide	0.010" thick by 0.031" wide
Tine Length	2.5 mm	2.5 mm
Geometry	Semi-cylindrical	Semi-cylindrical



Proposed Design **Current Design**

The figure above shows the proposed tine design change and the current Model 4092 tine design. The Model 4092/IMK 49B were originally designed with recessed areas behind the tines to attain a 7 French insertion size. This tine design is identical to the tine design of the unipolar CapSure Z Model 5033. The change to the 0.010" thick tines no longer necessitates the recessed areas to achieve the 7 French insertion size.

Since U.S. market release of the Model 4092/IMK49B, Medtronic has received comments from several key opinion leaders that they prefer the tine design of the original CapSure SP leads. This group of physicians report that the tines of the Model 4092/IMK 49B often catch on the vasculature and heart tissue making the lead more difficult to implant as compared to the CapSure SP Models 4023 and 4024. [In contrast, these same physicians prefer the atrial Model 4592 with the current stiffer tines to the original CapSure SP Models 4523 and 4524.] It is for this reason that Medtronic is requesting approval to change the tine design to that on the Models 4023 and 4024.

Manufacturing Site:

Medtronic Puerto Rico, Inc. (MPRI)
Villalbla
Puerto Rico, 22066
Establishment Registration Number: 2182208

Previous Similar Design Changes:

Reference P830061/S10 and S12, approved 8/07/91 and 8/19/91, respectively, for the Models 4023 and 4024. The Models 4023 and 4024 designs incorporate an identical tine design as that requested for the Model 4092/IMK 49B. The PMA supplements for the Model 4023 and 4024 were supported by canine data and clinical data on the silicone CapSure SP Models 5023/5523.

Since market release of the Model 4023, more than (b)(4) leads have been sold with an actuarial survival probability of 99.5% (± 1.1) at 30 months. Over (b)(4) Model 4024 leads have been sold with an actuarial survival probability of 99.9% (± 0.3) at 69 months.

Qualification Testing:

The proposed Model 4092 design change would result in a ventricular lead with the distal CapSure SP tip electrode and tine design identical to the Model 4023. The tip pressure and composite pull strength are unaffected by the tine design change. Therefore, no bench testing and/or clinical testing is required to support this design change. Furthermore, there is no labeling change required as a result of the tine design change.

Sincerely,

Vicki Pearson, RAC
Product Regulation Manager
Cardiac Pacing Business

(612) 514-3099
(612) 514-6424 FAX
victoria.pearson@medtronic.com

Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432-3576 USA
www.medtronic.com

tel 612.514.4000

June 22, 1999

Office of Device Evaluation
IDE Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

Re: Amendment to the PMA Supplement for the Medtronic Model 4092
FINAL PRINTED LABELING
PMA Number **P830061/S30**

The Model 4092 design change which was the subject of the above referenced PMA supplement did not result in any changes to the previously approved labeling. Therefore, we are requesting an exemption from the requirement to submit approved labeling in final form.

Sincerely,

MEDTRONIC, INC.

Vicki Pearson, RAC
Sr. Product Regulation Manager
Cardiac Rhythm Management
(612) 514-3099
(612) 514-6424 FAX
victoria.pearson@medtronic.com

FDA/CDRH/OSE/DAD
Jun 23 11:43 AM '99

Medtronic

Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432-3576 USA
www.medtronic.com

tel 612.514.4000

August 11, 1999

Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Dr.
Rockville MD 20850

12 AUG 99 12 04
FDA/CDRH/CDE/DMC

Re: **Special PMA Supplement - Changes Being Effected**
P920015

Dear Sir/Madam:

Enclosed is a **Special PMA Supplement** for the Medtronic Sprint family of transvenous defibrillation leads (P920015). The purpose of this special PMA Supplement is to add a caution to the package labels of the following lead models:

6932	6943
6937	6945
6942	

In recent in-house bench testing, it was found that by withdrawing the above listed lead models through a SafeSheath introducer, that damage may occur to the shock coil of the defibrillation lead. Although the SafeSheath brand was the only introducer specifically tested, Medtronic feels the results of the testing are applicable to any introducer that includes a hemostasis valve in its construction. It should be noted that Medtronic has not received any information from the field that any defibrillation leads have been pulled back through a hemostasis valve and been damaged. In good clinical practice, this may never occur, but Medtronic feels responsible to add a caution to our labeling based upon the results of in-house testing.

Furthermore, Medtronic wants to advise users to use a larger introducer size than what is currently recommended on the lead labeling when using an introducer that features a hemostasis valve. This is due to the tight fit of the lead passing through the hemostasis valve. It is not necessary to advise a specifically larger introducer size as even a half size larger introducer size than what the labeling recommends will be sufficient.

The text of the added caution would read:

> CAUTION: Inserting the lead using a lead introducer that features a hemostasis valve may require a larger introducer than the size recommended on the labeling. Do not withdraw the lead through a hemostasis valve to avoid distortion of the coil electrode.

Specific details of each affected lead's name, description, and intended use are provided in **ATTACHMENT A.** Samples of the package labels are provided in **ATTACHMENT B.**

Medtronic intends to implement this revision to the package labeling 30 days after this PMA Supplement has been filed.

This submission is provided in triplicate in accordance with 21 CFR Part 814. This submission contains confidential commercial or trade secret information and Medtronic requests that it be given maximum protection provided by the law. If additional information is required, please contact the undersigned.

Sincerely,
MEDTRONIC, INC.

Robert McNamer

Robert McNamer
Sr. Product Regulation Manager
Cardiac Rhythm Management, MS T276
7000 Central Ave. N.E.
Minneapolis MN 55432

phone: (612) 514-4458
fax: (612) 514-6424

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

March 11, 1999

MEDTRONIC, INC.
7000 CENTRAL AVENUE N.E.
MINNEAPOLIS, MN 55432

Dear Sirs:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) acknowledges receipt of your PMA REPORT. This PMA REPORT has been assigned the following unique document control number. Failure to reference this assigned number in future correspondence may result in processing delays.

PMA Number: P920015/R005
Dated: 10-MAR-1999
Received: 11-MAR-1999
Device: MEDTRONIC(R) TRANSVENE LEAD SYSTEM

Any questions concerning this submission should be directed to the undersigned at (301)443-8320. All future correspondence regarding this PMA should be identified with the PMA number assigned above and should be submitted with the required number of copies to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

Sincerely yours,

Janet L. Donelson
Assistant Director for Program Operations
Division of Cardiovascular,
Respiratory, and Neurological
Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

2

Ms. Jeanmarie Sales
Senior Product Regulation Manager
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

NOV 23 1998

Re: P920015/S15
Medtronic® Models 6943 and 6945 Leads
Filed: September 28, 1998

Dear Ms. Sales:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for a manufacturing and sterilization site located at Medtronic Puerto Rico, Inc., Villalba West Industrial Area, Villalba, Puerto Rico 00766. This supplement qualified for review under the PMA supplement pilot described in the March 20, 1996, Dear President or CEO letter regarding changes in manufacturing sites. This approval order applies to the specific request for a new manufacturing site only. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the Federal Food, Drug, and Cosmetic Act.

If you have questions concerning this approval order, please contact Mervin O. Parker, Jr. at (301) 594-2186.

Sincerely yours,

Philip J. Phillips
Deputy Director
Science and Regulatory Policy
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

[DO NOT SHOW ON ORIGINAL]

cc :
HFZ-306 (Field Programs)
HFZ-401 (DMC)
HFZ-402 (PMA Staff)
HFZ-450
D.O.

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFZ-402	M. Carlson	11/27/91						

☆ U.S. GOVERNMENT PRINTING OFFICE 1991-519-771

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Ms. Jeanmarie Sales
Senior Product Regulation Manager
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

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Medtronic® Models 6943 and 6945 Leads
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Sincerely yours,

Philip J. Phillips
Deputy Director
Science and Regulatory Policy
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

68

OCT - 2 1998

Ms. Jeanmarie Sales
Senior Product Regulation Manager
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S15
Medtronic® Models 6943 and 6945 Leads
Filed: September 28, 1998

Dear Ms. Sales:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) supplement which requests approval for the manufacturing and sterilization facility located at Medtronic Puerto Rico, Inc., Villalba West Industrial Area, Villalba, Puerto Rico 00766.

Your PMA supplement is approvable and will be placed on hold until CDRH's Office of Compliance determines the manufacturing and sterilization facility identified above is in compliance with the Good Manufacturing Practice (GMP) regulation (21 CFR 820). An approval order will promptly issue once this determination is made.

Where appropriate, amend the PMA to include any relevant information regarding the manufacturing facilities, methods or controls not previously submitted. If you have a manufacturing facility which is not prepared for production of the device, amend the PMA supplement as soon as possible and notify your District Office to indicate when the facility will be prepared to produce the device so that the FDA inspection can be scheduled. If you have any questions regarding the status of your GMP inspection, please contact your District Office or the Office of Compliance at (301) 594-4695.

You may not begin marketing of the device manufactured at your facility until your receipt of the approval order.

All amendments to the PMA supplement should be submitted in triplicate to the address below and reference the above PMA supplement number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions concerning this approvable letter, please contact Mervin O. Parker, Jr. at (301) 594-2186.

Sincerely yours,

Philip J. Phillips
Deputy Director, Science and
Regulatory Policy
Office of Device Evaluation
Center for Devices and
Radiological Health

cc:
HFZ-300 (Field Programs - GMP)
HFZ-401 (DMC)
HFZ-402 (PMA Staff)
HFZ-450
D.O.
APPROVABLE LETTER FOR A PMA SUPPLEMENT WHEN THE REQUEST IS FOR A SITE CHANGE ONLY - POS WILL DO FOR THE DIVISION'S AND WILL ALSO ISSUE THE APPROVAL ORDER WHEN CLEARANCE IS RECEIVED FROM OC Modified 3-1-97

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE

☆ U.S. GOVERNMENT PRINTING OFFICE 1991-519-771

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

OCT 2 1998

Ms. Jeanmarie Sales
Senior Product Regulation Manager
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S15
Medtronic® Models 6943 and 6945 Leads
Filed: September 28, 1998

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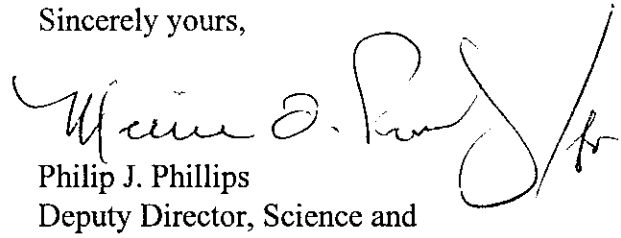
PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions concerning this approvable letter, please contact Mervin O. Parker, Jr. at (301) 594-2186.

Sincerely yours,



Philip J. Phillips
Deputy Director, Science and
Regulatory Policy
Office of Device Evaluation
Center for Devices and
Radiological Health

AUG 12 1998

Ms. Vicki Pearson, RAC
Sr. Product Regulation Manager
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, NE
Minneapolis, Minnesota 55432-3576

Re: P830061/S028
P850089/S039
P890003/S055
P920015/S014
P930039/S006
P950024/S001
Cardioventus Defibrillators and Pacing Leads
Filed: April 20, 1998

Dear Ms. Pearson:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplements, which requested approval for a manufacturing site located at Medtronic Puerto Rico, Inc. (MPRI), Road 149, Rm. 56.3, Villalba, Puerto Rico 00755. These supplements qualified for review under the PMA supplement pilot described in the March 20, 1996, Dear President or CEO letter regarding changes in manufacturing sites. This approval order applies to the specific request for a new manufacturing site only. Based upon the information submitted, the PMA supplements are approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the devices as modified by your PMA supplements upon receipt of this letter.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the Federal Food, Drug, and Cosmetic Act.

If you have questions concerning this approval order, please contact Mervin O. Parker, Jr. at (301) 594-2186.

Sincerely yours,

Philip J. Phillips
Deputy Director for
Science and Regulatory Policy
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

cc:
HFZ-306 (Field Programs Branch - GMP)
HFZ-401 (DMC)
HFZ-402 (PMA Staff)
HFZ-450
D.O.

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
	M. Parker	8/1/95						

* U.S. GOVERNMENT PRINTING OFFICE 1991-519-771

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Ms. Vicki Pearson, RAC
Sr. Product Regulation Manager
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, NE
Minneapolis, Minnesota 55432-3576

AUG 12 1998

Re: P830061/S028
P850089/S039
P890003/S055
P920015/S014
P930039/S006
P950024/S001
Cardioventus Defibrillators and Pacing Leads
Filed: April 20, 1998

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If you have questions concerning this approval order, please contact Mervin O. Parker, Jr. at (301) 594-2186.

Sincerely yours,

Philip J. Phillips
Deputy Director for
Science and Regulatory Policy
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

PREMARKET

INSPECTION

P920015/S11

P920015/S11

7/1/96 - PMA Supp. read & assigned to Jay L., due 7/17/96.
also a request for a 10-day check.
7/15 Jay returned w/approval recom
7/15 Sent 10-Day to STN
7/23/96 - Clearance & final approval memo issued to ODE.

7/1 Supplement was assigned for review. Due date: 7/17/96

Review did not reveal any GMP deviations **BUT** the component acceptance procedures were not in English. I drafted a memo recommending review by DOE III for issuance of deficiency letter for not submitting all procedures in English.

Marje signed off on my memo, but asked me to confirm the letter was in order for not submitting the procedures in English. Marje also said she did not object to my issuing the deficiency letter or contacting the firm (b)(5) (b)(5) (b)(5) (b)(5)

Allen said he thought a deficiency was in order, but since our regulatory environment has evolved in the last year I may want to confirm with Wes.

7/5 Wes agreed with Allen and I that the letter was in order, but since it was such a small part of the submission, he agreed that a call to the firm to request submission of the procedures in English was probably the best way to resolve the issue.

I left a voice mail for the submitter, Rachel Libi, Medtronic, Inc.

7/8 I talked with Rachel Libi (Medtronic was closed 7/5). She said that she would request an English translation from the San Juan site, but that it may take several days for her to receive it.

Rachel asked the best way to send me the information to review. I suggested that she FAX the information to me and send a hard copy to ODE as an amendment to the PMA supplement.

I will review the procedures once they are recieved.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20850

M E M O R A N D U M

DATE: July 24, 1996

FROM: Field Programs Branch, CDRH, **HFZ-306**

2649622

SUBJECT: **CLEARANCE and FINAL APPROVAL**
PMA P920015/S11

Mfr.: Medtronic Puerto Rico, Inc.
Villalba West Industrial Area
Villalba, PR 00766

TO: Premarket Approval Coordinator
HFZ-402

Applicant: Same as Above

Product: Medtronic Sprint (TM)
Model 6932 Lead

An inspection of the above referenced manufacturer was accomplished on 10-26-95.

On the basis of the information reviewed, the firm has an acceptable GMP program.

Attached, please find a copy of the district office's concurrence with final approval of this PMA Supplement.

This should complete all of the sites awaiting inspection that are currently outstanding concerning this PMA.

Vertleen Covington

Vertleen Covington

cc:
HFZ-306
HFA-224
#96-72

(b)(5)

(b)(5)

96-133

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20850

MEMORANDUM

DATE: July 15, 1996

FROM: Vertleen Covington, Field Programs Branch, DPO
OC/CDRH, HFZ-306, 301-594-4695

SUBJECT: PMA FINAL APPROVAL REQUEST
PMA P920015/S11

Mfr.: Medtronic Puerto Rico, Inc.
Villalba West Industrial Area
Villalba, PR 00766

TO: District Director
SJN-DO, HFR-SE500

Applicant: Same as above - CFN# 2649622

Product: Medtronic Sprint (TM)
Model 6932 Lead

The above Premarket Approval (PMA) application is now ready for final approval. In accordance with CP 7383.001 (Part II, pg. 2, transmittal #93-1, dated 10-5-92), we require the district's concurrence or non-concurrence for final approval. This is an opportunity for the district to report any current information which has changed the previous approvable status of the firm. THIS IS NOT A REQUEST FOR ANY ADDITIONAL INSPECTIONAL ACTIVITY AT THE FIRM.

On 10-26-95 your office completed an inspection regarding the above PMA. At that time, the facility was considered approvable for the PMA.

1. Is the facility still approvable? [X] CONCUR [ ] NOT CONCUR

2. If not, please state the reason (use an additional sheet if necessary).

3. If it is not approvable, will it be re-inspected? [ ] Yes [ ] No

4. If yes, when is the inspection planned? Date:_____

5. If no, please state the reason (use an additional sheet if necessary).

→ TO RESPOND, PLEASE FAX (do NOT send via the FDA electronic mail system) THIS FORM BY CLOSE OF BUSINESS ON 7-24-96 TO VERTLEEN COVINGTON AT 301-594-4715.

This response must be signed by the District Director or authorized designee.

Date: 7/22/96

Vicina Smalley for
District Director

5

DATE: July 15, 1996

FROM: Joy B. Lazaroff, Consumer Safety Officer
Field Programs Branch, DPO, OC

SUBJECT: PMA P920015 Supplement 011

APPLICANT: Medtronic, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432

DEVICE(S): *Medtronic ® Model 6932 Lead*

TO: Vertie Covington, Field Programs Branch, HFZ-306

THROUGH: Marje Hoban, Chief, FPB

FPB RECOMMENDATION: Approval

I have reviewed the PMA supplement from Medtronic, Inc. requesting approval of Medtronic Puerto Rico, Inc., as an alternate manufacturing facility for the subject device. The last device GMP inspection of the proposed site was a GMP inspection conducted 10/26/95, covering (b)(4) (b)(4) Fabrication; the firm was found acceptable for device GMPs and no 483 was issued.

Review of the PMA supplement and additional information submitted July 11, 1996, did not reveal any deviations with the requirements of the device GMP regulations.

FPB RECOMMENDATION: Approval

Joy B. Lazaroff

6

Ms. Vicki Pearson, RAC
Sr. Product Regulation Manager
Cardiac Pacing Business
Medtronic, Inc.
7000 Centeral Ave., NE
Minneapolis, MN 55432-3576

APR 22 1998

Re: P830061/S028
P850089/S039
P890003/S055
P920015/S014
P930039/S006
P950024/s001
Cardioventus Defibrilators, and Pacing Leads
Filed: April 20, 1998

Dear Ms. Pearson:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has received your premarket approval application (PMA) supplement which requests approval for the manufacturing facility located at Medtronic Puerto Rico, Inc., Road PR-149, km 56.3, Villalba, PR. The supplement will be processed in accordance with the PMA supplement pilot program for manufacturing and/or sterilization site changes described in the March 20, 1996 "Dear President or CEO" letter.

Your PMA supplement is approvable and will be placed on hold until CDRH's Office of Compliance finds the manufacturing facilities, methods and controls in compliance with the applicable requirements of the Quality System Regulation (21 CFR Part 820). The document, Guidance For Preparation of PMA Manufacturing Information, that you received earlier, is based on the original Good Manufacturing Practice (GMP) Regulation. That regulation was superseded by the Quality System Regulation, which became effective on June 1, 1997.

The guidance document is currently under revision to conform with the additional requirements for design control established by the Quality System Regulation. Until the new guidance is available, you are not required to describe the design controls used for the PMA device. During the PMA inspection, however, you may be asked to demonstrate that any design operations for the PMA device, conducted after June 1, 1997, are in compliance with the design control requirements of 21 CFR 820.30.

If you have not already done so, please notify CDRH as soon as possible in the form of an amendment to the PMA if there will be a delay in setting up your manufacturing facility for production of the device, and provide the expected date that the facility will be prepared for an FDA inspection. If you have any questions regarding the status of your Quality System inspection please contact the Office of Compliance at (301)-594-4695, or your District Office.

If necessary, amend the PMA supplement to include any relevant information not previously submitted.

Any amendment to this PMA supplement number above and should be submitted in duplicate to to the address below and reference the above PMA supplement number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

At the same time, please submit an identical copy to:

CDRH Office of Compliance
Field Programs Branch
2098 Gaither Road
Rockville, MD 20850

If you have any questions concerning this approvable letter, please contact Mr. Mervin Parker, Jr. at (301) 594-2186.

Sincerely yours,

Philip J. Phillips
Deputy Director
Office of Device Evaluation
Center for Devices and
Radiological Health

[DO NOT SHOW ON ORIGINAL]

cc:HFZ-300 (Field Programs Branch - GMP)
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ- [ODE DIVISION)
HFZ-100 (OST Reviewer - if appropriate _____)
D.O.
APPROVABLE LETTER FOR A PMA SUPPLEMENT - GMP PILOT (SADPILOT) Modified 10-30-96

FILE
COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HOD		4/21/98						
		4/21/98						

☆ U.S. GOVERNMENT PRINTING OFFICE 1991-5

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Ms. Vicki Pearson, RAC
Sr. Product Regulation Manager
Cardiac Pacing Business
Medtronic, Inc.
7000 Centeral Ave., NE
Minneapolis, MN 55432-3576

APR 22 1998

Re: P830061/S028
P850089/S039
P890003/S055
P920015/S014
P930039/S006
P950024/s001
Cardioventus Defibrilators, and Pacing Leads
Filed: April 20, 1998

Dear Ms. Pearson:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has received your premarket approval application (PMA) supplement which requests approval for the manufacturing facility located at Medtronic Puerto Rico, Inc., Road PR-149, km 56.3, Villalba, PR. The supplement will be processed in accordance with the PMA supplement pilot program for manufacturing and/or sterilization site changes described in the March 20, 1996 "Dear President or CEO" letter.

Your PMA supplement is approvable and will be placed on hold until CDRH's Office of Compliance finds the manufacturing facilities, methods and controls in compliance with the applicable requirements of the Quality System Regulation (21 CFR Part 820). The document, Guidance For Preparation of PMA Manufacturing Information, that you received earlier, is based on the original Good Manufacturing Practice (GMP) Regulation. That regulation was superseded by the Quality System Regulation, which became effective on June 1, 1997.

The guidance document is currently under revision to conform with the additional requirements for design control established by the Quality System Regulation. Until the new guidance is available, you are not required to describe the design controls used for the PMA device. During the PMA inspection, however, you may be asked to demonstrate that any design operations for the PMA device, conducted after June 1, 1997, are in compliance with the design control requirements of 21 CFR 820.30.

80

If you have not already done so, please notify CDRH as soon as possible in the form of an amendment to the PMA if there will be a delay in setting up your manufacturing facility for production of the device, and provide the expected date that the facility will be prepared for an FDA inspection. If you have any questions regarding the status of your Quality System inspection please contact the Office of Compliance at (301)-594-4695, or your District Office.

If necessary, amend the PMA supplement to include any relevant information not previously submitted.

Any amendment to this PMA supplement number above and should be submitted in duplicate to to the address below and reference the above PMA supplement number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

At the same time, please submit an identical copy to:

CDRH Office of Compliance
Field Programs Branch
2098 Gaither Road
Rockville, MD 20850

If you have any questions concerning this approvable letter, please contact Mr. Mervin Parker, Jr. at (301) 594-2186.

Sincerely yours,

Philip J. Phillips
Deputy Director
Office of Device Evaluation
Center for Devices and
Radiological Health

SEP 10 1997

Ms. Jeanmarie Sales
Product Regulation Manager
Tachyarrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S13
Medtronic® Sprint™ Models 6943 and 6945 Leads
Filed: July 21, 1997
Amended: August 21, 1997

Dear Ms. Sales:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for Medtronic® Sprint™ Models 6943 and 6945 Leads. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

In addition under section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under section 522(a)(1)(A) the above noted device as requiring postmarket surveillance.

Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

Postmarket Studies Document Center
1350 Piccard Drive (HFZ-544)
Rockville, Maryland 20850

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will be considered violations of section 522.

In accordance with the Medical Device Amendments of 1992, failure of a manufacturer to meet its obligations under section 522 is a prohibited act under section 301(q)(1)(C) of the act (21 U.S.C. 331(q)(1)(C)). Further, under section 502(t)(3) of the act (21 U.S.C. 352(t)(3), a device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the act. Violations of sections 301 or 502 may lead to regulatory actions including seizure of your product, injunction, prosecution, or civil money penalties or other FDA enforcement actions including (but not limited to) withdrawal of your PMA.

If you have any questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch, at (301) 594-0639.

Under section 519(e) of the act (as amended by the Safe Medical Devices Act in 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of device user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonably likely to have serious adverse consequences.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR § 821.20(b) and the devices that FDA has designated for tracking at 21 CFR § 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705-10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)).

If you have questions concerning this approval order, please contact Doris Terry at (301) 443-8609.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Director
Division of Cardiovascular,
Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

cc: HFZ-544 (Postmarket Surveillance Branch if appropriate)
HFZ-300 (Field Programs Branch - GMP)
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 (DCNRD)
HFZ-100 (OST Reviewer - if appropriate _____)
D.O.

APPROVAL ORDER FOR A PMA SUPPLEMENT (SA) Modified 6-9-95
NOTE. ENCLOSURE - INCLUDE THE CONDITIONS OF APPROVAL

Prepared by:DTerry:att/9/4/97

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450	Terry	9/4/97	450	Ciarkowski	/			
450	Devin	9/8/97	/	for Callahan	9/8/97			
			HFZ402	M. Parker	9/10/97			

U.S. GPO 1986-169-089

Constat search 9/10/97 indicates firm is ACCEPTABLE
M. Parker 94

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20856

SEP 10 1997

Ms. Jeanmarie Sales
Product Regulation Manager
Tachyarrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S13
Medtronic® Sprint™ Models 6943 and 6945 Leads
Filed: July 21, 1997
Amended: August 21, 1997

Dear Ms. Sales:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for Medtronic® Sprint™ Models 6943 and 6945 Leads. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

95

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

In addition under section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under section 522(a)(1)(A) the above noted device as requiring postmarket surveillance.

Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

Postmarket Studies Document Center
1350 Piccard Drive (HFZ-544)
Rockville, Maryland 20850

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will be considered violations of section 522.

In accordance with the Medical Device Amendments of 1992, failure of a manufacturer to meet its obligations under section 522 is a prohibited act under section 301(q)(1)(C) of the act (21 U.S.C. 331(q)(1)(C)). Further, under section 502(t)(3) of the act (21 U.S.C. 352(t)(3), a device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the act. Violations of sections 301 or 502 may lead to regulatory actions including seizure of your product, injunction, prosecution, or civil money penalties or other FDA enforcement actions including (but not limited to) withdrawal of your PMA.

If you have any questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch, at (301) 594-0639.

Under section 519(e) of the act (as amended by the Safe Medical Devices Act in 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of device user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonably likely to have serious adverse consequences.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR § 821.20(b) and the devices that FDA has designated for tracking at 21 CFR § 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705-10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)).

If you have questions concerning this approval order, please contact Doris Terry at (301) 443-8609.

Sincerely yours,

for Thomas J. Callahan, Ph.D.
Director
Division of Cardiovascular,
Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20856

SEP 10 1997

Ms. Jeanmarie Sales
Product Regulation Manager
Tachyarrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S13
Medtronic® Sprint™ Models 6943 and 6945 Leads
Filed: July 21, 1997
Amended: August 21, 1997

Dear Ms. Sales:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for Medtronic® Sprint™ Models 6943 and 6945 Leads. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

In addition under section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under section 522(a)(1)(A) the above noted device as requiring postmarket surveillance.

Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

Postmarket Studies Document Center
1350 Piccard Drive (HFZ-544)
Rockville, Maryland 20850

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will be considered violations of section 522.

In accordance with the Medical Device Amendments of 1992, failure of a manufacturer to meet its obligations under section 522 is a prohibited act under section 301(q)(1)(C) of the act (21 U.S.C. 331(q)(1)(C)). Further, under section 502(t)(3) of the act (21 U.S.C. 352(t)(3), a device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the act. Violations of sections 301 or 502 may lead to regulatory actions including seizure of your product, injunction, prosecution, or civil money penalties or other FDA enforcement actions including (but not limited to) withdrawal of your PMA.

If you have any questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch, at (301) 594-0639.

Under section 519(e) of the act (as amended by the Safe Medical Devices Act in 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of device user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonably likely to have serious adverse consequences.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR § 821.20(b) and the devices that FDA has designated for tracking at 21 CFR § 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705-10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)).

If you have questions concerning this approval order, please contact Doris Terry at (301) 443-8609.

Sincerely yours,

for Thomas J. Callahan, Ph.D.
Director
Division of Cardiovascular,
Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

Ms. Jeanmarie Sales
Product Regulation Manager
Tachyarrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S12
Medtronic® Sprint™ Model 6942 Lead
Filed: March 18, 1997
Amended: June 12, and July 9, 1997

Dear Ms. Sales:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for the Medtronic® Sprint™ Model 6942 Lead System. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

Expiration dating for this device has been established and approved at two (2) years from the sterilization date. The storage temperature should be below 40° C (104° F).

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

In addition under section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under section 522(a)(1)(A) the above noted device as requiring postmarket surveillance.

Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

Postmarket Studies Document Center
1350 Piccard Drive (HFZ-544)
Rockville, Maryland 20850

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will be considered violations of section 522.

In accordance with the Medical Device Amendments of 1992, failure of a manufacturer to meet its obligations under section 522 is a prohibited act under section 301(q)(1)(C) of the act (21 U.S.C. 331(q)(1)(C)). Further, under section 502(t)(3) of the act (21 U.S.C. 352(t)(3), a device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the act. Violations of sections 301 or 502 may lead to regulatory actions including seizure of your product, injunction, prosecution, or civil money penalties or other FDA enforcement actions including (but not limited to) withdrawal of your PMA.

If you have any questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch, at (301) 594-0639.

Under section 519(e) of the act (as amended by the Safe Medical Devices Act in 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of device user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonably likely to have serious adverse consequences. FDA has designated your device for tracking.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR § 821.20(b) and the devices that FDA has designated for tracking at 21 CFR § 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705-10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)).

If you have questions concerning this approval order, please contact James Lee at (301) 443-8609.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Director
Division of Cardiovascular,
Respiratory, and Neurological Devices_
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

cc: HFZ-544 (Postmarket Surveillance Branch if appropriate)
HFZ-300 (Field Programs Branch - GMP)
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 (DCRND)
HFZ-100 (OST Reviewer - if appropriate ____________________)
D.O.

APPROVAL ORDER FOR A PMA SUPPLEMENT (SA) Modified 6-9-95
NOTE. ENCLOSURE - INCLUDE THE CONDITIONS OF APPROVAL.

Prepared by:JLee:att/7/16/97

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450	[signature]	7/15	450	[signature]				
450	[signature]	7/15		[signature]	7/16/97			
400	[signature]	7/17	HFZ-402	[signature]	7/17/97			

Constant search 7/17/97 indicates firm is ACCEPTABLE
[signature]
107

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUL 18 1997

Ms. Jeanmarie Sales
Product Regulation Manager
Tachyarrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S12
Medtronic® Sprint™ Model 6942 Lead
Filed: March 18, 1997
Amended: June 12, and July 9, 1997

Dear Ms. Sales:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for the Medtronic® Sprint™ Model 6942 Lead System. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

Expiration dating for this device has been established and approved at two (2) years from the sterilization date. The storage temperature should be below 40° C (104° F).

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

In addition under section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under section 522(a)(1)(A) the above noted device as requiring postmarket surveillance.

Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

Postmarket Studies Document Center
1350 Piccard Drive (HFZ-544)
Rockville, Maryland 20850

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will be considered violations of section 522.

In accordance with the Medical Device Amendments of 1992, failure of a manufacturer to meet its obligations under section 522 is a prohibited act under section 301(q)(1)(C) of the act (21 U.S.C. 331(q)(1)(C)). Further, under section 502(t)(3) of the act (21 U.S.C. 352(t)(3), a device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the act. Violations of sections 301 or 502 may lead to regulatory actions including seizure of your product, injunction, prosecution, or civil money penalties or other FDA enforcement actions including (but not limited to) withdrawal of your PMA.

If you have any questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch, at (301) 594-0639.

Under section 519(e) of the act (as amended by the Safe Medical Devices Act in 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of device user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonably likely to have serious adverse consequences. FDA has designated your device for tracking.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR § 821.20(b) and the devices that FDA has designated for tracking at 21 CFR § 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705-10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)).

If you have questions concerning this approval order, please contact James Lee at (301) 443-8609.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Director
Division of Cardiovascular,
Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

POSTMARKET

INSPECTION

P920015

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration, Center for Devices and Radiological Health

Memorandum

DATE: JAN 23 1995

FROM: PMA Postmarket Coordinator, FPB, DPO, OC, CDRH, (HFZ-306)

SUBJECT: **POSTMARKET INSPECTION REQUEST**

TO: District Director, MIN-DO, HFR-MW300

TO: International & Technical Operations Branch, HFC-135

THRU: Foreign Program Coordinator, HFZ-306____

"7+ LWS

PMA NO.: P920015

DEVICE: Medtronic® Transvene® Lead System

APPLICANT: Medtronic, Inc., Rice Creek Facility, 7000 Central Avenue, N.E. Minneapolis, MN 55432

MANUFACTURER: Same as Above Applicant (May be Fridley, MN 55432) (10/22/93 Previous EI) 2/7/95 NAI

12/92 EI was F/u to 1/92 OAI

Medtronic B.V. - CFN# UN 20065 Wenckeback Straat 10, 6466 NC Kerkrade West Netherlands (12/18/92 Previous EI) OAI/VAI Data Classified 4/3/95 OAI 8/10/95 WL Response adequate

A Premarket Approval application was approved on **December 9, 1993,** for the above referenced product. In accordance with C.P. 7383.001 - Medical Device Premarket Approval and Postmarket Inspections, the postmarket PMA inspection of the manufacturer is targeted to be scheduled within eight to twelve months following the application approval date which would be between **August and December 1994.** 2/2/95 NAI

Your district may have already scheduled the necessary postmarket inspection, or could be currently conducting an on-going inspection of this firm.

During the postmarket inspection, emphasis should be placed upon examining any changes the firm may have made in the design, manufacturing process and/or quality assurance systems relative to the PMA device or the manufacturing process. Attachment B of the Compliance Program provides detailed

guidance for conducting the inspection. Further, the attached guidance specific to the device and manufacturing process(es) from the Division of Enforcement III, Cardiovascular and Neurological Devices Branch, HFZ-341 is provided for use during the inspection.

Attached is a Notification of Postmarket Inspection form which should be returned by facsimile to me with the expected start date of the inspection. Upon receipt of this form, and approximately 30 days before the planned inspection date, I will send copies of all the cover letters for any PMA Supplements submitted by the firm since this Original PMA was approved.

I have also attached a PMA Supplement Report. Query of the OSCAR database resulted in no MDR reports at this time.

If this postmarket inspection has already taken place, the Field Programs Branch would also like to be notified of the District's decision for this inspection.

Please report the inspectional time to PAC 83001 - Medical Device Premarket Approval and Postmarket Inspections - C.P. 7383.001. If the District Decision results in an OAI classification, please forward the EIR to HFZ-306 as stated in the C.P. and mark the coversheet **"PMA POSTMARKET INSPECTION"**.

In addition, for postmarket data tracking purposes, please fill out the requested postmarket inspection data listed on the Notification of Postmarket Inspection form. Please FAX the completed form to me with a copy of the EIR coversheets with endorsement.

The following reporting data is provided for your information. If you need any further information, please do not hesitate to contact me.

Product Code: 74
PAC: 83001
Priority: Routine
Est. Comp. Time: 30 Hours

Contact: Ann Sheapp
2098 Gaither Road
Rockville, Maryland 20850
Phone: 301-594-4695
FAX: 301-594-4715

Ann Sheapp
Ann L. Sheapp

Attachments

IE ASSGND: 3/95 CS#: PRIORITY: DATE INSPD: 4/3-6/95 GRP:
ENTRAL FILE NO. 9610980 JD/TA: CNTY: PHONE: 045-438585
EMPL NO: 600

NAME: Medtronic B.V. STREET: Wenckebachstraat 10
CITY: Kerkrade, The Netherlands STATE: ZIP: 6466NV DISTRICT:%

ENDORSEMENT

page 2

Management stated they will correct 4 of the items and part of an additional item pending review and approval by Medtronics Corporate office.

Its recommended that because the firm is a large manufacturer of sterile devices and time is limited the next inspection should a team inspection ie Microbiologist and CSO.

RECOMMENDATION: Issue Warning Letter for serious packaging, sealing and sterilization deviations. No response has been received from the firm regarding the FD-483 issued to them.

CLASSIFIED: OAI

F/U: Re-inspect per CDRH/ITOB guidelines

km 5/8/95

VOLUNTARY CORRECTION DATA

PAC	PROBLEM TYPE	CORRECTIVE ACTION	EST. COST OF ACTION	DATE ACTION VERIFIED	CORRECTING UNIT	REPORTING DISTRICT

SIGNATURE James R. Flakenstein, ASCSO DATE: 4/24/95

DISTRIBUTION:

TE ASSGND: 3/95 CS#: PRIORITY: DATE INSPD: 4/3-6/95 GRP:
ENTRAL FILE NO.: 9610980 JD/TA: CNTY: PHONE:045-438585
EMPL NO:600

NAME:Medtronic B.V. STREET:Wenckebachstraat
ITY:Kerkrade, The Netherlands STATE: ZIP:6466 NV DISTRICT: %

ENDORSEMENT

This inspection was conducted per ITOB and HFZ-306 request to conduct a PMA Post Market inspection of Medtronic Transvene Lead System (TLS) PMA No P920015 including supplement NOS. S1,S2 and S3. This inspection was conducted per CP7383.001, 7382.830 and 7382.830A. Attachment B, Sterilization Checklist, was completed.

The last inspection of 12/92 was conducted as a follow-up to a previous 1/92 inspection which resulted in Automatic Detention of the firm's devices on 6-16-92. The 12/92 inspection was initially Classified OAI but was downgraded by CDRH resulting in removal of the Automatic Detention.

The PMA lists this location as an alternate manufacturing site. The firm has not shipped any devices to the US. The primary manufacturing site for this device for the U.S. is Medtronic in Minneapolis, MN.

The current inspection did not find any major problems with the Post Market PMA requirements. However, a 6 item FDA-483 was issued for serious GMP problems including the following sterilization and packaging validation observations:

(1) No validation of TLS packages sealed on the Kerkrade sealing machine.
(2) The most current validation of the Kerkrade sealing machine dated 6/92 did not prove reproductability.
(3) The 9/94 re-validation of the ETO sterilizer was conducted using empty packages although the report states the study included "fully load packaging". The firm has not conducted studies correlating full packages VS empty packages on packages sealed at KerKrade

VOLUNTARY CORRECTION DATA

PAC	PROBLEM TYPE	CORRECTIVE ACTION	EST.COST OF ACTION	DATE ACTION VERIFIED	CORRECTING UNIT	REPORTING DISTRICT

SIGNATURE James R. Flocken, ASCSC DATE: 4/24/95

DISTRIBUTION: HFC-135; HFA-224; HFZ-306 w/exhibits; HFZ-306 FOI; LOS-DO-DIB; HFC-170; HFC-135 Alertfile; Marvin Appleton, investigator, Canoga Park RP

5

INSPECTIONAL GUIDANCE (MIN-DO)

December 1, 1992

SUBJECT: PMA P920015A

FIRM: Medtronic, Inc.
Rice Creek Facility
7000 Central Avenue NE
Minneapolis, Minnesota 55432

DEVICE: PCD Transvene Lead System;
Model 6963 and 6999

CDRH/OCS
REVIEWER: David Kunin, MQAB, HFZ-~~332~~ 341, (301) 427-1128

This PMA amendment, P920015A, is for the production of the Model 6963 and 6999 leads manufactured at the Medtronic Rice Creek Facility. The last inspection was conducted January 21 through February 8, 1992, and the firm was found to be an acceptable manufacturer.

During the postmarket inspection of Medtronic, Rice Creek Facility, please pay particular attention to the following areas: [820.81(a)]

Model 6963 Lead

For the following operations, verify that the approved and appropriate method sheets are being used:

Electrode Sub-Assembly:

1. Crimp distal sleeve to coil; [(b)(4)]
2. Cut coil to length;
3. String tubing and bond distal tubing; [(b)(4)]
4. Crimp proximal sleeve to coil and bond proximal sleeve; [(b)(4)]
5. Laser weld; and, [(b)(4)]
6. Silicone backfill. [(b)(4)] Are specifications and inspection characteristics established for this operation? Is the minimum insulation thickness measured? Is the measurement recorded?

Final Assembly:

7. Crimp coil; [(b)(4)]
8. String tubing;
9. Crimp tip; [(b)(4)]
10. Cut to length;
11. Crimp connector pin; [(b)(4)]
12. Assemble connector pin; [(b)(4)]
13. Install molded tip; [(b)(4)] and,

14. Bond tip/connector sleeve; (b)(4)
15. Are all crimped and bonded interfaces tested for integrity? [820.160]
16. Verify the final functional inspection is performed according to (b)(4) [820.160]
17. Verify that the leads deliver pacing, cardioversion, and defibrillation pulses that correspond with the range of programmable detection rhythms.(A specification should be available which establishes the pulse to be delivered at the detection of a specific cardiac electrical rhythm. Verify the delivery of the appropriate pulse with the corresponding rhythm.) [820.100(b)(2)]
18. Verify that the tests for electrical resistance, continuity, and leakage are performed in accordance with the appropriate procedure. [820.160]

MODEL 6999

For the following operations, verify:

19. Defibrillator coil assembly;
20. Manifold patch;
21. Manifold assembly:
    a. Crimp manifold; (b)(4)
    b. Stake defibrillator coils; (b)(4)
    c Cut tubing/coil to length.
22. Bond manifold assembly:
    a. Bond defibrillator coil assembly (b)(4)
23. Connector assembly:
    a. Crimp connector pin; (b)(4)
    b. Backfill voids. (b)(4)
24. Manifold patch:
    a. Attach patch;
    b. Attach connector sleeve;
    c. Serial number label.
25. Backfill connector sleeve and backfill air bubbles (b)(4)
26. Are all crimped and bonded interfaces tested for integrity? [820.160]
27. Verify the final functional inspection is performed according to the appropriate procedure. [820.160]
28. Verify that the leads deliver pacing, cardioversion, and programmable detection rhythms. (A specification should be available which establishes the pulse to be delivered at the detection of a specific cardiac electrical rhythm. Verify the delivery of the appropriate pulse with the corresponding rhythm.) [820.100(b)(2)]
29. Verify that the tests for electrical resistance, continuity, and leakage are performed in accordance with the appropriate procedure. [820.160]

Concerning both model leads:

30. Verify that biological indicators are placed in the locations specified in the sterilization procedure. [820.100(b)(2)]

31. Verify that the sterile package is tested according to a written procedure. [820.160]
32. Verify that quality system audits are conducted according to a written procedure and schedule. [820.20(b)]

33. Are complaints of device failure, injury, and death being investigated and the results documented? [820.198]

34. Verify that the leads are tested in accordance with all labeled device voltage ratings. [820.160]

THIS DOCUMENT MAY NOT BE SHOWN OR PROVIDED TO THE FIRM

DATE: December 1, 1992

TO: Mary Ann Fitzgerald, PDAB, HFZ-331

THRU: Acting Chief, MQAB, HFZ-332 SAM 12/2/92

FROM: David Kunin, MQAB, HFZ-332

SUBJECT: PMA Amendment P920015A, dated October 26, 1992

APPLICANT: Medtronic, Inc.
7000 Central Ave. N.E.
Minneapolis, Minnesota 55432-3576

MANUFACTURER: Medtronic, Inc.
Rice Creek Facility
7000 Central Ave. N.E.
Minneapolis, Minnesota 55432-3576

DEVICE: Pacer-Cardioversion-Defibrillation Lead System; for use with Medtronic PCD Model 5355 external tachyarrhythmia control device (ECTCD), and Model 9788 MemoryMod Software Module. (critical device)

Model 6963 CS Lead (critical device)
Model 6999 SQ Patch Lead (critical device)

SITUATION: 2 (In accordance with Part V of Compliance Program 7382.830, dated 9/1/91)

MQAB RECOMMENDATION: 1. PMA AMENDMENT APPROVAL
2. POSTMARKET INSPECTION

This PMA amendment, P920015A, dated October 26, 1992, is for the manufacture of Medtronic's Model 6963 and 6999 Leads for use with the PCD Model 5355 external tachyarrhythmia control device (ECTD). The manufacturing site for this amendment is the Rice Creek facility. The last inspection of this location was January 21 through February 8, 1992. The firm was classified NAI for sterilization and VAI-2 for GMP compliance. MIN-DO concurred with PMA approval. The firm's response to an OCS deficiency letter, dated August 26, 1992, adequately addressed the eleven concerns indicated.

A review of the amendment indicates the firm has met its PMA commitments concerning the Manufacturing Control Section requirements. There is a minimal probability that unsafe and ineffective devices will be produced and distributed. MQAB recommends a postmarket inspection be scheduled at the Rice Creek facility.

Guidance is included for use during the postmarket inspection.

David Kunin

AUG - 6

Ms. Rachel Libi
Product Regulation Manager
Tacharrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S10
Medtronic® Sprint™ Model 6932 Lead
Filed: May 17, 1995
Amended: July 15, 1996

Dear Ms. Libi:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for the Medtronic® Sprint™ Model 6932 Lead. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the Federal Food, Drug, and Cosmetic Act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

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Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

In addition under section 522(a) of the Federal Food, Drug, and Cosmetic Act, (the act) manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under section 522(a)(1)(A) the above noted device as requiring postmarket surveillance.

Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

Postmarket Studies Document Center
1350 Piccard Drive (HFZ-544)
Rockville, Maryland 20850

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will be considered violations of section 522.

In accordance with the Medical Device Amendments of 1992, failure of a manufacturer to meet its obligations under section 522 is a prohibited act under section 301(q)(1)(C) of the Federal Food, Drug and Cosmetic Act (the act) 921 U.S.C. 331(q)(1)(C). Further, under section 502(t)(3) of the act (21 U.S.C. 352(t)(3), a device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the act. Violations of sections 301 or 502 may lead to regulatory actions including seizure of your product, injunction, prosecution, or civil money penalties or other FDA enforcement actions including (but not limited to) withdrawal of your PMA.

If you have any questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch, at (301) 594-0639.

Under section 519(e) of the act (as amended by the Safe Medical Devices Act in 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of device user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonably likely to have serious adverse consequences. FDA has designated your device for tracking.

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If you have questions concerning this approval order, please contact Doris Terry at (301) 443-8609.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Director
Division of Cardiovascular,.
Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

cc: HFZ-544 (Postmarket Surveillance Branch if appropriate)
HFZ-300 (Field Programs Branch - GMP)
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 (DCRND)
HFZ-100 (OST Reviewer - if appropriate _____)
D.O.

APPROVAL ORDER FOR A PMA SUPPLEMENT (SA) Modified 6-9-95
NOTE. ENCLOSURE - INCLUDE THE CONDITIONS OF APPROVAL.

Prepared by:DTerry:att/7/23/96

FILE COPY

Comstat database search - acceptable 8/6/96 DM Melling

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450	Zenz	8/5/96	450	Garkavi	—			
450	Quinn	8/5/96	—	for Callahan	8/5/96			
450	Phillips	8/5/96	402	DM Melling	8/6/96			

U.S. GPO 1986-169 089

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG - 6 1996

Ms. Rachel Libi
Product Regulation Manager
Tacharrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

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Filed: May 17, 1995
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the devices that FDA has designated for tracking at 21 CFR § 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705-10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)).

If you have questions concerning this approval order, please contact Doris Terry at (301) 443-8609.

Sincerely yours,

for Beth A. Clarkowski

Thomas J. Callahan, Ph.D.
Director
Division of Cardiovascular,
Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Ms. Rachel Libi
Product Regulation Manager
Tachyarrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

JUL 26 1996

Re: P920015/S11
Medtronic® Model 6932 Lead
Filed: May 20, 1996
Amended: July 12, 1996

Dear Ms. Rachel:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for the Medtronic Puerto Rico, Inc., Villalba West Industrial Area, Villalba, Puerto Rico to manufacture the Medtronic® Model 6932 Lead. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

In addition under section 522(a) of the act manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under section 522(a)(1)(A) the above noted device as requiring postmarket surveillance.

Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

Postmarket Studies Document Center
1350 Piccard Drive (HFZ-544)
Rockville, Maryland 20850

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will be considered violations of section 522.

In accordance with the Medical Device Amendments of 1992, failure of a manufacturer to meet its obligations under section 522 is a prohibited act under section 301(q)(1)(C) of the act (21 U.S.C. 331(q)(1)(C)). Further, under section 502(t)(3) of the act (21 U.S.C. 352(t)(3), a

device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the act. Violations of sections 301 or 502 may lead to regulatory actions including seizure of your product, injunction, prosecution, or civil money penalties or other FDA enforcement actions including (but not limited to) withdrawal of your PMA.

If you have any questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch, at (301) 594-0639.

Under section 519(e) of the act (as amended by the Safe Medical Devices Act in 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of device user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonably likely to have serious adverse consequences.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR § 821.20(b) and the devices that FDA has designated for tracking at 21 CFR § 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705-10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)).

If you have questions concerning this approval order, please contact Ms. Doris Terry at (301) 443-8609.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Director
Division of Cardiovascular, Respiratory,
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

[DO NOT SHOW ON ORIGINAL]

cc: HFZ-544 (Postmarket Surveillance Branch if appropriate)
HFZ-300 (Field Programs Branch - GMP)
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 [ODE Division]
HFZ-100 (OST Reviewer - if appropriate _____)
D.O.

FILE COPY

GMP Clearance ~ Final Approval dated 7/24/96.

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
460		7/24/96						
402	DM Melling	7/26/96						

U.S. GPO 1996-169-089

116

DEPARTMENT OF H[illegible]TH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Ms. Rachel Libi
Product Regulation Manager
Tachyarrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

JUL 26 1996

Re: P920015/S11
Medtronic® Model 6932 Lead
Filed: May 20, 1996
Amended: July 12, 1996

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Food and Drug Administration
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Rockville, Maryland 20850

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Rockville, Maryland 20850

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If you have questions concerning this approval order, please contact Ms. Doris Terry at (301) 443-8609.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Director
Division of Cardiovascular, Respiratory,
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Ms. Rachel Libi
Product Regulation Manager
Tachyarrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S9
Medtronic® Model 6707 Adapter
Filed: February 5, 1996

Dear Ms. Libi:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for the Model 6707 Adapter. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the Federal Food, Drug, and Cosmetic Act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

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At that time you should submit five (5) copies to:

Postmarket Studies Document Center
1350 Piccard Drive (HFZ-544)
Rockville, Maryland 20850

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will be considered violations of section 522.

In accordance with the Medical Device Amendments of 1992, failure of a manufacturer to meet its obligations under section 522 is a prohibited act under section 301(q)(1)(C) of the Federal Food, Drug and Cosmetic Act (the act)(21 U.S.C. 331(q)(1)(C)). Further, under section 502(t)(3) of the act (21 U.S.C. 352(t)(3), a device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the act. Violations of sections 301 or 502 may lead to regulatory actions including seizure of your product, injunction, prosecution, or civil money penalties or other FDA enforcement actions including (but not limited to) withdrawal of your PMA.

If you have any questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch, at (301) 594-0639.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

If you have questions concerning this approval order, please contact Doris Terry at (301) 443-8609.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Director
Division of Cardiovascular,
Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

cc: HFZ-544 (Postmarket Surveillance Branch if appropriate)
HFZ-300 (Field Programs Branch - GMP)
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 (DCRND)
HFZ-100 (OST Reviewer - if appropriate ____________________)
D.O.

APPROVAL ORDER FOR A PMA SUPPLEMENT (SA) Modified 6-9-95
NOTE. ENCLOSURE - INCLUDE THE CONDITIONS OF APPROVAL.

Prepared by:DTerry;att/4/1/96

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450	Terry	4/3/96	HFZ-450	[illegible]	4/8/96			
450	[illegible]	4/4/96						
450	[illegible]	4/5/96						

U.S. GPO 1986-169-069

Consultant check 4/4/96 indicates form is acceptable m. p 24

DEPARTMENT OF ..TH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Ms. Rachel Libi
Product Regulation Manager
Tachyarrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

APR - 8 1996

Re: P920015/S9
Medtronic® Model 6707 Adapter
Filed: February 5, 1996

Dear Ms. Libi:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for the Model 6707 Adapter. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

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If you have questions concerning this approval order, please contact Doris Terry at (301) 443-8609.

Sincerely yours,

Wolf Sperstein M.D
for

Thomas J. Callahan, Ph.D.
Director
Division of Cardiovascular,
Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

MAR 22 1996

Ms. Rachel Libi
Product Regulation Manager
Tacharrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S5
Medtronic® Model 6937 Transvene® Superior Vena Cava Lead
Filed: June 29, 1995
Amended: February 20, 1996

Dear Ms. Libi:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for the Medtronic® Model 6937 Transvene® Superior Vena Cava Lead. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

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Sincerely yours,

Thomas J. Callahan, Ph.D.
Director
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Center for Devices and
Radiological Health

Enclosure

cc: HFZ-544 (Postmarket Surveillance Branch if appropriate)
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HFZ-450 (DCRND)
HFZ-100 (OST Reviewer - if appropriate _____)
D.O.

APPROVAL ORDER FOR A PMA SUPPLEMENT (SA) Modified 6-9-95
NOTE. ENCLOSURE - INCLUDE THE CONDITIONS OF APPROVAL.

Prepared by:DTerry:att/3/1/96
Revised:MBrown:att/3/12/96

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450	[illegible]	3/12/96	450	Carlous L	—			
450	[illegible]	3/12/96	—	for Callahan	3/20/96			
450	Phillips	3/12/96	HFZ 400	[illegible]	3/22/96			

U.S. GPO 1986-169-069

133

Comstat search 3/22/96 indicates firm is ACCEPTABLE
[illegible]

DEPARTMENT OF H & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Ms. Rachel Libi
Product Regulation Manager
Tacharrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

MAR 22 1996

Re: P920015/S5
Medtronic® Model 6937 Transvene® Superior Vena Cava Lead
Filed: June 29, 1995
Amended: February 20, 1996

Dear Ms. Libi:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for the Medtronic® Model 6937 Transvene® Superior Vena Cava Lead. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the Federal Food, Drug, and Cosmetic Act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

In addition under section 522(a) of the Federal Food, Drug, and Cosmetic Act, (the act) manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under section 522(a)(1)(A) the above noted device as requiring postmarket surveillance.

Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

Postmarket Studies Document Center
1350 Piccard Drive (HFZ-544)
Rockville, Maryland 20850

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will be considered violations of section 522.

Further, under section 502(t)(3) of the act (21 U.S.C. 352(t)(3), a device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the act. Violations of sections 301 or 502 may lead to regulatory actions including seizure of your product, injunction, prosecution, or civil money penalties or other FDA enforcement actions including (but not limited to) withdrawal of your PMA.

If you have any questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch, at (301) 594-0639.

Under section 519(e) of the act (as amended by the Safe Medical Devices Act in 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of device user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonably likely to have serious adverse consequences. FDA has designated your device for tracking.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR § 821.20(b) and the devices that FDA has designated for tracking at 21 CFR § 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705-10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)).

If you have questions concerning this approval order, please contact Doris Terry at (301) 443-8609.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Director
Division of Cardiovascular,
Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

AR 13

Ms. Rachel Libi
Product Regulation Manager
Tacharrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S7
Medtronic® Model 6934S Transvene®-Right Ventricular Lead
Filed: August 7, 1995
Amended: February 20, 1996

Dear Ms. Libi:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for the Medtronic® Model 6934S Transvene® Right Ventricular Lead. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the Federal Food, Drug, and Cosmetic Act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

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Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

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Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

Postmarket Studies Document Center
1350 Piccard Drive (HFZ-544)
Rockville, Maryland 20850

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will be considered violations of section 522.

Further, under section 502(t)(3) of the act (21 U.S.C. 352(t)(3), a device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the act. Violations of sections 301 or 502 may lead to regulatory actions including seizure of your product, injunction, prosecution, or civil money penalties or other FDA enforcement actions including (but not limited to) withdrawal of your PMA.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

If you have questions concerning this approval order, please contact Doris Terry at (301) 443-8609.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular,
Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

cc: HFZ-544 (Postmarket Surveillance Branch if appropriate)
HFZ-300 (Field Programs Branch - GMP)
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 (DCRND)
HFZ-100 (OST Reviewer - if appropriate _____)
D.O.

APPROVAL ORDER FOR A PMA SUPPLEMENT (SA) Modified 6-9-95
NOTE. ENCLOSURE - INCLUDE THE CONDITIONS OF APPROVAL.

Prepared by:DTerry:att/3/1/96

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450	Terry	3/4/96	450	Spyker	3/7			
450	Dunn	3/4/96	HFZ-402	M Parker	3/13/96			
450	Phillips	3/4/96						

U.S. GPO 1986-169-089

Constant search 3/13/96 indicate firm's ACCEPTABLE
M Parker
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DEPARTMENT OF HE & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Ms. Rachel Libi
Product Regulation Manager
Tacharrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

MAR 13

Re: P920015/S7
Medtronic® Model 6934S Transvene®-Right Ventricular Lead
Filed: August 7, 1995
Amended: February 20, 1996

Dear Ms. Libi:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for the Medtronic® Model 6934S Transvene® Right Ventricular Lead. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

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Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

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Rockville, Maryland 20850

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If you have questions concerning this approval order, please contact Doris Terry at (301) 443-8609.

Sincerely yours,

for Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular,
Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

DEC 18 1995

Ms. Rachel Gibbs
Product Regulation Manager
Tacharrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S7
Medtronic® Model 6934S Transvene® Right Ventricular (RV) Lead
Filed: August 7, 1995

Dear Ms. Gibbs:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement which requested approval for the Model 6934S Transvene® Right Venticular (RV) Lead. We regret to inform you that CDRH has determined that your PMA supplement is not approvable based on the requirements of 21 CFR 814.44(f), which also requires FDA, where practical, to identify measures required to place the PMA supplement in approvable form. Accordingly, to place your PMA supplement in approvable form, you must amend it to include the following:

> Please provide data on at least (b)(4) patients implanted with the Model 6934S Lead and followed for (b)(4) months. These data should be presented and analyzed as those in the original PMA supplement.

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period up to 180 days. As provided by 21 CFR 814.37(c) you may decline to submit a major amendment requested by FDA in which case the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

As provided by 21 CFR 814.44(f), you may amend your PMA supplement as requested above, withdraw the PMA supplement, or consider this letter to be a denial of approval of the PMA supplement under 21 CFR 814.45 and request administrative review. Any request for administrative review either through a hearing or

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review by an independent advisory committee, under section 515(d)(3) and 515(g) of the Federal Food, Drug, and Cosmetic Act must be submitted in the form of a petition for reconsideration (21 CFR 10.33) and in accordance with the general administrative procedures for submission of documents to the Dockets Management Branch (21 CFR 10.20). Any petition for reconsideration must be submitted to the Food and Drug Administration, Dockets Management Branch (HFA-305), Room 1-23, 12420 Parklawn Drive, Rockville, Maryland 20857, within 30 days of the date you receive this letter. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issues to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

As provided under 21 CFR 814.44(g), FDA will consider this PMA supplement to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA supplement amendment. You may, however, amend the PMA supplement within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA supplement within the 180-day period to (1) correct the above deficiency, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA supplement and will be assigned a new number. Under these circumstances, any resubmission will be given a new PMA supplement number and will be subject to the requirements of 21 CFR 814.20. A resubmission should be complete and self-contained because of potential difficulties in assembling files from storage.

Information correcting the above deficiency should be submitted in the form of an amendment. All amendments to the PMA supplement should be submitted in triplicate to the address below and reference the above PMA supplement number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

If you have questions concerning this not-approvable letter, please contact Doris Terry at (301) 443-8609.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular,
Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

cc: HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 (DCRND)
HFZ-100 (OST Reviewer - if appropriate _____)
D.O.

NOT APPROVABLE LETTER FOR A PMA SUPPLEMENT (SNP) Modified 10-7-94

Prepared by:DTerry:att/12/12/95

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450		12/13/95	450	Ciarkowski				
450		12/14/95		for Callahan	12/18/95			
450		12/14/95	402	A. Alpert	12/18/95			

U.S. GOVERNMENT PRINTING OFFICE 1991 619-771

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Ms. Rachel Gibbs
Product Regulation Manager
Tacharrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

DEC 18 1995

Re: P920015/S7
Medtronic® Model 6934S Transvene® Right Ventricular (RV) Lead
Filed: August 7, 1995

Dear Ms. Gibbs:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement which requested approval for the Model 6934S Transvene® Right Venticular (RV) Lead. We regret to inform you that CDRH has determined that your PMA supplement is not approvable based on the requirements of 21 CFR 814.44(f), which also requires FDA, where practical, to identify measures required to place the PMA supplement in approvable form. Accordingly, to place your PMA supplement in approvable form, you must amend it to include the following:

> Please provide data on at least (b)(4) patients implanted with the Model 6934S Lead and followed for (b)(4) months. These data should be presented and analyzed as those in the original PMA supplement.

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period up to 180 days. As provided by 21 CFR 814.37(c) you may decline to submit a major amendment requested by FDA in which case the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

As provided by 21 CFR 814.44(f), you may amend your PMA supplement as requested above, withdraw the PMA supplement, or consider this letter to be a denial of approval of the PMA supplement under 21 CFR 814.45 and request administrative review. Any request for administrative review either through a hearing or

review by an independent advisory committee, under section 515(d)(3) and 515(g) of the Federal Food, Drug, and Cosmetic Act must be submitted in the form of a petition for reconsideration (21 CFR 10.33) and in accordance with the general administrative procedures for submission of documents to the Dockets Management Branch (21 CFR 10.20). Any petition for reconsideration must be submitted to the Food and Drug Administration, Dockets Management Branch (HFA-305), Room 1-23, 12420 Parklawn Drive, Rockville, Maryland 20857, within 30 days of the date you receive this letter. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issues to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

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Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

If you have questions concerning this not-approvable letter, please contact Doris Terry at (301) 443-8609.

Sincerely yours,

for Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular,
Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

DEC 18

Dennis Connolly, M.D.
Product Regulation Manager
Tacharrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S5
Medtronic® Model 6937 Transvene Superior Vena Cava (SVC) Lead
Filed: June 29, 1995

Dear Dr. Connolly:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement which requested approval for the Model 6937 Lead Transvene® Superior Vena Cava (SVC) Lead. We regret to inform you that CDRH has determined that your PMA supplement is not approvable based on the requirements of 21 CFR 814.44(f), which also requires FDA, where practical, to identify measures required to place the PMA supplement in approvable form. Accordingly, to place your PMA supplement in approvable form, you must amend it to include the following:

> Please provide data on at least 50 patients implanted with the Model 6937 Lead and followed for 6 months. These data should be presented and analyzed as those in the original PMA supplement.

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period up to 180 days. As provided by 21 CFR 814.37(c) you may decline to submit a major amendment requested by FDA in which case the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

As provided by 21 CFR 814.44(f), you may amend your PMA supplement as requested above, withdraw the PMA supplement, or consider this letter to be a denial of approval of the PMA supplement under 21 CFR 814.45 and request administrative review. Any request for administrative review either through a hearing or

review by an independent advisory committee, under section 515(d)(3) and 515(g) of the Federal Food, Drug, and Cosmetic Act must be submitted in the form of a petition for reconsideration (21 CFR 10.33) and in accordance with the general administrative procedures for submission of documents to the Dockets Management Branch (21 CFR 10.20). Any petition for reconsideration must be submitted to the Food and Drug Administration, Dockets Management Branch (HFA-305), Room 1-23, 12420 Parklawn Drive, Rockville, Maryland 20857, within 30 days of the date you receive this letter. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issues to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

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Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

If you have questions concerning this not-approvable letter, please contact Doris Terry at (301) 443-8609.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular,
Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

cc: HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 (DCRND)
HFZ-100 (OST Reviewer - if appropriate _____)
D.O.

NOT APPROVABLE LETTER FOR A PMA SUPPLEMENT (SNP) Modified 10-7-94

Prepared by:DTerry:att/12/12/95

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450	[illegible]	12/12/95	450	Gartowski				
450	Dunin	12/12/95	402	for Callahan	12/18/95			
				[illegible]	12/18/95			

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180

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Dennis Connolly, M.D.
Product Regulation Manager
Tacharrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

DEC 18 1995

Re: P920015/S5
Medtronic® Model 6937 Transvene Superior Vena Cava (SVC) Lead
Filed: June 29, 1995

Dear Dr. Connolly:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement which requested approval for the Model 6937 Lead Transvene® Superior Vena Cava (SVC) Lead. We regret to inform you that CDRH has determined that your PMA supplement is not approvable based on the requirements of 21 CFR 814.44(f), which also requires FDA, where practical, to identify measures required to place the PMA supplement in approvable form. Accordingly, to place your PMA supplement in approvable form, you must amend it to include the following:

> Please provide data on at least 50 patients implanted with the Model 6937 Lead and followed for 6 months. These data should be presented and analyzed as those in the original PMA supplement.

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period up to 180 days. As provided by 21 CFR 814.37(c) you may decline to submit a major amendment requested by FDA in which case the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

As provided by 21 CFR 814.44(f), you may amend your PMA supplement as requested above, withdraw the PMA supplement, or consider this letter to be a denial of approval of the PMA supplement under 21 CFR 814.45 and request administrative review. Any request for administrative review either through a hearing of

review by an independent advisory committee, under section 515(d)(3) and 515(g) of the Federal Food, Drug, and Cosmetic Act must be submitted in the form of a petition for reconsideration (21 CFR 10.33) and in accordance with the general administrative procedures for submission of documents to the Dockets Management Branch (21 CFR 10.20). Any petition for reconsideration must be submitted to the Food and Drug Administration, Dockets Management Branch (HFA-305), Room 1-23, 12420 Parklawn Drive, Rockville, Maryland 20857, within 30 days of the date you receive this letter. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issues to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

As provided under 21 CFR 814.44(g), FDA will consider this PMA supplement to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA supplement amendment. You may, however, amend the PMA supplement within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA supplement within the 180-day period to (1) correct the above deficiency, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA supplement and will be assigned a new number. Under these circumstances, any resubmission will be given a new PMA supplement number and will be subject to the requirements of 21 CFR 814.20. A resubmission should be complete and self-contained because of potential difficulties in assembling files from storage.

Information correcting the above deficiency should be submitted in the form of an amendment. All amendments to the PMA supplement should be submitted in triplicate to the address below and reference the above PMA supplement number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

If you have questions concerning this not-approvable letter, please contact Doris Terry at (301) 443-8609.

Sincerely yours,

for Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular,
Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Dennis Connolly, M.D.
Product Regulation Manager
Tachyarrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S8
Medtronic® Transvene® Lead System
Filed: August 10, 1995

Dear Dr. Connolly:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for use of an alternate sterilization process and a modification to the distal end of the Transvene® Leads. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

In addition under section 522(a) of the Federal Food, Drug, and Cosmetic Act, (the act) manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under section 522(a)(1)(A) the above noted device as requiring postmarket surveillance.

Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

Postmarket Studies Document Center
1350 Piccard Drive (HFZ-544)
Rockville, Maryland 20850

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will be considered violations of section 522.

In accordance with the Medical Device Amendments of 1992, failure of a manufacturer to meet its obligations under section 522 is a prohibited act under section 301(q)(1)(C) of the Federal Food, Drug and Cosmetic Act (the act)(21 U.S.C. 331(q)(1)(C)). Further, under section 502(t)(3) of the act (21 U.S.C. 352(t)(3), a device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the act. Violations of sections 301 or 502 may lead to regulatory actions including seizure of your product, injunction, prosecution, or civil money penalties or other FDA enforcement actions including (but not limited to) withdrawal of your PMA.

If you have any questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch, at (301) 594-0639.

Under section 519(e) of the act (as amended by the Safe Medical Devices Act in 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of device user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonably likely to have serious adverse consequences. FDA has designated your device for tracking.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR § 821.20(b) and the devices that FDA has designated for tracking at 21 CFR § 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705-10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)).

If you have questions concerning this approval order, please contact Doris Terry at (301) 443-8609.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular,
Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

cc: HFZ-544 (Postmarket Surveillance Branch if appropriate)
HFZ-300 (Field Programs Branch - GMP)
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 (DCRN)
HFZ-100 (OST Reviewer - if appropriate _____)
D.O.

APPROVAL ORDER FOR A PMA SUPPLEMENT (SA) Modified 6-9-95

Prepared by:DTerry:att/11/9/95

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450		11/9/95	450	Garlowski				
450	Connolly	11/9/95		for Callahan	12/5/95			
450	Phillips	11/9/95	402		12/6/95			

U.S. GOVERNMENT PRINTING OFFICE 1991 419-771

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Dennis Connolly, M.D.
Product Regulation Manager
Tachyarrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

DEC - 7 1995

Re: P920015/S8
Medtronic® Transvene® Lead System
Filed: August 10, 1995

Dear Dr. Connolly:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for use of an alternate sterilization process and a modification to the distal end of the Transvene® Leads. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

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PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

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Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

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1350 Piccard Drive (HFZ-544)
Rockville, Maryland 20850

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will be considered violations of section 522.

In accordance with the Medical Device Amendments of 1992, failure of a manufacturer to meet its obligations under section 522 is a prohibited act under section 301(q)(1)(C) of the Federal Food, Drug and Cosmetic Act (the act)(21 U.S.C. 331(q)(1)(C)). Further, under section 502(t)(3) of the act (21 U.S.C. 352(t)(3), a device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the act. Violations of sections 301 or 502 may lead to regulatory actions including seizure of your product, injunction, prosecution, or civil money penalties or other FDA enforcement actions including (but not limited to) withdrawal of your PMA.

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FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR § 821.20(b) and the devices that FDA has designated for tracking at 21 CFR § 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705-10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)).

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Sincerely yours,

for Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular,
Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Dennis Connolly, M.D.
Product Regulation Manager
Tachyarrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

DEC - 7 1995

Re: P920015/S8
Medtronic® Transvene® Lead System
Filed: August 10, 1995

Dear Dr. Connolly:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for use of an alternate sterilization process and a modification to the distal end of the Transvene® Leads. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

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Rockville, Maryland 20850

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If you have any questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch, at (301) 594-0639.

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If you have questions concerning this approval order, please contact Doris Terry at (301) 443-8609.

Sincerely yours,

for Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular,
Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

AUG 17 [illegible]

Dennis Connolly, M.D.
Product Regulation Manager
Tachyarrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S6
Medtronic® Defibrillation Leads: Transvene® Models 6966, 6936, 6963, and 6933 and Models 6939 and 6999 Patch Leads - Elimination of Chlorofluorocarbon (CFC)
Filed: July 18, 1995

Dear Ms. Gibbs:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval to eliminate CFC to manufacture the referenced defibrillation leads. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the Federal Food, Drug, and Cosmetic Act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

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Rockville, Maryland 20850

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Rockville, Maryland 20850

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Sincerely yours,

Thomas J. Callahan, Ph.D.
Acting Director
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  Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
  Radiological Health

Enclosure

cc: HFZ-544 (Postmarket Surveillance Branch if appropriate)
HFZ-300 (Field Programs Branch - GMP)
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 (DCRN)
HFZ-100 (OST Reviewer - if appropriate _____)
D.O.

APPROVAL ORDER FOR A PMA SUPPLEMENT (SA) Modified 6-9-95

Prepared by:DTerry:att/7/27/95

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFZ-450		7/27/95	HFZ-450	Clarkowski				
HFZ-450		7/31/95		for Callahan	8/4/95			
HFZ-450		7/31/95	HFZ-402		8/4/95			

U.S. GOVERNMENT PRINTING OFFICE 1991-519-771

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Dennis Connolly, M.D.
Product Regulation Manager
Tachyarrhythmia Management Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

AUG 17 1995

Re: P920015/S6
Medtronic® Defibrillation Leads: Transvene® Models 6966, 6936, 6963, and 6933 and Models 6939 and 6999 Patch Leads - Elimination of Chlorofluorocarbon (CFC)
Filed: July 18, 1995

Dear Ms. Gibbs:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval to eliminate CFC to manufacture the referenced defibrillation leads. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

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Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the Federal Food, Drug, and Cosmetic Act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

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9200 Corporate Boulevard
Rockville, Maryland 20850

In addition under section 522(a) of the Federal Food, Drug, and Cosmetic Act, (the act) manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under section 522(a)(1)(A) the above noted device as requiring postmarket surveillance.

Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

Postmarket Studies Document Center
1350 Piccard Drive (HFZ-544)
Rockville, Maryland 20850

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will be considered violations of section 522. In accordance with the Medical Device Amendments of 1992, failure of a manufacturer to meet its obligations under section 522 is a prohibited act under section 301(q)(1)(C) of the Federal Food, Drug and Cosmetic Act (the act)(21 U.S.C. 331(q)(1)(C)). Further, under section 502(t)(3) of the act (21 U.S.C. 352(t)(3), a device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the act. Violations of sections 301 or 502 may lead to regulatory actions including seizure of your product, injunction, prosecution, or civil money penalties or other FDA enforcement actions including (but not limited to) withdrawal of your PMA.

If you have any questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch, at (301) 594-0639.

Under section 519(e) of the act (as amended by the Safe Medical Devices Act in 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of device user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonably likely to have serious adverse consequences. FDA has designated your device for tracking.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR § 821.20(b) and the devices that FDA has designated for tracking at 21 CFR § 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705-10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)).

If you have questions concerning this approval order, please contact Doris Terry at (301) 443-8609.

Sincerely yours,

for Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular,
Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Dennis H. Connolly, M.D.
Product Regulation Manager
Cardiac Pacing Business Unit
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S4
Transvene Lead Models 6936, 6933, and 6939
Filed: January 20, 1995

Dear Dr. Connolly:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for modifications to the Transvene® Lead Technical Manuals. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the Federal Food, Drug, and Cosmetic Act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

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Rockville, Maryland 20850

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If you have any questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch, at (301) 594-0639.

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If you have questions concerning this approval order, please contact Doris Terry at (301) 443-8609.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular,
  Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
  Radiological Health

Enclosure

cc: HFZ-544 (Postmarket Surveillance Branch if appropriate)
HFZ-300 (Field Programs Branch - GMP)
HFZ-401 (Document Mail Center)
HFZ-402 (PMA Staff)
HFZ-450 (DCND)
HFZ-100 (OST Reviewer - if appropriate _____)
D.O.

APPROVAL ORDER FOR A PMA SUPPLEMENT (SA) Modified 6-9-95

Prepared by:DTerry:att/7/11/95

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450		7/11/95	450	Carkowski	8/9/95	402		8/14/95
450	HOT	7/11/95	450	Carkowski	8/10/95			
450		7/11/95		for T.Callol				

☆ U.S. GOVERNMENT PRINTING OFFICE 1991-619-771

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG 14 1995

Dennis H. Connolly, M.D.
Product Regulation Manager
Cardiac Pacing Business Unit
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S4
Transvene Lead Models 6936, 6933, and 6939
Filed: January 20, 1995

Dear Dr. Connolly:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for modifications to the Transvene® Lead Technical Manuals. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

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You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

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PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

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Rockville, Maryland 20850

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If you have any questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch, at (301) 594-0639.

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If you have questions concerning this approval order, please contact Doris Terry at (301) 443-8609.

Sincerely yours,

Arthur A. Carhouski

for Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular,
Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

JUL 20 1994

Dennis H. Connolly, M.D.
Product Regulation Manager
Tachyarrhythmia Division
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S3
Medtronic® Transvene Lead System
Filed: April 25, 1994
Amended: June 29, 1994

Dear Dr. Connolly:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval to modify the DF-1 connector pins of the Transvene® Lead Models 6936 and 6939. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Expiration dating for this device has been establish and approved at 2 years. This is to advise you that the protocol used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(8).

act)(21 U.S.C. 331(q)(1)(C)). Further, under section 502(t)(3) of the act (21 U.S.C. 352(t)(3), a device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the act. Violations of sections 301 or 502 may lead to regulatory actions including seizure of your product, injunction, prosecution, or civil money penalties or other FDA enforcement actions including (but not limited to) withdrawal of your PMA.

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If you have questions concerning this approval order, please contact Doris Terry at (301) 594-1523.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular, Respiratory,
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the Federal Food, Drug, and Cosmetic Act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

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Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

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Postmarket Studies Document Center
Suite 405 (HFZ-544)
1801 Rockville Pike
Rockville, Maryland 20852

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cc: HFZ-544
HFZ-300
HFZ-401
HFZ-402
HFZ-450
D.O.

APPROVAL ORDER FOR A PMA SUPPLEMENT (SA) Modified 5-27-94
Prepared by:DTERRY:jau:7/11/94

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450		7/14/94	402		7/18/94			
U		7/15						
450		7/15/94						

☆ U.S. GOVERNMENT PRINTING OFFICE 1991 0-311-771

DEPARTMENT OF HEAL. & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville MD 20850

JUL 20 1994

Dennis H. Connolly, M.D.
Product Regulation Manager
Tachyarrhythmia Division
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S3
Medtronic® Transvene Lead System
Filed: April 25, 1994
Amended: June 29, 1994

Dear Dr. Connolly:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval to modify the DF-1 connector pins of the Transvene® Lead Models 6936 and 6939. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

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194

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If you have questions concerning this approval order, please contact Doris Terry at (301) 594-1523.

Sincerely yours,

Lynne Reamer

for Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular, Respiratory,
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

JUN 24 [illegible]

Dennis H. Connolly, M.D.
Product Regulation Manager
Tachyarrhythmia Division
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S3
Medtronic® Transvene® Lead Models 6936 and 6939
Filed: April 25, 1994

Dear Dr. Connolly:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) supplement, which requests approval to modify the DF-1 connector pins of the Transvene® Lead Models 6936 and 6939. We are pleased to inform you that CDRH has determined that the PMA supplement is approvable subject to your submission of the following:

> Provide a description and the results of verification and/or quality control checks performed on a sample of the leads.

In addition to the above, an FDA inspection must find that the manufacturing facilities, methods and controls comply with applicable device Good Manufacturing Practice Regulations (21 CFR Part 820). If you have a manufacturing facility which is not prepared for production of the device, amend the PMA supplement as soon as possible and notify your District Office to indicate when the facility will be prepared to produce the device so that the FDA inspection can be rescheduled. If you have any questions regarding the status of your GMP inspection please contact your District Office or the Office of Compliance at (301) 594-4695.

Following receipt of an approvable letter, an applicant is required by 21 CFR 814.20(e) to update its pending PMA supplement with new safety and effectiveness information pertinent to the requested change or modification and learned about the device from ongoing or completed studies that may reasonably affect an evaluation of the safety or effectiveness of the device or that may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling. This updated reporting is limited to studies sponsored by the applicant or to which the applicant has reasonable access. The clinical update must be consistent with the data reporting provisions of the protocol.

CDRH will issue an approval order after the requested information has been reviewed and determined to be acceptable. You may not begin commercial distribution of the device as modified by this PMA supplement until you have received an approval order and final printed labeling has been submitted to FDA.

You may amend your PMA supplement as requested or withdraw it, or you may treat this letter as a formal denial of approval. If you choose the latter, you may request administrative review, either through a hearing or review by an independent advisory committee, under section 515(d)(3) and 515(g) of the Federal Food, Drug, and Cosmetic Act by filing a petition with the Food and Drug Administration, Dockets Management Branch (HFA-305), Room 1-23, 12420 Parklawn Drive, Rockville, Maryland 20857, within 30 days of the date you receive this letter. A petition for administrative review must be submitted in accordance with general administrative procedures for submission of documents to the Dockets Management Branch (21 CFR 10.20) and in the form of a petition for reconsideration (21 CFR 10.33). After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issues to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

As provided under 21 CFR 814.44(g), FDA will consider this PMA supplement to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA supplement amendment. You may, however, amend the PMA supplement within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA supplement within the 180-day period to (1) correct the above deficiency, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA supplement and will be assigned a new number. Under these circumstances, any resubmission will be given a new PMA supplement number and will be subject to the requirements of 21 CFR 814.20. A resubmission should be complete and self-contained because of potential difficulties in assembling files from storage.

In addition, under Section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under Section 522(a)(1)(A) the above noted device as requiring postmarket surveillance.

Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that

clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

Postmarket Studies Document Center
Suite 405 (HFZ-544)
1801 Rockville Pike
Rockville, Maryland 20852

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will cause your product to be misbranded and could lead to the imposition of civil money penalties or other regulatory actions. Any distribution of a misbranded device is a violation of the act and may result in a number of FDA enforcement actions, including (but not limited to) withdrawal of your PMA.

If you have questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch at (301) 594-0639.

Under Section 519(e) of the act (as amended by the Safe Medical Devices Act of 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of devices user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under Section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonable likely to have serious health consequences. FDA has designated your device for tracking.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR 821.20(b) and the devices that FDA has designated for

tracking at 21 CFR 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705 - 10709 (March 27, 1991), 57 FR 22973 - 22975 (May 29, 1992), and 58 FR 43451 - 43455 (August 16, 1993)).

If you have questions concerning this approvable letter, please contact Doris Terry at (301) 594-1523 or Arnold Alpert, Ph.D., at (301) 594-2186.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular, Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

HFZ-544

cc: HFZ-331
HFZ-401
HFZ-402
HFZ-450
D.O.
801:4-22-91
Prepared by:DTERRY:jau:5/17/94

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☆ U.S. GOVERNMENT PRINTING OFFICE 1991-[illegible]

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DEPARTMENT OF HEAL[illegible] & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville MD 20850

JUN 24 1994

Dennis H. Connolly, M.D.
Product Regulation Manager
Tachyarrhythmia Division
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S3
Medtronic® Transvene® Lead Models 6936 and 6939
Filed: April 25, 1994

Dear Dr. Connolly:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) supplement, which requests approval to modify the DF-1 connector pins of the Transvene® Lead Models 6936 and 6939. We are pleased to inform you that CDRH has determined that the PMA supplement is approvable subject to your submission of the following:

> Provide a description and the results of verification and/or quality control checks performed on a sample of the leads.

In addition to the above, an FDA inspection must find that the manufacturing facilities, methods and controls comply with applicable device Good Manufacturing Practice Regulations (21 CFR Part 820). If you have a manufacturing facility which is not prepared for production of the device, amend the PMA supplement as soon as possible and notify your District Office to indicate when the facility will be prepared to produce the device so that the FDA inspection can be rescheduled. If you have any questions regarding the status of your GMP inspection please contact your District Office or the Office of Compliance at (301) 594-4695.

Following receipt of an approvable letter, an applicant is required by 21 CFR 814.20(e) to update its pending PMA supplement with new safety and effectiveness information pertinent to the requested change or modification and learned about the device from ongoing or completed studies that may reasonably affect an evaluation of the safety or effectiveness of the device or that may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling. This updated reporting is limited to studies sponsored by the applicant or to which the applicant has reasonable access. The clinical update must be consistent with the data reporting provisions of the protocol.

CDRH will issue an approval order after the requested information has been reviewed and determined to be acceptable. You may not begin commercial distribution of the device as modified by this PMA supplement until you have received an approval order and final printed labeling has been submitted to FDA.

You may amend your PMA supplement as requested or withdraw it, or you may treat this letter as a formal denial of approval. If you choose the latter, you may request administrative review, either through a hearing or review by an independent advisory committee, under section 515(d)(3) and 515(g) of the Federal Food, Drug, and Cosmetic Act by filing a petition with the Food and Drug Administration, Dockets Management Branch (HFA-305), Room 1-23, 12420 Parklawn Drive, Rockville, Maryland 20857, within 30 days of the date you receive this letter. A petition for administrative review must be submitted in accordance with general administrative procedures for submission of documents to the Dockets Management Branch (21 CFR 10.20) and in the form of a petition for reconsideration (21 CFR 10.33). After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issues to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

As provided under 21 CFR 814.44(g), FDA will consider this PMA supplement to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA supplement amendment. You may, however, amend the PMA supplement within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA supplement within the 180-day period to (1) correct the above deficiency, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA supplement and will be assigned a new number. Under these circumstances, any resubmission will be given a new PMA supplement number and will be subject to the requirements of 21 CFR 814.20. A resubmission should be complete and self-contained because of potential difficulties in assembling files from storage.

In addition, under Section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under Section 522(a)(1)(A) the above noted device as requiring postmarket surveillance.

Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that

clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

Postmarket Studies Document Center
Suite 405 (HFZ-544)
1801 Rockville Pike
Rockville, Maryland 20852

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will cause your product to be misbranded and could lead to the imposition of civil money penalties or other regulatory actions. Any distribution of a misbranded device is a violation of the act and may result in a number of FDA enforcement actions, including (but not limited to) withdrawal of your PMA.

If you have questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch at (301) 594-0639.

Under Section 519(e) of the act (as amended by the Safe Medical Devices Act of 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of devices user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under Section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonable likely to have serious health consequences. FDA has designated your device for tracking.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR 821.20(b) and the devices that FDA has designated for

tracking at 21 CFR 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705 - 10709 (March 27, 1991), 57 FR 22973 - 22975 (May 29, 1992), and 58 FR 43451 - 43455 (August 16, 1993)).

If you have questions concerning this approvable letter, please contact Doris Terry at (301) 594-1523 or Arnold Alpert, Ph.D., at (301) 594-2186.

Sincerely yours,

for

Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular, Respiratory,
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

1994

Mr. Timothy D. Samsel
Director, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015/S1
Medtronic® Transvene Lead System
Filed: March 3, 1994
Amended: March 24, 30, April 5 and 13, 1994

Dear Mr. Samsel:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for the Transvene® DF-1 Lead Models 6933, 6936 and 6939, for revisions to the labeling and adding a caution regarding lead/defibrillator compatibility to the labeling. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter and upon concurrent submission of all approved labeling in final printed form.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the approved labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Expiration dating for this device has been establish and approved at 2 years. This is to advise you that the protocol used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(8).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

All required documents must be submitted in triplicate, unless otherwise specified, to the address below and shall reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

In addition, under Section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under Section 522(a)(1)(A) the device cleared for marketing by this order as requiring postmarket surveillance.

Within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you are required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

Submit five (5) copies to:

Postmarket Studies Document Center
Suite 405 (HFZ-544)
1801 Rockville Pike
Rockville, Maryland 20852

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will cause your product to be misbranded and could lead to the imposition of civil money penalties or other regulatory actions. Any distribution of a misbranded device is a violation of the act and may result in a number of FDA enforcement actions, including (but not limited to) withdrawal of your PMA.

If you have questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch at (301) 594-0639.

Under Section 519(e) of the act (as amended by the Safe Medical Devices Act of 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent

implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of devices user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under Section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonable likely to have serious health consequences. FDA has designated your device for tracking.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR 821.20(b) and the devices that FDA has designated for tracking at 21 CFR 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705 - 10709 (March 27, 1991), 57 FR 22973 - 22975 (May 29, 1992), and 58 FR 43451 - 43455 (August 16, 1993)).

If you have questions concerning this approval order, please contact Doris Terry at (301) 594-1523 or Arnold Alpert, Ph.D., at (301) 594-2186.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular, Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosures

cc: HFZ-~~107~~ 544
HFZ-331
HFZ-401
HFZ-402
HFZ-450
D.O.
801:4-22-91
Prepared by:DTERRY:jau:5/13/94
Revised:PMASTAFF:jau:6/14/94

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OK to correction (withdrawn needed)

☆ U.S. GOVERNMENT PRINTING OFFICE 1991-519-771

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville MD 20850

Mr. Timothy D. Samsel
Director, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

JUN 24 1994

Re: P920015/S1
Medtronic® Transvene Lead System
Filed: March 3, 1994
Amended: March 24, 30, April 5 and 13, 1994

Dear Mr. Samsel:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for the Transvene® DF-1 Lead Models 6933, 6936 and 6939, for revisions to the labeling and adding a caution regarding lead/defibrillator compatibility to the labeling. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter and upon concurrent submission of all approved labeling in final printed form.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the approved labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Expiration dating for this device has been establish and approved at 2 years. This is to advise you that the protocol used to establish this expiration dating is considered an approved protocol for the purpose of extending the expirstion dating as provided by 21 CFR 814.39(a)(8).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

All required documents must be submitted in triplicate, unless otherwise specified, to the address below and shall reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

In addition, under Section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under Section 522(a)(1)(A) the device cleared for marketing by this order as requiring postmarket surveillance.

Within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you are required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

Submit five (5) copies to:

Postmarket Studies Document Center
Suite 405 (HFZ-544)
1801 Rockville Pike
Rockville, Maryland 20852

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will cause your product to be misbranded and could lead to the imposition of civil money penalties or other regulatory actions. Any distribution of a misbranded device is a violation of the act and may result in a number of FDA enforcement actions, including (but not limited to) withdrawal of your PMA.

If you have questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch at (301) 594-0639.

Under Section 519(e) of the act (as amended by the Safe Medical Devices Act of 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent

implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of devices user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under Section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonable likely to have serious health consequences. FDA has designated your device for tracking.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR 821.20(b) and the devices that FDA has designated for tracking at 21 CFR 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705 - 10709 (March 27, 1991), 57 FR 22973 - 22975 (May 29, 1992), and 58 FR 43451 - 43455 (August 16, 1993)).

If you have questions concerning this approval order, please contact Doris Terry at (301) 594-1523 or Arnold Alpert, Ph.D., at (301) 594-2186.

Sincerely yours,

Lynne Reamer

for Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular, Respiratory,
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

Mr. Timothy D. Samsel
Director, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

MAY 25 1994

Re: P920015/S2 and P900061/S4
Medtronic® Model 7217B PCD® Tachyarrhythmia Control Device
and Epicardial and Subcutaneous Patch Lead Models 6721 S/M/L,
6921 S/M/L, 6939, and 6999
Filed: September 27, 1993
Amended: October 4, 1993 and March 11 and 25, 1994

Dear Mr. Samsel:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplements, which requests approval for a modification of the epicardial and subcutaneous patch leads. Based upon the information submitted, the PMA supplements are approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplements upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act.

The device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the approved labeling specifies the requirements that apply to the training of physicians who may use the device.

Expiration dating for this device has been establish and approved at 2 years. This is to advise you that the protocol used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(8).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

All required documents must be submitted in triplicate, unless otherwise specified, to the address below and shall reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

In addition, under Section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under Section 522(a)(1)(A) the device cleared for marketing by this order as requiring postmarket surveillance.

Within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you are required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

Submit five (5) copies to:

Postmarket Studies Document Center
Suite 405 (HFZ-107)
1801 Rockville Pike
Rockville, Maryland 20852

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will cause your product to be misbranded and could lead to the imposition of civil money penalties or other regulatory actions. Any distribution of a misbranded device is a violation of the act and may result in a number of FDA enforcement actions, including (but not limited to) withdrawal of your PMA.

If you have questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch at (301) 594-0639.

Under Section 519(e) of the act (as amended by the Safe Medical Devices Act of 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent

implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of devices user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under Section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonable likely to have serious health consequences. FDA has designated your device for tracking.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR 821.20(b) and the devices that FDA has designated for tracking at 21 CFR 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705 - 10709 (March 27, 1991), 57 FR 22973 - 22975 (May 29, 1992), and 58 FR 43451 - 43455 (August 16, 1993)).

If you have questions concerning this approval order, please contact Doris Terry at (301) 594-1523 or Arnold Alpert, Ph.D., at (301) 594-2186.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular, Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosures

cc: HFZ-107
HFZ-331
HFZ-401
HFZ-402
HFZ-450
D.O.
801:4-22-91
Prepared by:DTERRY:jau:5/13/94

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450	Terry	5/14/94	402	A. Alpert	5/25/94			
"	Salvatore	5/17						
450	Reamer	5/18/94						

☆ U.S. GOVERNMENT PRINTING OFFICE 1991-5(1-77)

186

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville MD 20850

Mr. Timothy D. Samsel
Director, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

MAY 25 1994

Re: P920015/S2 and P900061/S4
Medtronic® Model 7217B PCD® Tachyarrhythmia Control Device
and Epicardial and Subcutaneous Patch Lead Models 6721 S/M/L,
6921 S/M/L, 6939, and 6999
Filed: September 27, 1993
Amended: October 4, 1993 and March 11 and 25, 1994

Dear Mr. Samsel:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplements, which requests approval for a modification of the epicardial and subcutaneous patch leads. Based upon the information submitted, the PMA supplements are approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplements upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act.

The device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the approved labeling specifies the requirements that apply to the training of physicians who may use the device.

Expiration dating for this device has been establish and approved at 2 years. This is to advise you that the protocol used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(8).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

All required documents must be submitted in triplicate, unless otherwise specified, to the address below and shall reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

In addition, under Section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under Section 522(a)(1)(A) the device cleared for marketing by this order as requiring postmarket surveillance.

Within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you are required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

Submit five (5) copies to:

Postmarket Studies Document Center
Suite 405 (HFZ-107)
1801 Rockville Pike
Rockville, Maryland 20852

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will cause your product to be misbranded and could lead to the imposition of civil money penalties or other regulatory actions. Any distribution of a misbranded device is a violation of the act and may result in a number of FDA enforcement actions, including (but not limited to) withdrawal of your PMA.

If you have questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch at (301) 594-0639.

Under Section 519(e) of the act (as amended by the Safe Medical Devices Act of 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent

implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of devices user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under Section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonable likely to have serious health consequences. FDA has designated your device for tracking.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR 821.20(b) and the devices that FDA has designated for tracking at 21 CFR 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705 - 10709 (March 27, 1991), 57 FR 22973 - 22975 (May 29, 1992), and 58 FR 43451 - 43455 (August 16, 1993)).

If you have questions concerning this approval order, please contact Doris Terry at (301) 594-1523 or Arnold Alpert, Ph.D., at (301) 594-2186.

Sincerely yours,

Lynne Reamer

for Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular, Respiratory,
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

APR 20 1994

Mr. Timothy D. Samsel
Director, Regulatory Affairs
Cardiac Pacing Business
Tachyarrhythmia Division
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

RE: P920015/S1
Medtronic® Transvene® DF-1 Lead Models 6933, 6936 and 6939
Filed: March 3, 1994
Amended: March 24, 30, April 5 and 13, 1994

Dear Mr. Samsel:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for the Medtronic® Transvene® DF-1 Lead Models 6933, 6936, and 6939. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act.

The device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the approved labeling specifies the requirements that apply to the training of physicians who may use the device.

Expiration dating for this device has been established and approved at 2 years. This is to advise you that the protocol used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(8).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

All required documents must be submitted in triplicate, unless otherwise specified, to the address below and shall reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

In addition, under Section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under Section 522(a)(1)(A) the device cleared for marketing by this order as requiring postmarket surveillance.

Within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you are required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

Submit five (5) copies to:

Postmarket Studies Document Center
Suite 405 (HFZ-107)
1801 Rockville Pike
Rockville, Maryland 20852

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will cause your product to be misbranded and could lead to the imposition of civil money penalties or other regulatory actions. Any distribution of a misbranded device is a violation of the act and may result in a number of FDA enforcement actions, including (but not limited to) withdrawal of your PMA.

If you have questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch at (301) 594-0639.

Under Section 519(e) of the act (as amended by the Safe Medical Devices Act of 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent

implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of devices user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under Section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonable likely to have serious health consequences. FDA has designated your device for tracking.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR 821.20(b) and the devices that FDA has designated for tracking at 21 CFR 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705 - 10709 (March 27, 1991), 57 FR 22973 - 22975 (May 29, 1992), and 58 FR 43451 - 43455 (August 16, 1993)).

If you have questions concerning this approval order, please contact Doris Terry at (301) 594-1523 or Arnold Alpert, Ph.D., at (301) 594-2186.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular, Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosures

cc: HFZ-107
HFZ-331
HFZ-401
HFZ-402
HFZ-450
D.O.
801:4-22-91
Prepared by:DTERRY:jau:4/6/94

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450	Terry	4/7/94	450	Reamer	4/18/94			
"	[illegible]	4/13	402	A. Alpert	4/9/94			
"	Dahm	4/13						

☆ U.S. GOVERNMENT PRINTING OFFICE 1991-619-771

213

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville MD 20850

Mr. Timothy D. Samsel
Director, Regulatory Affairs
Cardiac Pacing Business
Tachyarrhythmia Division
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

APR 20 1994

RE: P920015/S1
Medtronic® Transvene® DF-1 Lead Models 6933, 6936 and 6939
Filed: March 3, 1994
Amended: March 24, 30, April 5 and 13, 1994

Dear Mr. Samsel:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for the Medtronic® Transvene® DF-1 Lead Models 6933, 6936, and 6939. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act.

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Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

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Suite 405 (HFZ-107)
1801 Rockville Pike
Rockville, Maryland 20852

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implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of devices user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under Section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonable likely to have serious health consequences. FDA has designated your device for tracking.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR 821.20(b) and the devices that FDA has designated for tracking at 21 CFR 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705 - 10709 (March 27, 1991), 57 FR 22973 - 22975 (May 29, 1992), and 58 FR 43451 - 43455 (August 16, 1993)).

If you have questions concerning this approval order, please contact Doris Terry at (301) 594-1523 or Arnold Alpert, Ph.D., at (301) 594-2186.

Sincerely yours,

Lynne Reamer

for Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular, Respiratory,
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

PREMARKET

INSPECTION

P920015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20850

M E M O R A N D U M

DATE: December 8, 1993

FROM: Field Programs Branch, CDRH, HFZ-331

SUBJECT: **FINAL APPROVAL - DOMESTIC AND FOREIGN FIRM**
PMA P920015

Mfrs.: Medtronic, Inc.
7000 Central Avenue NE
Fridley, MN 55432

Medtronic BV
Wenckebachstraat 10
6466 NC Kerkrade West
The Netherlands

TO: Chief, Program Operations Staff
HFZ-402

Applicant: Medtronic, Inc.
7000 Central Avenue NE
Fridley, MN 55432

Product: Transvene Lead System

This is in response to your request for final approval regarding the above PMA application. OC concurs with final approval for this PMA.

Vertleen Covington

Vertleen Covington

cc:
HFZ-331
DOE III
HFA-224
#92-79

DATE: December 6, 1993

TO: Vertleen J. Covington, PMA Coordinator,
Field Programs Branch

THRU: Acting Chief, Cardiovascular Branch, DOE III KAT 12/6/93

FROM: CSO, Cardiovascular Branch, DOE III TRACKING # 34914

SUBJECT: PMA P920015
Pre-Approval Inspection EIR Review
Inspection of 10/18-22/93

Manufacturer/
PMA Applicant: Medtronic, Inc.
7000 Cental Avenue, NE
Fridlay, MN 55432

PRODUCT: Transvene Defibrillator Lead Model 6966, and Bradycardia Pacing Leads Models 4004/M, 4016, 4016A, 4058/M, and 4082

DISTRICT: MIN-DO

DISTRICT
RECOMMENDATION: NAI, PMA Approval

INVESTIGATOR: Joseph M. Edwin and Timothy G. Philips

SITUATION: Situation 2 (In accordance with Part V of Compliance Program 7382.830, dated 9-1-91)

CB/DOE III
RECOMMENDATION: PMA Approval and Postmarket Inspection

An evaluation of the EIR for the inspection which took place on 10/18-22/93 at Medtronic, Inc., Fridley, Minnesota, and the exhibits indicate that the criteria for a Situation 2 have been met, in accordance with the requirements of Part V of Compliance Program 7382.830, dated 9-1-91. Conditions exist whereby there is a minimal probability that unsafe or ineffective devices will be produced and distributed.

Medtronic was last inspected on 5/10-14, 24, 25, and 27/93. The district found numerous GMP violations and did not concur with approval of the PMA. An FDA-483 was issued.

The current inspection was a followup to the above inspection concerning the Transvene Lead, Model 6966, to determine the firm's corrective actions to the FDA-483 issued at that inspection.

No FDA-483 was issued at the current inspection, however, Medtronic must continue to closely monitor the problem the leads are exhibiting with respect to corrosion. There have been recalls on the leads and the firm has attempted to alter the insulation, but it appears that the leads are still prone to metal ion oxidation (MIO). The Office of Surveillance and Biometrics (OSB) and the Office of Science Technology (OST) are aware of the problems and they have been working together and actively monitoring the MIO testing being performed at Medtronic. As yet, no compound has been developed to inhibit the degredation of the metal in the leads.

The district office will need to closely monitor the situation at the firm. A post-approval inspection is recommended.

Mary Ann Fitzgerald

DATE:	October 15, 1993
TO:	Vertleen J. Covington, PMA Coordinator, Field Programs Branch
THRU:	Acting Chief, Cardiovascular Branch, DOE III
FROM:	Consumer Safety Officer Cardiovascular Branch, DOE III
SUBJECT:	Amended Review PMA P920015 Pre-Approval Inspection May 10-14, 24, 25, 27, 1993 Manufacturer: Medtronic, Inc. 7000 Central Avenue NE Fridley, MN 55432
CFN:	2182208
PRODUCT:	Transvene Lead System
DISTRICT RECOMMENDATION:	Recommend non-concurrence with the PMA approval and that the district send a non-concurrence letter to the firm.
INVESTIGATORS:	Karen A. Coleman, ATL-DO Joseph M. Edwin, MIN-DO
SITUATION:	Situation 1 (In accordance with Part V of Compliance Program 7382.830, dated 9-1-91)
CDRH/OC RECOMMENDATION:	PMA Non-Approval

A review of the EIR, FDA 483, exhibits for Medtronic, Inc. facility, and the firm's response to the FDA 483 indicate that the criteria for a Situation 1 has been met, in accordance with the requirements of Part V of Compliance Program 7382.830, dated 9-1-91. Conditions exist whereby there is a reasonable probability that unsafe or ineffective devices will be produced and distributed.

The following is an evaluation of the EIR, exhibits, FDA 483, and firm's response to the FDA 483.

5

21 CFR 820.100(a)(1)

Failure to establish procedures for specification control measures to assure that the design basis for the device is correctly translated into approved specifications, as required by 21 CFR 820.100(a)(1). For example: 1. the firm has not validated critical Tachy Lead Manufacturing Operations currently used in production including but not limited to: Welding, Crimping, and Bonding Operations. Firm does not have data showing they have run a minimum of three consecutive successful runs to provide assurance these processes are validated; 2. a review of sterilization certification 1029 reports dated 4/10/85 (adding Permanent Lead Introducer [PLI]) and 3/4/92 (adding 6966 Tachy RV Lead), and 3/30/93 (update certification adding a Micromax 2 controller system) revealed: a) D values were determined using the samples in sterilization chambers loaded with "Dummy Packages". (Dummy Packages do not contain product or simulated product). Firm's documents and SOP's do not define or describe "Dummy Packages". As of 5/13/93 firm did not have a written explanation correlating product load density characteristics of a fully loaded sterilization chamber of product in packages versus a fully loaded chamber of "dummy packages". b) Firm does not have a report correlating the results contained in the 4/10/85 and 3/4/92 certificates with conclusions that show the PLI is actually the "worst case" product for this certification group. The PLI is routinely used as the sample for requalifying products or adding new products to this group. c) D value calculations for sterilization certificate 1029 dated 3/4/92 and 3/30/93 only shows the D value at confidence intervals calculated at (b)(4) Firm's SOP (b)(4) requires they calculate it at (b)(4) d) Certifications dated 3/4/92 and 3/30/93 do not identify the actual Sterility Assurance Level that will be obtained; 3. Coil Part Number 136213-005 3 filar .007" diameter (b)(4) process has not been validated.

This charge is supported by: 1. the discussions on pages 2 & 3 of the EIR; Exhibits F1-3, L1-6, N1-4, M1-6, G1-11, O1-4, J1, K2, F1-3, G1-11, and G8; and FDA 483 #1; 2. the discussion on pages 5-7 of the EIR; Exhibits P1-14, A1-22, E1-43, D1-13, B1-10, and C1-11; and FDA 483 #4; 3. the discussion on page 7 of the EIR, Exhibits Q1-9 and S1-26, and FDA 483 #5.

The firm's response to item #1 in the FDA 483 is inadequate. Their response discusses process monitoring and controls which are not acceptable procedures for validating their critical manufacturing operations.

The firm's response to item #4 in the FDA 483 is inadequate. Their response discusses preparing a report which will correlate the data they have already collected for their sterilization process. Unfortunately, the variables are different and therefore cannot be correlated. The firm must submit an acceptable procedure for validating their sterilization process.

Firm's response to item #5 in the FDA 483 is adequate.

21 CFR 820.181

Failure to prepare, date, and sign by a designated individual device master records, as required by 21 CFR 820.181. For example, a review of the Plans and Qualification Reports for the (b)(4) (b)(4) Model 6884 Split Build; and Lead Model 6966 Connector Subassembly revealed the following: a) The plans did not require process validation. b) Sampling plans were not identified. c) Test methods or procedures are not always identified. d) They do not describe how the results will be interpreted and/or analyzed.

This charge is supported by the discussions on pages 3 & 4 of the EIR; Exhibits F1-3, G1-11, L1-6, M1-6, N1-4, and O1-4; and FDA 483 #2.

Firm's response to item #2 in the FDA 483 is adequate.

21 CFR 820.160

Failure to check and, where necessary, test for conformance with device specifications each production run, lot, or batch prior to release for distribution, as required by 21 CFR 820.160. For example, Transvene Leads have not been tested under simulated use conditions.

This charge is supported by the discussion on pages 7 and 8, of the EIR and FDA 483 #6.

Firm's response to item #6 in the FDA 483 is adequate.

7

21 CFR 820.162

Failure to investigate any failure of a device to meet performance specifications after it has been released for distribution, as required by 21 CFR 820.162. For example, Transvene Lead Model 6884 (b)(4) was returned and found to have cosmetic MIO on both the inner and middle coil insulation. The coils were not analyzed/examined to verify that the platinum sputtering process was done to specification.

This charge is supported by the discussion on page 8 of the EIR; exhibits S1-26, Q1-9, T1-4, and U1-3; and FDA 483 #7.

Firm's response to item #7 of the FDA 483 is adequate.

UNSUPPORTABLE FDA 483 OBSERVATIONS

FDA 483 #3 - **There is no GMP requirement for design issues.**

Kent A. Berthold

Prep:KABerthold:10-15-93
Review:KATrautman: KAT 11/29/93
Final:

bcc:
HFA-224
HFZ-300
DOE III Chronological File
Firm File
Kent A. Berthold
Kimberly A. Trautman

C:\WP51\LETTER\MEDTRONC.PMA

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20850

M E M O R A N D U M

DATE: July 19, 1993

FROM: Field Programs Branch CDRH, HFZ-331

SUBJECT: GMP Inspection **NONCLEARANCE**
PMA P920015

TO: Premarket Approval Coordinator
HFZ-402

Mfrs.: Medtronic, Inc.
7000 Central Avenue NE
Fridley, MN 55432

Medtronic B.V.
Wenckebatchstraat 10
Kerkrade, The Netherlands

Applicant: Medtronic, Inc.
7000 Central Avenue NE
Fridley, MN 55432

Product: Transvene Lead System

An inspection of the above referenced manufacturers was accomplished on 5-27-93 and 12-18-92. On the basis of the information reviewed, Medtronic Inc., located in Fridley, MN, has an unacceptable GMP program.

Attached, please find a copy of the review performed by the Manufacturing Quality Assurance Branch which details the GMP deficiencies revealed by the inspection.

On the basis of the information reviewed, Medtronic B.V., located in The Netherlands, has an acceptable GMP program.

PLEASE NOTE THAT NEITHER A COPY OF THIS EVALUATION MAY BE SENT TO THE FIRM, NOR MAY ITS CONTENTS BE DISCUSSED WITH THEM.

A follow-up inspection is being requested for the above manufacturing site. When that inspection has been completed and we have had an opportunity to review the results, you will be advised of the findings of the inspection.

This should complete all of the sites awaiting inspection that are currently outstanding concerning this PMA.

Vertleen Covington

Vertleen Covington

Attachment
cc:
HFZ-331
HFA-224
HFZ-332
HFR-MW300
#92-79

10

MAF

DATE:	July 6, 1993
TO:	Vertleen J. Covington, PMA Coordinator, Field Programs Branch
THRU:	Acting Chief, Cardiovascular Branch, DOE III 7/7/93
FROM:	Consumer Safety Officer Cardiovascular Branch, DOE III
SUBJECT:	PMA P920015 Pre-Approval Inspection May 10-14, 24, 25, 27, 1993 Manufacturer: Medtronic, Inc. 7000 Central Avenue NE Fridley, MN 55432
CFN:	2182208
PRODUCT:	Transvene Lead System
DISTRICT RECOMMENDATION:	Recommend non-concurrence with the PMA approval and that the district send a non-concurrence letter to the firm.
INVESTIGATORS:	Karen A. Coleman, ATL-DO Joseph M. Edwin, MIN-D)
SITUATION:	Situation 1 (In accordance with Part V of Compliance Program 7382.830, dated 9-1-91)
CDRH/OCS RECOMMENDATION:	PMA Non-Approval

A review of the EIR, FDA 483, and exhibits for Medtronic, Inc. facility indicate that the criteria for a Situation 1 has been met, in accordance with the requirements of Part V of Compliance Program 7382.830, dated 9-1-91. Conditions exist whereby there is a reasonable probability that unsafe or ineffective devices will be produced and distributed.

The following is an evaluation of the EIR, exhibits, and FDA 483. The firm did not respond to the observations made by the investigator on the FDA 483.

11

21 CFR 820.100(a)(1)

Failure to establish procedures for specification control measures to assure that the design basis for the device is correctly translated into approved specifications, as required by 21 CFR 820.100(a)(1). For example: 1. the firm has not validated critical Tachy Lead Manufacturing Operations currently used in production including but not limited to: Welding, Crimping, and Bonding Operations. Firm does not have data showing they have run a minimum of three consecutive successful runs to provide assurance these processes are validated; 2. a review of sterilization certification 1029 reports dated 4/10/85 (adding Permanent Lead Introducer [PLI]) and 3/4/92 (adding 6966 Tachy RV Lead), and 3/30/93 (update certification adding a Micromax 2 controller system) revealed: a) D values were determined using the samples in sterilization chambers loaded with "Dummy Packages". (Dummy Packages do not contain product or simulated product). Firm's documents and SOP's do not define or describe "Dummy Packages". As of 5/13/93 firm did not have a written explanation correlating product load density characteristics of a fully loaded sterilization chamber of product in packages versus a fully loaded chamber of "dummy packages". b) Firm does not have a report correlating the results contained in the 4/10/85 and 3/4/92 certificates with conclusions that show the PLI is actually the "worst case" product for this certification group. The PLI is routinely used as the sample for requalifying products or adding new products to this group. c) D value calculations for sterilization certificate 1029 dated 3/4/92 and 3/30/93 only shows the D value at confidence intervals calculated at (b)(4) Firm's SOP (b)(4) requires they calculate it at (b)(4) d) Certifications dated 3/4/92 and 3/30/93 do not identify the actual Sterility Assurance Level that will be obtained; 3. Coil Part Number 136213-005 3 filar .007" diameter platinum coil sputtering process has not been validated.

This charge is supported by: 1. the discussions on pages 2 & 3 of the EIR; Exhibits F1-3, L1-6, N1-4, M1-6, G1-11, O1-4, J1, K2, F1-3, G1-11, and G8; and FDA 483 #1; 2. the discussion on pages 5-7 of the EIR; Exhibits P1-14, A1-22, E1-43, D1-13, B1-10, and C1-11; and FDA 483 #4; 3. the discussion on page 7 of the EIR, Exhibits Q1-9 and S1-26, and FDA 483 #5.

21 CFR 820.181

Failure to prepare, date, and sign by a designated individual device master records, as required by 21 CFR 820.181. For example, a review of the Plans and Qualification Reports for the New Laser Source; Model 6884 Split Build; and Lead Model 6966 Connector Subassembly revealed the following: a) The plans did not require process validation. b) Sampling plans were not identified. c) Test methods or procedures are not always identified. d) They do not describe how the results will be interpreted and/or analyzed.

This charge is supported by the discussions on pages 3 & 4 of the EIR; Exhibits F1-3, G1-11, L1-6, M1-6, N1-4, and O1-4; and FDA 483 #2.

21 CFR 820.160

Failure to check and, where necessary, test for conformance with device specifications each production run, lot, or batch prior to release for distribution, as required by 21 CFR 820.160. For example, Transvene Leads have not been tested under simulated use conditions.

This charge is supported by the discussion on pages 7 and 8, of the EIR and FDA 483 #6.

21 CFR 820.162

Failure to investigate any failure of a device to meet performance specifications after it has been released for distribution, as required by 21 CFR 820.162. For example, Transvene Lead Model 6884 (b) (6) (b)(6) was returned and found to have cosmetic MIO on both the inner and middle coil insulation. The coils were not analyzed/examined to verify that the platinum sputtering process was done to specification.

This charge is supported by the discussion on page 8 of the EIR; exhibits S1-26, Q1-9, T1-4, and U1-3; and FDA 483 #7.

UNSUPPORTABLE FDA 483 OBSERVATIONS

FDA 483 #3 - There is no GMP requirement for design issues.

Kent A. Berthold

DATE: April 8, 1993 and amended May 4, 1993

FROM: CSO, MQAB, HFZ-332

THROUGH: Acting Chief, GDS, MQAB, HFZ-332

TO: Chief, MQAB, HFZ-332

SUBJECT: Review of foreign reinspection EIR

Medtronic B.V.
Wenckebatchstraat 10
Kerkrade, The Netherlands

EIR, dated 12/14-18/92
Firm's responses, dated 1/26/93 and 4/21/93,
Telecon between Kopesky et al., and Mowitt, dated 4/28/93

CFN: 9610980

DEVICE: Pacemakers and pacer leads (critical devices)

INVESTIGATOR: Nicholas Nance

IPTSB RECOMMENDATION: Maintain automatic detention

SITUATION: Situation 2, in accordance with criteria of Part V of CP 7382.830, dated 9/1/91

A review of the EIR, dated 12/14-18/92, and the firm's responses, dated 1/26/93, and 4/21/93, indicates that the criteria may be downgraded to Situation 2, in accordance with the criteria of Part V of CP 7382.830, dated 9/1/91. Due to mailing problems, the review was confined to a draft version of the inspection report without exhibits.

The firm was placed on Automatic Detention on 3/25/92, following an inspection in January 1992. That inspection was a pre-approval inspection for PMA P900061, a multiprogrammable tachyarrhythmia control system including an implantable pacer-cardioverter-defibrillator (PCD) pulse generator. This PMA has been withdrawn by the firm since the initial inspection, and the product is being manufactured at the Minnesota facility. Following the initial review of the inspection report on April 8, 1993, it was felt that additional information was required before making a final decision. The firm was sent a list of outstanding questions (see attached). The firm sent responses to these questions on April 21, 1993, and the responses were discussed with them on the telephone on 4/28/93.

A letter written on August 3, 1992, by MQAB informed the firm that it may request reinspection, and that two questions remained unresolved and would be covered during any reinspection. The first related to the determination of residuals following the (b)(4) sterilization

cycle, and was adequately answered by information provided by the firm in its 1/26/93 response.

The second question of MQAB's letter was not covered during the recent inspection, but is addressed in a memo written by the firm on 12/17/93. Since the question related to the testing matrix, which had been evaluated and questioned previously by Al Taylor in OST, a copy of the current response was sent to Al Taylor with a request for his evaluation of the adequacy of the response. After his review, Al said that the firm's response appears reasonable, and that it has demonstrated that all issues have been addressed. While he might quibble with some details, Al said that overall the response is adequate, and that, if subsequently there are failures in components, we can reassess the relevant details.

The following supportable deficiencies were noted on the FDA 483:

1. 21 CFR 820.100(b)(2)

   Failure to conduct all processing control operations in a manner designed to assure that the device conforms to all applicable specifications, as required by 21 CFR 820.100(b)(2). For example:

   a. Corrective action records indicate at least 15 sterilization process deviations since 4/14/92, with six occurring between 9/20/92, and 12/16/92. Three of these six deviations resulted in positive growth of biological indicators.

      The charge is supported by item 3 of the FDA 483.

      The firm's response appear to be adequate. The response included a table showing the deviations, the subsequent investigational analyses, and the actions taken. The investigations appear to be thorough, and the actions taken appear to be appropriate on the whole. In most cases, the lots were resterilized.

      The firm undertook an analysis of the positive BI's. The analysis concluded that the problem was due to inadequate pre-humidification for the indicator ampules which have hydrophobic lids designed to prevent contamination and media evaporation during incubation. It was theorized that the lids retard humidification of the spore in the ampule and that devices in the load would not be similarly affected. The firm has not had problems with inoculated devices. The sterilization process includes minimal pre-humidification with no external preconditioning and only [64] minutes of pre-humidification in the chamber under ambient conditions. Studies found that pre-humidification under vacuum solved the problem. The cycle was changed to require pre-humidification [64] minutes] to be done under vacuum.

      The firm submitted summaries and processing records for two sets of half-cycle validation studies. One reported results

with inoculated product ([redacted] minute half cycles) and one reported results for biological indicators [redacted] minute half-cycles). Documentation indicates a full cycle of [redacted] minutes. The validation studies appear to be adequate.

During the 4/27/93 phone conversation, representatives of the firm said that they use only two cycles for all products, one [redacted] minutes and one [redacted] hours. The pre-humidification under vacuum was incorporated in the [redacted] minute cycle only, because the [redacted] hour cycle has had no indication of problems, i.e., no positive BIs. The firm has no current plans for using the [redacted] minute cycle for devices produced for exportation to the U.S. Between the responses of 1/26 and 4/21/93, the firm has had one positive BI for the [redacted] minute cycle. After investigation, the firm attributed the problem to an outlayer BI. During the next inspection, the firm should be asked about any further positive BIs.

b. Medtronic's sterilization procedures indicate the dwell temperature parameters are [redacted], but in fact, Medtronic allows for a "cold spot" dwell minimum temperature of [redacted]

The charge is supported by item 4 of the FDA 483.

The firm's response appears to be adequate. The firm provided evidence that it has validated that sterilization occurs at the "cold spot" with the given specifications. Data was included showing successful sterilization of inoculated products and BIs placed in the cold spot during validation studies. The firm provided evidence that the specifications have been changed to allow temperatures of [redacted] during the first [redacted] minutes of the cycle. Since the validation study included these same conditions, the change to the specifications appears to be acceptable.

2. **21 CFR 820.20(a)(4)**

Failure to assure that all quality assurance checks are appropriate and adequate for their purpose, as required by 21 CFR 820.20(a)(4). For example, requirements for incoming inspectional procedures for biological indicators (BIs) were changed to eliminate the determination of the lethality of the indicators and there is no documentation of the justification for eliminating these tests.

The charge is supported by item 6 of the FDA 483.

The firm was questioned in the April 8, 1993, "Outstanding Questions," about the appropriateness of dropping lethality testing in light of the fact that the firm has suspected that BIs being used have appeared to vary in lethality and since testing by the BI manufacturer suggested that shipping might effect lethality.

In its April 21, 1993, response, the firm quoted USP XXII which states that users of BIs are unlikely to have the specialized and

standardized testing equipment to adequately test resistance of BIs. According to USP, the resistance characteristics of the same BI may differ from the original findings owing to differences in the sterilizing apparatus and conditions. Medtronic therefore, decided to rely on the certificate of (b)(4) the BI manufacturer. Medtronic also submitted results of a study of D-value for shipped and unshipped indicators. This study showed a difference of (b)(4) between the (b)(4) groups, which Medtronic points out is within the (b)(4) of the label claim required by USP. A letter was included in the response from (b)(4) which states that its experience shows no significant changes during shipping.

In the response, the firm said that it had not followed its own procedure requiring a description or rationale for a revision and change. The firm said that by February 15, 1993, it would have implemented a change in that procedure to include criteria for detailing the description or rationale for changes.

The firm's response appears to be adequate. Since we do not require lethality testing of incoming BIs at other firms, we can not require it of this firm. During the next inspection, the revision of the procedure should be confirmed.

3. **21 CFR 820.20(a)(2)**

Failure to have documentation showing approval or rejection of all manufacturing materials, as required by 21 CFR 820.20(a)(2). For example, incoming inspection records for Attest BIs do not show the actual quantity sampled, accepted, or rejected. Inspection forms indicate the need for testing, but the procedures do not.

The charge is supported by item 7 of the FDA 483.

The firm's response appears to be adequate. The procedure has been updated to clarify the exact quantity needed for testing and to eliminate inconsistencies between the inspection forms and the procedure. The inspection form was modified to provide for unambiguous recording of the quantity sampled, and the number rejected and accepted. Documentation submitted by the firm supports this claim.

4. **21 CFR 820.184**

Failure to maintain a device history record to demonstrate that the device is manufactured in accordance with the device master record, as required by 21 CFR 820.184. For example, incoming inspection records indicate that (b)(4) PCD hybrid boards p/n 403521-002, lot (b)(4) critical components, were accepted on 11/22/92 even though:

a. one board lacked evidence of required testing;
b. many vendor board certifications lacked required vendor manufacturing data; and,
c. evidence of unexplained/unauthorized/unrequired testing of some boards by Medtronic.

The charge is supported by item 8 of the FDA 483. The charge is particularly significant because previous correspondence with the firm has indicated that it relies heavily on the quality controls of suppliers and the certificates that they provide. The concern is as much that Medtronic failed to note the deficiencies itself during routine incoming inspection, as that the vendors failed to complete certificates correctly.

The firm's response may be adequate if the next inspection finds compliance with Medtronic's revised procedures. Following discovery of the problems by the FDA investigator, the firm placed a product hold order on all potentially affected devices. Investigations of each deficient certificate were performed and decisions made regarding the disposition of the affected components and devices. The investigations and decisions appear to be adequate. The vendor was informed about the problems and asked to implement corrective action. The certificate has been redesigned to minimize the potential for omissions and to include documentation of a records check by Medtronic as a part of the receiving inspection. Procedures were revised to include additional detail for incoming inspection of certificates. A vendor audit was to have been completed during the week of January 25, 1993.

The following charges cited on the FDA 483 are not supportable as GMP deficiencies:

1. Items 1 and 2 cite the firm for recreation of records. In the first instance, sterilization validation plans/records were recreated and resigned when the original was lost. The records were pulled from the computer and resigned (with a previous wrong date). In the second instance, a sterilization record was recreated for the FDA investigator. Since both were done in preparation for, or during, the FDA inspection, these examples are not indicative of systemic problems.

2. Item 5 cites the firm for using BIs from a specified lot in several sterilization lots when a decision had been made previously to stop the use of BIs from this lot. There is no documented release or justification for the use of this lot. The charge is not supportable because documentation is not available to indicate whether the original decision to stop using that lot had been documented, authorized, and issued as an official directive. The lot of BIs met the firm's documented specifications.

3. Item 9 cites the firm for not trending corrective actions, production and distribution hold orders, and for not documenting the reasons for corrective actions. The GMP regulation does not require such trending.

Sarah Mowitt

Sarah Mowitt

Medtronic B.V.
Kerkrade, The Netherlands

April 8, 1993

Inspection of 12/14/92

OUTSTANDING QUESTIONS

1. Regarding the sterilization failures (item 3 of the FDA 483):

   a. Since your January 26 letter, have there been any positive biological indicators resulting from sterilizing the leads in program 8?

   b. Provide processing records for the three (b)(4) minute half-cycles. Also, (b)(4) (page 11 of 18 of your attachment 3) indicates that biological indicators were to be used, but no results were given. Please provide these results for the indicators.

   c. What specifications have you established for the level of vacuum required during the pre-humidification phase?

   d. Which leads are to be sterilized with the (b)(4) minute cycle and which are to be sterilized by the (b)(4) hour cycle? Why are they sterilized differently?

   e. Have you determined whether the pre-humidification problem that you found in program 2 may also be a factor in your other sterilization programs?

2. Regarding temperature specifications for the sterilizer "cold spot" (item 4 of the FDA 483):

   Provide evidence that sterilization occurred during validation runs at the "cold spot." Evidence should include data showing successful sterilization of inoculated products or biological indicators which had been placed in the "cold spot" during the half-cycle runs. If such evidence does not exist, the dwell period during routine processing should not start until temperatures in all areas of the chamber, including the "cold spot" have attained (b)(4) your specification.

3. Regarding the elimination of the incoming test for lethality of biological indicators (item 6 of the FDA 483):

   Provide justification for the eliminating the lethality testing of incoming biological indicators in light of: 1) your recent experiences with variations in the lethality of indicators; and 2) testing by (b)(4) which suggested that shipping of the indicators might affect lethality. It would appear appropriate to either continue testing lethality during acceptance of the indicators, at least for awhile, or to further investigate the possibility that shipped indicators may have lethality that differs from the certified lethality.

INSPECTIONAL GUIDANCE - IPTSB

May 4, 1993

FIRM: Medtronic B.V.
Wenckebatchstraat 10
Kerkrade, The Netherlands

DEVICES: Pacemakers and pacemaker leads

CDRH/OCS Reviewer: Sarah Mowitt, CSO, MQAB, HFZ-332, (301) 427-1128

During the next inspection of this firm address the following:

1. Have there been any positive biological indicators following sterilization? The firm has experienced isolated incidences of positive BIs with the program (b)(4) sterilization cycle.

2. Do records for incoming testing of biological indicators show the actual quantity sampled, accepted, and rejected?

3. Do certificates provided by the suppliers include all required manufacturing and testing data?

4. Has the firm completed its revision of Procedure (b)(4) to include criteria for detailing the description or rationale for changes to be recorded on production operation documents?

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM, NOR SHOWN TO THEM DURING THE INSPECTION.

PMA NOTIFICATION FORMAT

DATE: 6/4/93

FROM: Director, Minneapolis District, HFR-MW 300

SUBJ: PMA 920015 --------/s------

TO: ~~Mary Ann Fitzgerald,~~ Kathleen Covington
FAX: Division of Compliance Programs--HFZ-331
301-427-1076

INFO: Medical Products Quality Assurance Staff, HFC-121
427-1963 (Notified via CI/OAI Notification EMS 6/3/93)

FAX: A.J. Beebe, Field Medical Device Committee
HFR-NE1 FAX: 718-965-5759

PRODUCT: TRANSVENE LEAD SYSTEM

APPLICANT: Name: Medtronic, Inc
City: Minneapolis
State: MN

ESTAB: CFN: 2182208
Name: Medtronic, Inc.
Street: 7000 Central Ave. NE.
City: MINNEAPOLIS
State: MN

ESTAB TYPE: MFG (MFG, REPACKER, LAB)

DISTRICT RECOMMENDATION:
WITHHOLD (APPROVE, WITHHOLD, PENDING)

DATE CONCURRENCE REQUESTED FROM CDRH: 6/3/93 (per telecon w/ Kim Trautman, CDRH)

DATE PMA AUDITED:
5/10-14, 24, 25, 27/93 (ENTER "NONE" IF NO PRODUCT SPECIFIC EI CONDUCTED)

COMMENTS:

John Feldman
Minneapolis
District Director

21

JMS

DATE : May 4, 1992

TO : James M. Simpson, Program Analyst, HFZ-331

THRU : Chief, MQAB, HFZ-332 5/5/92

FROM : David Kunin, CSO, MQAB, HFZ-332

SUBJECT : Original PMA : P920015, dated 3/31/92

Applicant : Medtronic Inc.
7000 Central Avenue, NE
Minneapolis, MN 55432-3576

Manufacturing Facility : Medtronic Inc.
Rice Creek Facility
7000 Central Avenue N.E.
Minneapolis, MN 55432
(Transvene Lead 6966)

Manufacturing Facility : Medtronic, B.V.
Wenchebachstraat 10
6466 NC Kerkrade West
The Netherlands
(Transvene LEAD 6963 AND 6999)

Manufacturing Facility : Medtronic Milaca
900 6th Ave. N.E.
Milaca, MN 56353
(System Components)

DEVICE : PCD Transvene System, Lead Models 6963, 6966, and 6999. Multiprogrammable Tachyarrhythmia Control System with Non-Thoracotomy Cardioversion and Defibrillation Electrodes. This is a critical device.

MQAB Recommendation : Deficiency Letter

This original PMA P920015, dated 3/31/92 is for Medtronics' PCD Transvene System. Medtronic, Rice Creek, Minnesota facility was last inspected by the FDA January 21-February 8, 1992 and was classified NAI. Medtronic, B.V. facility was last inspected by the FDA January 6-9, 1992, and as a result is currently on Automatic Detention.

A deficiency list is attached to this review, and must be sent to the Applicant.

David Kunin

MAR 25 1992

REGISTERED MAIL - RETURN RECEIPT REQUESTED

WARNING LETTER

Frank E. Sprengers
Vice President
Medtronic European Service and Technology Center
Medtronic B.V.
Wenckebachstraat 10
6466 NC Kerkrade, Holland

Dear Mr. Sprengers:

During an inspection of your facility located in Kerkrade, Holland on January 6 through 9, 1992, our investigator observed conditions which may contribute to serious violations of the Federal Food, Drug, and Cosmetic Act (the Act) and deviations from implementing regulations as follows:

The pacer-cardioverter-defibrillator (PCD) implantable pulse generators and other devices manufactured by your firm are or may become adulterated in accordance with Section 501(h) of the Act because the methods used in, and the facilities and controls used for the manufacture, packaging, storage, and installation of the devices are not in conformity with the Medical Device Good Manufacturing Practice regulations, as prescribed by Title 21, Code of Federal Regulations Part 820, as follows:

1. Failure to check and, where necessary, test for conformance with device specifications, each production run, lot or batch prior to release for distribution, as required by 21 CFR 820.160. For example:

   a. The ventricular fibrillation and ventricular tachycardia detection algorithm is not checked or tested in the finished device for all logic paths shown in the logic flow diagram in product specifications.

   b. Not all electrical specifications are checked or tested in the finished device for conformance to stated device specifications and there is no documentation to demonstrate conformance with specifications.

2. Failure to assure that a critical device or component which does not meet its performance specification is investigated, as required by 21 CFR 820.161. For example:

   a. Positive test results for two sterilization loads (b)(4) and (b)(4) were not adequately investigated for mechanism and cause of failure, nor were the sterilization loads preceding and following the failed loads.

   b. Statistical process control (SPC) charts for (b)(4) (b)(4) indicate seven incidences of range data exceeding upper control limits without any documented corrective action.

   c. SPC control charts for laser seam weld indicate a lot (b)(4) that did not conform to specified weld penetration at the required (b)(4) confidence level and numerous incidences of weld penetration measurement results below acceptance specifications with no indication of investigation or corrective action.

3. Failure to inspect, sample, and test components for conformance to specifications, as required by 21 CFR 820.81(a). For example, PCB Assembly (b)(4), a critical component for the PCD device, is not sampled and tested as an incoming component for conformance to electrical specifications. Failures in released PCD devices (serial numbers (b)(4) and (b)(4) were traced to the failure of the C7 capacitor which is located in PCB-ASSY (b)(4)

4. Failure of the quality assurance program to included procedures adequate to assure approval or rejection of all manufacturing materials, as required by 21 CFR 820.20(a)(2). For example, (b)(4) is received via a supplier certificate, but no verification of the certificate for conformance to specifications is performed.

5. Failure to assure that the design basis for the device is correctly translated into approved specifications, as required by 21 CFR 820.100(a)(1). For example, validation of the weld seam hardness is inadequate because:

   a. The number of hardness data points is not statistically valid to conclude hardness uniformity and consistency (only one seam point is tested in each of a limited number of samples).

b. Validation protocol requirements include inconsistencies in hardness specifications, at one point requiring a minimum of (b) (4) and at another requiring hardness not greater than (b) (4).

6. Failure to assure that the device history record demonstrates that the device is manufactured in accordance with the device master record, as required by 21 CFR 820.184. For example:

a. SPC control charts used to assess the adequacy of the laser seam welds are deficient in that they have no upper and lower control levels and data points for lots (b)(4) and (b)(4) are incorrectly located on the X graph.

b. Automated Testing Equipment (ATE) serial number entry errors were noted, in that:

i. Low power (b) (4)(b)(4) was entered into the ATE test record as (b)(4)

ii. A documentation entry error by the operator resulted in the wrong low power hybrid being tested by the inspector.

7. Failure of the device master record to include, or refer to the location of, device specifications and production process specifications, as required by 21 CFR 820.181. For example:

a. The device master record does not include a complete list of all available specification documents and their locations, and does not including engineering change notices and software information.

b. Electrical specifications are inconsistent for PCB assembly (b)(4) with receiving records requiring (b)(4) while engineering specification (b)(4) requires >.

8. Failure to assure that all production and quality assurance measurement equipment is calibrated according to written procedures, as required by 21 CFR 820.61. For example:

a. There is no written schedule and procedure for calibration of laser welding equipment.

b. Calibration of the pull tester (b) (4)(b)(4) is not always calibrated at the (b)(4) month interval required by the calibration procedure.

c. Laser calibration records do not include documentation of the items accomplished during calibration.

9. Failure to assure that environmental conditions are controlled to prevent contamination of the device, as required by 21 CFR 820.46. For example, trimming of lead above open hybrid devices could result in contamination with wire trimming.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure that all products manufactured, distributed, held, and labeled by your firm are in compliance with the provisions of the Act.

Given the serious nature of these violations, all medical devices from Medtronic B.V. in Kerkrade, Holland will be refused entry into the United States until these violations are corrected. Until these violations are corrected, federal agencies will be informed that the Food and Drug Administration recommends against the award of contracts for affected products. Additionally, no premarket approval (PMA) applications or PMA supplements will be approved until the above violations are corrected.

In order to remove your devices from this detention, it will be necessary for you to provide a written response to the charges in this Warning Letter for our review. After we notify you that the response is adequate, it will be your responsibility to schedule another inspection of your facility. As soon as this inspection has taken place, and the implementation of your corrections has been verified, your products may resume entry into this country.

Please advise us in writing as to the specific actions taken or intended to be taken to correct these deficiencies. We acknowledge receipt of your February 20, 1992, letter in response to the inspection, and you may choose to reference that letter in your response to this Warning Letter. Please include any and all documentation to show that adequate correction has been achieved. In the case of future corrections, an estimated date of completion, and documentation showing plans for correction, should be included with your response to this letter. To expedite our review, please provide an English translation of the supporting documentation with your response. Please address your response and any questions to:

Ms. Carol Shirk
U.S. Food and Drug Administration
CDRH, Office of Compliance and Surveillance (HFZ-331)
1390 Piccard Drive
Rockville, Maryland 20850

Should you require any assistance in understanding the contents of this letter, do not hesitate to contact Ms. Shirk at the above address or at (301) 427-1125 or FAX (301) 427-1076.

Sincerely yours,

Ronald M. Johnson
Director
Office of Compliance and
Surveillance
Center for Devices and
Radiological Health

HFA-224
HFC-120
HFC-134
HFC-230
HFI-35 (purged)
HFZ-300
HFZ-323
HFZ-325
HFZ-330
HFZ-331 (Shirk)
HFZ-331 (Fitzgerald)
HFZ-332 (FFile)
HFZ-332 (Mowitt)
HFR-MW340 (Medtronics Inc., Rice Creek, MN)
HFR-SE540
Redrafted by: dcq: 3/25/92
Final: dcq/3/25/92

DATE: December 1, 1992

TO: Mary Ann Fitzgerald, PDAB, HFZ-331

THRU: Acting Chief, MQAB, HFZ-332 SAM 12/2/92

FROM: David Kunin, MQAB, HFZ-332

SUBJECT: PMA Amendment P920015A, dated October 26, 1992

APPLICANT: Medtronic, Inc.
7000 Central Ave. N.E.
Minneapolis, Minnesota 55432-3576

MANUFACTURER: Medtronic, Inc.
Rice Creek Facility
7000 Central Ave. N.E.
Minneapolis, Minnesota 55432-3576

DEVICE: Pacer-Cardioversion-Defibrillation Lead System; for use with Medtronic PCD Model 5355 external tachyarrhythmia control device (ECTCD), and Model 9788 MemoryMod Software Module. (critical device)

Model 6963 CS Lead (critical device)
Model 6999 SQ Patch Lead (critical device)

SITUATION: 2 (In accordance with Part V of Compliance Program 7382.830, dated 9/1/91)

MQAB RECOMMENDATION: 1. PMA AMENDMENT APPROVAL
2. POSTMARKET INSPECTION

This PMA amendment, P920015A, dated October 26, 1992, is for the manufacture of Medtronic's Model 6963 and 6999 Leads for use with the PCD Model 5355 external tachyarrhythmia control device (ECTD). The manufacturing site for this amendment is the Rice Creek facility. The last inspection of this location was January 21 through February 8, 1992. The firm was classified NAI for sterilization and VAI-2 for GMP compliance. MIN-DO concurred with PMA approval. The firm's response to an OCS deficiency letter, dated August 26, 1992, adequately addressed the eleven concerns indicated.

A review of the amendment indicates the firm has met its PMA commitments concerning the Manufacturing Control Section requirements. There is a minimal probability that unsafe and ineffective devices will be produced and distributed. MQAB recommends a postmarket inspection be scheduled at the Rice Creek facility.

Guidance is included for use during the postmarket inspection.

David Kunin

INSPECTIONAL GUIDANCE (MIN-DO)

December 1, 1992

SUBJECT: PMA P920015A

FIRM: Medtronic, Inc.
Rice Creek Facility
7000 Central Avenue NE
Minneapolis, Minnesota 55432

DEVICE: PCD Transvene Lead System;
Model 6963 and 6999

CDRH/OCS
REVIEWER: David Kunin, MQAB, HFZ-332, (301) 427-1128

This PMA amendment, P920015A, is for the production of the Model 6963 and 6999 leads manufactured at the Medtronic Rice Creek Facility. The last inspection was conducted January 21 through February 8, 1992, and the firm was found to be an acceptable manufacturer.

During the postmarket inspection of Medtronic, Rice Creek Facility, please pay particular attention to the following areas: [820.81(a)]

Model 6963 Lead

For the following operations, verify that the approved and appropriate method sheets are being used:

Electrode Sub-Assembly:

1. Crimp distal sleeve to coil; [(b)(4)]
2. Cut coil to length;
3. String tubing and bond distal tubing; [(b)(4)]
4. Crimp proximal sleeve to coil and bond proximal sleeve; [(b)(4)]
5. Laser weld; and, [(b)(4)]
6. Silicone backfill. [(b)(4)] Are specifications and inspection characteristics established for this operation? Is the minimum insulation thickness measured? Is the measurement recorded?

Final Assembly:

7. Crimp coil; [(b)(4)]
8. String tubing;
9. Crimp tip; [(b)(4)]
10. Cut to length;
11. Crimp connector pin; [(b)(4)]
12. Assemble connector pin; [(b)(4)]
13. Install molded tip; [(b)(4)] and,

14. Bond tip/connector sleeve; (critical)
15. Are all crimped and bonded interfaces tested for integrity? [820.160]
16. Verify the final functional inspection is performed according to [(b)(4)] [820.160]
17. Verify that the leads deliver pacing, cardioversion, and defibrillation pulses that correspond with the range of programmable detection rhythms.(A specification should be available which establishes the pulse to be delivered at the detection of a specific cardiac electrical rhythm. Verify the delivery of the appropriate pulse with the corresponding rhythm.) [820.100(b)(2)]
18. Verify that the tests for electrical resistance, continuity, and leakage are performed in accordance with the appropriate procedure. [820.160]

MODEL 6999

For the following operations, verify:

19. Defibrillator coil assembly;
20. Manifold patch;
21. Manifold assembly:
    a. Crimp manifold; [(b)(4)]
    b. Stake defibrillator coils; [(b)(4)]
    c Cut tubing/coil to length.
22. Bond manifold assembly:
    a. Bond defibrillator coil assembly [(b)(4)]
23. Connector assembly:
    a. Crimp connector pin; [(b)(4)]
    b. Backfill voids. [(b)(4)]
24. Manifold patch:
    a. Attach patch;
    b. Attach connector sleeve;
    c. Serial number label.
25. Backfill connector sleeve and backfill air bubbles [(b)(4)]
26. Are all crimped and bonded interfaces tested for integrity? [820.160]
27. Verify the final functional inspection is performed according to the appropriate procedure. [820.160]
28. Verify that the leads deliver pacing, cardioversion, and programmable detection rhythms. (A specification should be available which establishes the pulse to be delivered at the detection of a specific cardiac electrical rhythm. Verify the delivery of the appropriate pulse with the corresponding rhythm.) [820.100(b)(2)]
29. Verify that the tests for electrical resistance, continuity, and leakage are performed in accordance with the appropriate procedure. [820.160]

Concerning both model leads:

30. Verify that biological indicators are placed in the locations specified in the sterilization procedure. [820.100(b)(2)]

31. Verify that the sterile package is tested according to a written procedure. [820.160]
32. Verify that quality system audits are conducted according to a written procedure and schedule. [820.20(b)]

33. Are complaints of device failure, injury, and death being investigated and the results documented? [820.198]

34. Verify that the leads are tested in accordance with all labeled device voltage ratings. [820.160]

THIS DOCUMENT MAY NOT BE SHOWN OR PROVIDED TO THE FIRM

DCRND

27-Oct-1992

PS 015/S000

mfc

FROM:	LETTER DATE	LOGIN DATE	DUE DATE
MEDTRONIC INC. ATTN: JENNIFER M. MARRONE 7000 CENTRAL AVENUE, N.E. MINNEAPOLIS,, MN 554323576	10/26/92	10/27/92	/ /
	DOCUMENT: PMA	CONTROL # P920015/S000 AMENDMENT	

SUBJECT:
MEDTRONIC(R) TRANSVENE LEAD SYSTEM

	OFFICE	DATE REFERRED
6 COPIES OF VOLUME 1	CK LA	10/27/92
____ COPIES OF VOLUME ____	DCRND	11/13/92
____ COPIES OF VOLUME ____		
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____ COPIES OF VOLUME ____		

Medtronic

Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576
Telephone: (612) 574-4000
Cable: Medtronic Telex: 29-0598
Telecopy: (612) 574-4879

October 26, 1992

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FDA/CDRH/OBE/DMC

Office of Device Evaluation
PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

Re: Amendment to Premarket Approval Application (PMA) for the Medtronic® Multiprogrammable Tachyarrhythmia Control System with Non-thoracotomy Cardioversion and Defibrillation Electrodes, i.e., the PCD™ Transvene System, Lead Models 6963, 6966 and 6999 (Document Control Number P920015) 1A C2 U1

This submission is an amendment to the PMA application for the Medtronic Transvene Lead System used in conjunction with the Model 7217B pacer-cardioverter-defibrillator (PCD), Model 5355 external tachyarrhythmia control device (ETCD) and Model 9788 MemoryMod Software Module.

The purpose of this PMA amendment is to obtain approval to manufacture the Model 6963 CS/SVC lead and the Model 6999 SQ patch lead at the Rice Creek facility. The 6963 and 6999 are currently manufactured at the Medtronic B.V. facility at Kerkrade, The Netherlands.

With the exception of sections F. (Production and Process Controls) and K. (Sterile Devices), which are specific to the manufacture of the Model 6963 and 6999 at Rice Creek, all other sections of this submission are the same as the manufacturing description of the Model 6966 at Rice Creek presented in Volume 2 of the original PMA.

Two manufacturing facilities will be used in the assembly, sterilization and packaging of the Models 6963 and 6999 Transvene leads. These are:

1. Medtronic, Inc.
   Rice Creek Facility
   7000 Central Avenue N.E.
   Minneapolis, MN 55432
   Tel: 612-574-4000
   Establishment Registration Number: 2182208
   Is presently prepared for inspection.
   Most recent FDA inspection: January 21 - February 8, 1992.

2

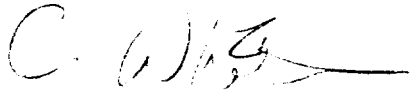
2. Medtronic, B.V.
Wenckebachstraat 10
6466 NC Kerkrade West
The Netherlands
Tel: 31-45-43-85-85
Is presently prepared for inspection.
Most recent FDA inspection: January 6-9, 1992.

The existence of this PMA application and its amendments and the data and other information they contain are confidential, and the protection afforded to such confidential information by 18 USC 1905 and other applicable laws is hereby claimed.

Six copies of this application are enclosed. Should additional information be required by the Agency, please contact the undersigned.

Sincerely,

MEDTRONIC, INC.



Chip Whitacre
Product Regulation Manager
Cardiac Pacing Business
(612) 574-8556
(612) 574-6424 FAX

Attachment

3

Models
6963 + 6999

4

- Manufacture of the Model 6963 CS/SVC Lead and Model 6999 SQ Patch

- Medtronic, Rice Creek Facility, Minneapolis, MN

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Model 6963 and 6999 Technical Manuals
Package Labeling

Description

II. Device Description: Model 6963 Coronary Sinus/Superior Vena Cava and Model 6999 Subcutaneous Patch Leads

Illustrations of these leads are provided on the pages following this discussion.

The Medtronic Tachyarrhythmia Control System uses a tripolar, screw-in, right ventricular lead for (RV) pacing, sensing, cardioversion and defibrillation; a unipolar, coronary sinus/superior vena cava lead (CS/SVC); and a unipolar, subcutaneous oval patch electrode (SQ). The available models of the system are as follows:

- Model 6963 CS/SVC Lead
- Model 6966 RV Lead
- Model 6999 SQ Lead

Part 1-Page 469 ↓ Part 1-Page 655

The Model 6963 and 6999 leads are intended to be used with the Model 7217B PCD Device. The leads have a 6.5 mm connector intended for direct insertion into a 6.5 mm port of the 7217B PCD Device.

The Model 6963 lead is intended for use in the coronary sinus or superior vena cava. The lead features a platinum alloy electrode coil which provides the necessary surface area for cardioversion and defibrillation. Silicone insulation surrounds a low-resistance metal-alloy conductor coil.

The Model 6999 lead is intended for use subcutaneously, submuscularly, or directly on the periosteum of the ribs. The lead features platinum alloy electrode coils and a low-resistance metal-alloy conductor surrounded by silicone insulation. Four helical coils are partially embedded into the silicone patch and provide the necessary surface area for cardioversion and defibrillation. A polyester mesh is molded into the patch and provides support for sutures. There are three nodes in the center and two nodes at the junction of the lead body and patch electrode of one side of the patch electrode. These nodes are intended to designate the insulated side of the patch electrode.

The following section describes the functional components, device properties, and principles of operation for the Model 6963 and 6999 leads.

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10

Part 1 - Page 470

MODEL 6963 CS/SVC LEAD

MEDTRONIC CONFIDENTIAL

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MODEL 6999 SUBCUTANEOUS PATCH LEAD

MEDTRONIC CONFIDENTIAL

a. Functional Components

1) Platinum Alloy Electrode Coil

The Model 6963 coronary sinus/superior vena cava lead features a platinum alloy coil electrode that delivers cardioversion and defibrillation pulses to the heart. The Model 6963 lead uses silicone adhesive to help prevent tissue in-growth and aid in chronic lead removal.

The conductive surface of the Model 6999 subcutaneous patch electrode consists of [(b)(4)] helical coils partially embedded in molded silicone rubber. These coils serve as the electrodes that deliver cardioversion and defibrillation pulses to the heart. Inside the helical coils is silicone rubber to help prevent tissue in-growth and aid in chronic lead removal.

2) Low Resistance Metal Alloy Conductor Coil

This conductor coil consists of [(b)(4)] that provides a low resistance pathway for delivery of cardioversion and defibrillation pulses from the tachyarrhythmia control device to the platinum alloy electrode coils. The [(b)(4)] was selected for use due to its proven long term reliability when used in implanted bradycardia lead systems. The use of [(b)(4)] cored coil provides the low resistance needed for the delivery of high voltage pulses. The coils used on the Model 6963 and 6999 are not [(b)(4)]

3) Insulation

The Model 6963 and 6999 leads are comprised of silicone rubber insulation. This material has a long history (since 1962) of use on Medtronic pacing leads. Insulation wall thickness for both the 6963 and 6999 is [(b)(4)] inches.

4) Anchoring Sleeve

There are two anchoring sleeves positioned on the lead body of the Model 6963. They are intended to be used for fixation of the lead body to soft tissues. The distal anchoring sleeve is intended to fix the lead near the site of insertion of the lead into the vein at the time of the implant. It is designed to protect the lead from undue strains and stresses at the point of fixation. The proximal anchoring sleeve may be used to anchor the lead at either end of the tunnel to the PCD pocket.

5) Polyester Mesh Embedded into Silicone Rubber

Polyester mesh is embedded into the Model 6999 subcutaneous patch and provides support when suturing the lead to the subcutaneous muscle.

6) Stylets

Stylets are wires which stiffen the lead and/or temporarily alter its shape during implant. This is accomplished through a controlled stiffness of the distal tip, allowing it to bend with the application of excessive force. Stylets are also designed to help minimize damage to the coil during insertion and removal. The Model 6963 uses a stylet, the Model 6999 does not.

7) Connector Assembly

The Model 6963 and 6999 leads feature a 6.5 mm terminal assembly consisting of a stainless steel connector pin and silicone rubber sleeve. The distal part of the sleeve provides a strain relief area.

b. Device Properties

The Model 6963 and 6999 non-thoracotomy leads are designed for sensing, pacing, cardioversion and defibrillation. These leads have application where implantable tachyarrhythmia control devices are indicated. Reference the technical manuals for the Model 6963 and 6999 leads for specific device features.

c. Principles of Operation

The PCD Transvene System uses leads which do not require open-chest surgery to implant. Multiple configurations involving either two or three different leads may be used to deliver cardioversion and defibrillation pulses. These configurations are comprised of a tripolar, right ventricular (RV) lead (Model 6966), and either a coronary sinus (CS) lead (Model 6963) or a subcutaneous (SQ) lead (Model 6999), or all three of these leads. The Model 6963 lead can be placed in either the coronary sinus/great cardiac vein or the superior vena cava (SVC).

In these systems, the helical tip and ring of the RV lead is used for sensing, thus providing standard, bipolar sensing. The tip electrode is termed PACE/SENSE and the ring electrode is termed SENSE 2. Bradycardia pacing takes place between the tip (PACE/SENSE) and the COMMON defibrillation electrode.

A system using two leads delivers cardioversion and defibrillation pulses between two coils (one on each lead). A system using three leads delivers cardioversion and defibrillation pulses either simultaneously or sequentially from the anode electrodes (PULSE 1 and PULSE 2) to the COMMON defibrillation electrode.

To detect VT/VF, the PCD device monitors the cardiac cycle length for fulfillment of the programmed VT/VF detection criteria. When the programmed criteria are fulfilled, the PCD device detects the VT or VF episode and delivers the first programmed therapy. If this therapy is ineffective and the VT/VF is again detected, the next programmed therapy is delivered. This progression continues until the PCD confirms episode termination or delivers all programmed therapies.

The performance of the Models 6966, 6963, and 6999 are evaluated at the following times:

1) At implant by the evaluation of the pacing and sensing thresholds and defibrillation efficacy when treating VT/VF.

2) Chronically by evaluation of stability of chronic defibrillation efficacy in induced episodes of VT/VF and successful termination of spontaneous episodes of VT/VF.

Manufacturing
methods
+
Control

III. Manufacturing Description:

Model 6999 Subcutaneous Lead
Model 6963 Coronary Sinus/Superior Vena Cava Lead

Medtronic, Rice Creek Facility, Minneapolis, MN

The following Manufacturing Description has been prepared in conformance with the "Guidance for Preparation of PMA Manufacturing Information" made available by FDA August 21, 1991.

This section contains a complete description of the methods used in, and the facilities and controls used for, the manufacture, processing, packaging, storage and distribution of the Models 6999 and 6963 Nonthoracotomy (NTL) Leads. Process qualification testing and results are included in Section F.3. As requested, a summary describing how applicable GMP requirements are met has been provided for each area identified. Copies of actual procedures are provided when specifically requested by the Guidance.

The Models 6999 and 6963 Leads meet the definition of a critical device; implantable leads are currently on the Critical Device List. We have thus addressed specifically additional controls that are in place to meet the critical device requirements.

A

9

A. Organization and Personnel

(1) Company policy and objectives for controlling quality and how they are made known to employees.

A dimension of the Medtronic Corporate Mission relates specifically to quality and is as follows:

[(b)(4)]

The corporate policy of achieving this mission is summarized as a series of Quality Principles. These principles are communicated via new employee quality training and are part of a publication called **"Quality at Medtronic"** that the Corporate Quality Assurance Group prepares and distributes to each employee. The quality principles are as follows:

- [(b)(4)]
- [(b)(4)]
- [(b)(4)]
- [(b)(4)]
- [(b)(4)]
- [(b)(4)]

- [(b)(4)]

The quality function within the Tachy Manufacturing Group includes responsibility for quality as part of each individual job within the organization. Additionally, there is a dedicated staff of manufacturing quality assurance engineers [

[(b)(4)

[(b)(4)

The policies cover the dimensions of a Quality Assurance function as outlined in the GMP (21CFR Section 820.20). These dimensions are summarized as follows:

1. Production records review.

   The production records required are defined as are the requirements for documentation and use. Specific requirements include the following:

   - [(b)(4)]
   - [(b)(4)]

2. Approval/rejection of components, materials, packaging, labeling, subassemblies and devices.

   The process by which review and disposition of components, materials, packaging, labeling, subassemblies and devices occur is summarized as follows:

   - [(b)(4)]
   - [(b)(4)]
   - [(b)(4)]
   - [(b)(4)]

3. Identifying and resolving quality assurance problems.

   Process, product or system related issues are identified in a variety of ways such as process monitoring, defect reporting, complaint reporting, audits, etc. The corrective actions are accomplished by appropriate representatives from Manufacturing and Quality Assurance Engineering as well as Design, Product Assurance and other functional groups as needed, and include the following activities:

   - [(b)(4)]
   - [(b)(4)]
   - [(b)(4)]
   - [(b)(4)]

- [(b)(4)]

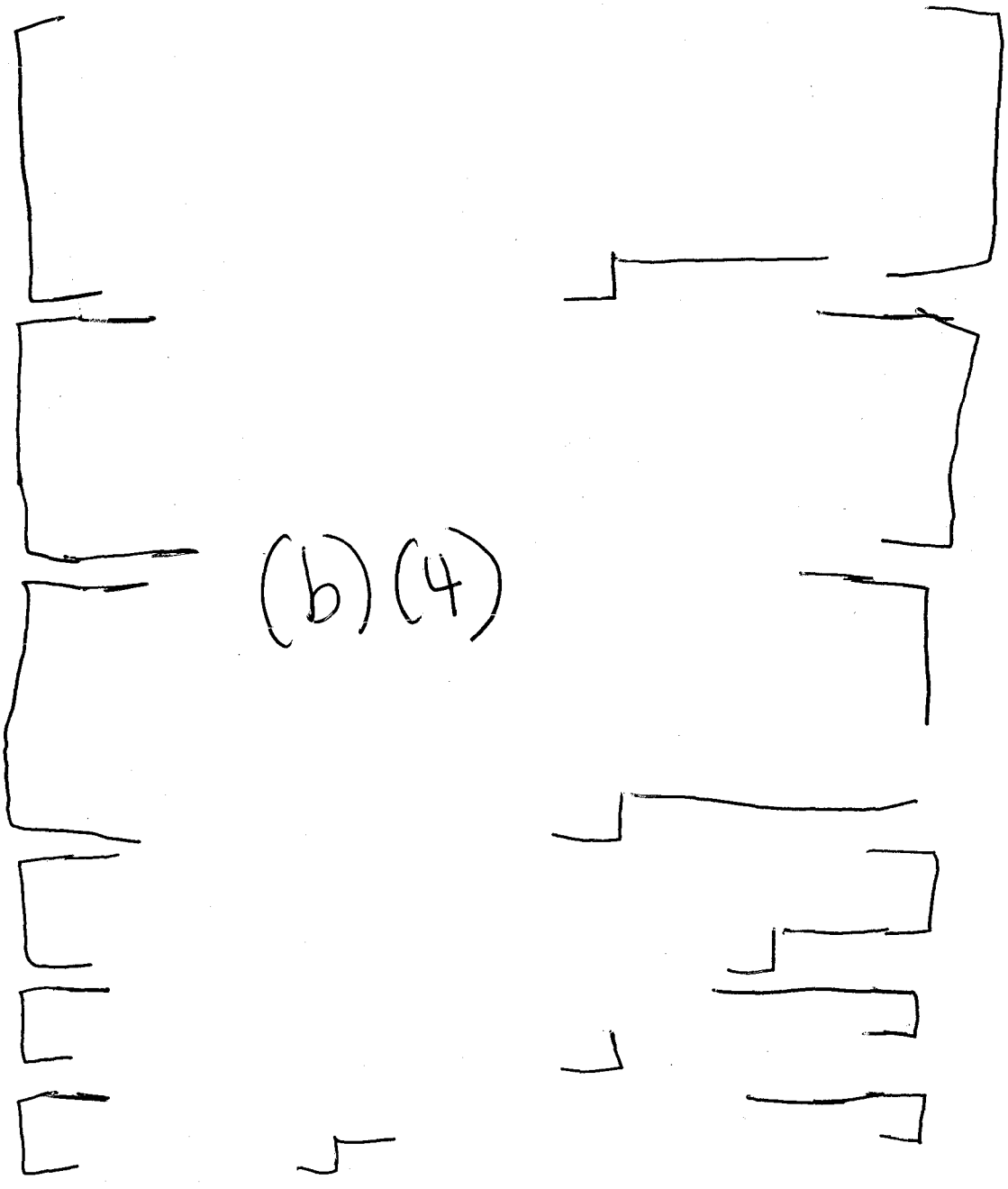
The effectiveness of the corrective action may be measured by subsequent process monitoring, defect and/or complaint reports and internal audits.

4. Quality Assurance checks.

Product, material, component and process qualifications assess the appropriateness and effectiveness of all quality assurance inspections. The requirements for these qualifications are clearly outlined in the appropriate Product Assurance and Manufacturing Development Plan. The results of these qualifications are reviewed by the appropriate management within the Product Assurance and Manufacturing Engineering Departments, as necessary, prior to approval of product for distribution. Assurance that the quality inspections are performed correctly is provided by process and defect monitoring results as well as internal audits within manufacturing.

A. Organization and Personnel

(2) Organizational structure, including the quality system and the responsibilities and channels for identification, documentation and resolution of product quality problems, including responsibilities for assuring that corrective action is implemented.



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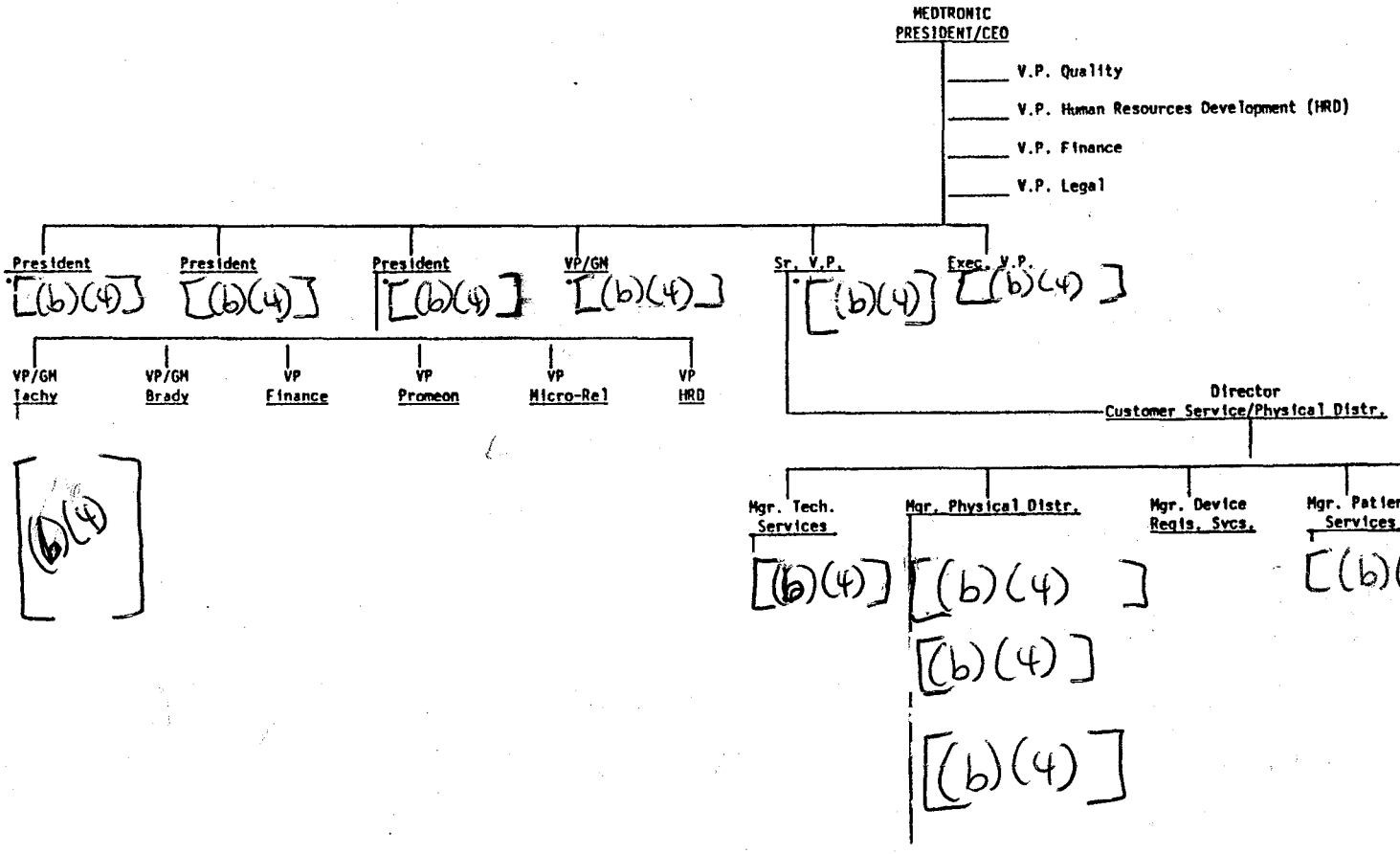


FIGURE 1. BUSINESS ORGANIZATION

MEDTRONIC CONFIDENTIAL

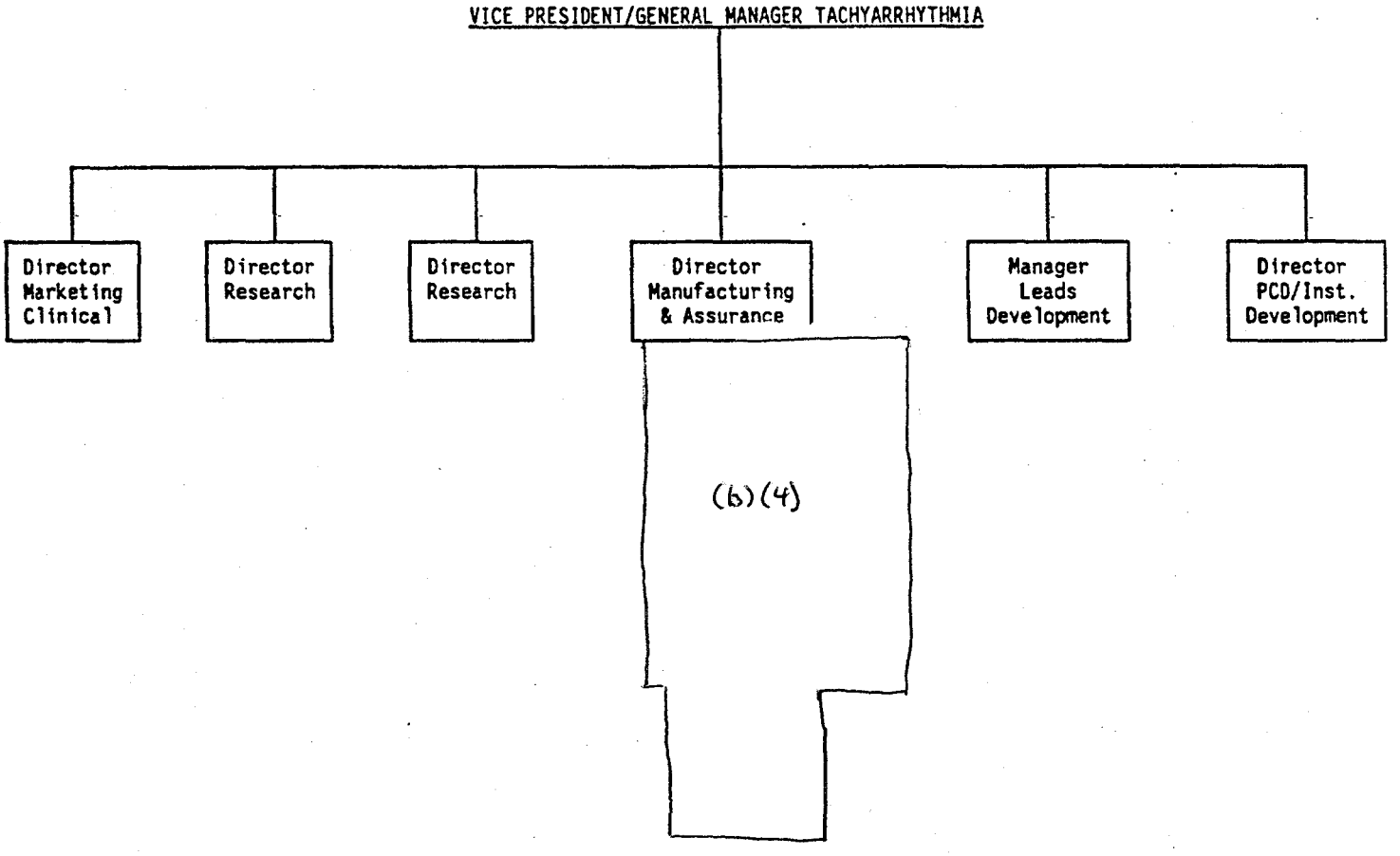
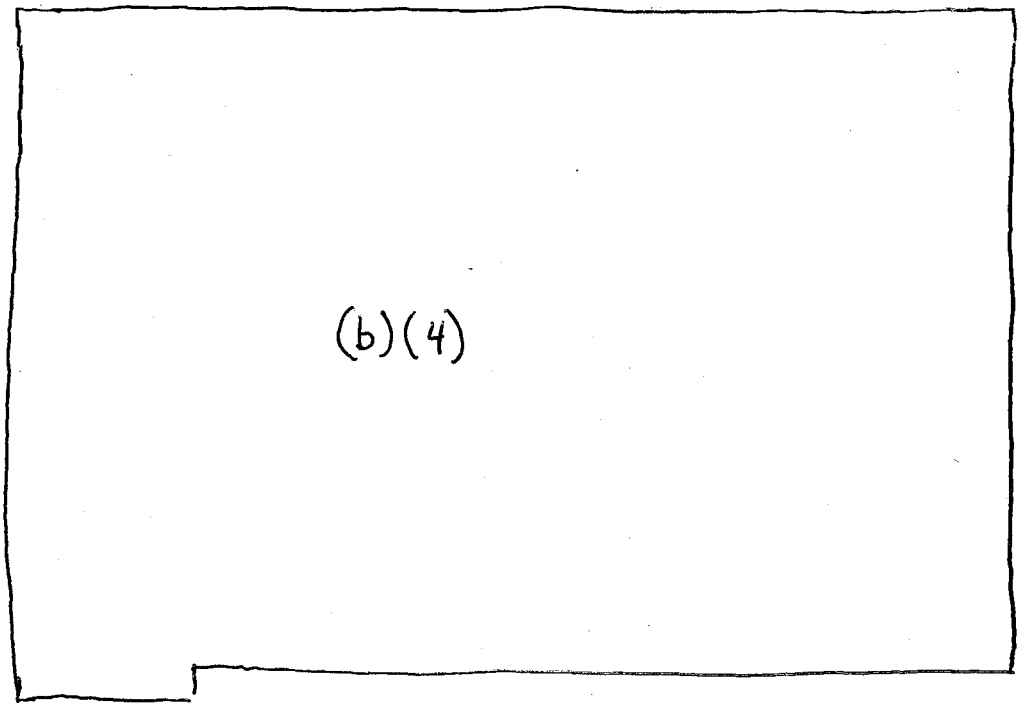


FIGURE 2. MANUFACTURING ORGANIZATION
RICE CREEK

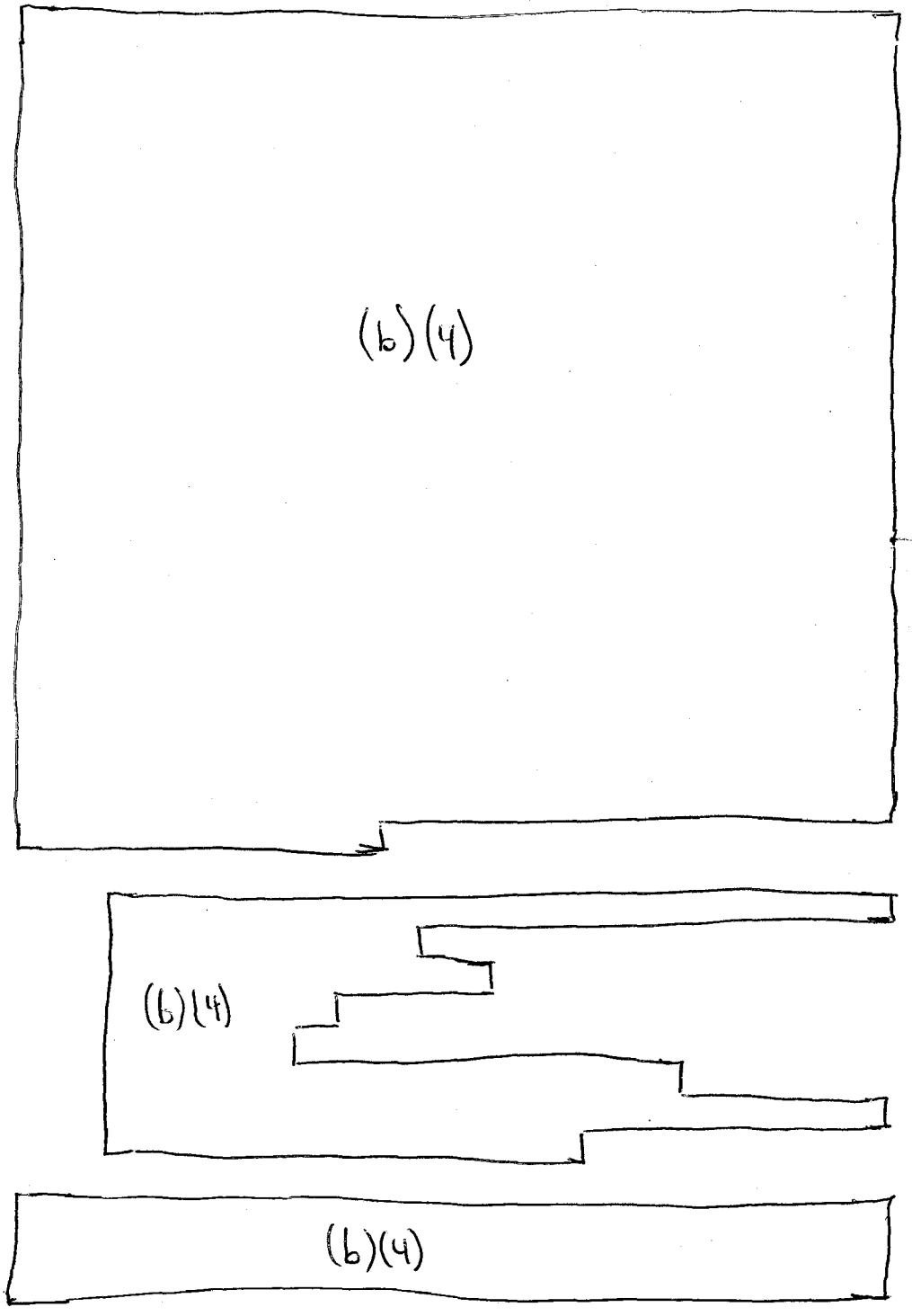
A. Organization and Personnel

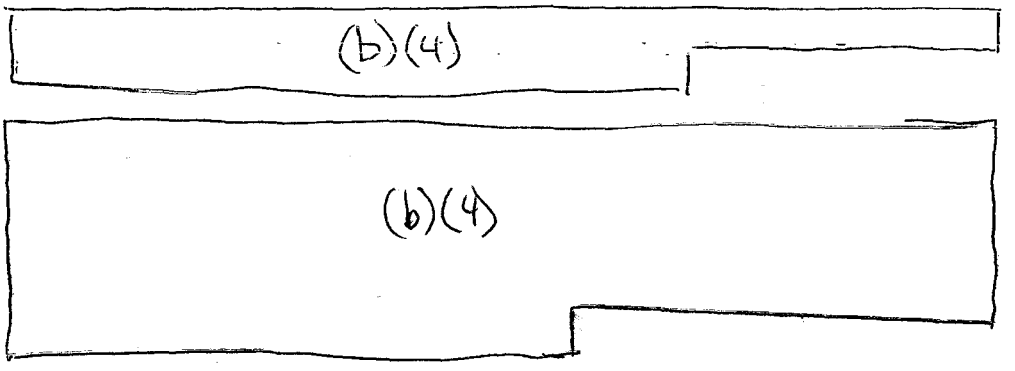
(3) Methods used to assure that personnel have proper training and experience for the operations performed.



A. Organization and Personnel

(4) Design and implementation of training programs, including methods for identifying training needs, qualification of personnel for special processes and operations, and documentation of training.




(b)(4)
(b)(4)

B. Quality Audit

(1) Design and implementation of the quality audit program including procedures for assessing that audits are reviewed by upper management, all appropriate areas are audited, corrective action is implemented, independence from functions audited is maintained, and auditors are qualified.

(b)(4)

(b)(4)

(b)(4)

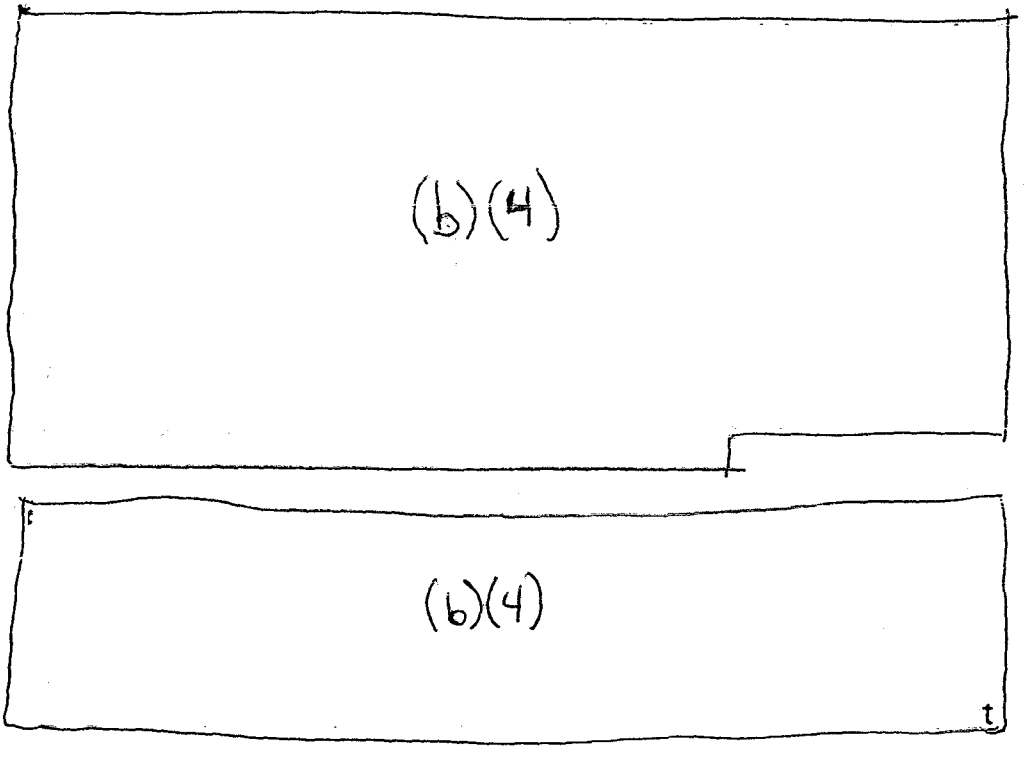
(b)(4)

C. Buildings

(1) Methods and procedures used to assure orderly handling and to avoid mixups of components, finished devices, labeling, packaging and manufacturing materials during routine operations and storage.

The Medtronic Rice Creek facility is a one-story concrete block and steel facility covering over (b)(4) square feet. It was designed to have adequate space for all the quality assurance, documentation, manufacturing and support activities associated with the manufacture of medical devices such as implantable cardiac leads and pulse generators. There are defined areas for:

- Component receiving and verification
- Manufacturing functions
- Quality Assurance functions
- Equipment calibration
- Manufacturing
- Manufacturing Documentation
- Component storage
- Packaging
- Sterilization, microbiological testing and quarantine
- Material analysis and metallurgical laboratories
- Finished product storage



number, a sequentially assigned computer generated lot number, quantity received, inspection code and acceptance status.

Parts or materials requiring inspection are routed to the inspection area. If no inspection is required, parts are routed to Central Stores.

Any suspected damaged parts or materials are segregated and either returned to the supplier or sent to a designated MRB (Material Review Board) area for engineering disposition.

(b)(4)

The Receiving Inspection Department (b)(4)

(b)(4)

(b)(4)

(b)(4)

Central Stores (b)(4)

(b)(4)

(b)(4)

(b)(4)

The production areas are designed and laid out so that sufficient

(b)(4)

C. Buildings

(2) Methods and procedures used to control and monitor environmental conditions when environmental conditions could adversely affect a device's fitness for use.

(b)(4)

(b)(4)

(b)(4)

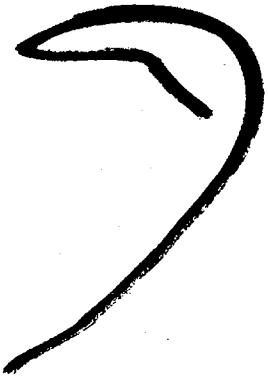
(b)(4)

(b)(4)

(b)(4)

(b)(4)

"Facility Clean": Three procedures which provide the detail instruction for cleaning, sanitation and pest control of the manufacturing facilities. These are specific procedures which call out the schedule and steps for performing the cleaning functions, mixing of cleaning solutions, location of cleaning areas and equipment, recording of results and appropriate action for noncompliant results.



D. Equipment

(1) Methods and procedures established to assure proper maintenance and calibration of equipment used for production and quality control including procedures used to assure the adequacy of automated equipment.

(b)(4)

(b)(4)

POLICIES

The Procedure Statement: The purpose of this policy is to establish a uniform procedure for the development, coordination, review, authorization and publication of Equipment Support Department policy and procedure statements. It defines "policy" as the

(b)(4)

Maintenance of Equipment: The purpose of this policy is to provide the requirements for the maintenance and calibration of all

equipment used to research, design, manufacture and quality-check marketable product. These requirements are general requirements covering the identification of equipment requiring calibration and maintenance, environmental controls, reference and transfer standards, intervals, maintenance procedures, records and labeling; the specific procedures addressing each of these are included in the separate procedures documents.

Equipment History: This policy establishes the requirements for the documentation (History Files) of equipment covered and work performed by the (b)(4)

Maintenance Procedures: This policy establishes the requirements for procedures written to cover maintenance performed by the (b)(4) They specify what is to be included in the procedures, and how they will be documented, approved, distributed and controlled. Any change of data to a procedure is identified in the (b)(4)

PROCEDURES

Maintenance Procedures: These are specific instructions for how to initiate and format new maintenance procedures and change existing procedures. (There are procedures covering (b)(4) used in device manufacturing and receiving inspection. The master copy of each procedure is maintained in the (b)(4) working copies are available in the Each of them is written and controlled per this procedure.)

Use of Labels and ID Stamps: This procedure establishes a uniform procedure for the use of (b)(4) (b)(4) and IDE stamps. It contains instructions for the use of such labels as "Calibration," Certified," "Certified for R&D Only," "Danger Do Not Use," "Defective Do Not Use," "Out of Service," "Pressure Tested," "Special Calibration," "Void if Broken," "Functional," and "This Equipment Does not Require Calibration."

Work Reports:

(b)(4)

40

interval, action taken history, NIST traceability, date completed, date next calibration due etc.

History File: This procedure establishes the format for entering data into the Equipment Support Department History File.

Initial Certification of In-House Built Gauging: This procedure establishes a procedure for Tool Inspection to do initial verification of In-House built gauging and allow the [(b)(4)]

Development and Control of Software: This procedure establishes a uniform procedure regarding the development and control of computer software. Applies only to programs written by personnel of the [(b)(4)]

E

E. Acceptance and Control of Components

(1) Methods and procedures used to define how purchased finished devices, components, packaging, labeling and manufacturing materials are to be inspected or verified as conforming to requirements.

[(b)(4)]

[(b)(4)]

[(b)(4)]

a) [(b)(4)]
b)
c)
d)
e)
f)
g)
h)
i)]

HB

[(b) (4)]

[(b) (4)]

E. Acceptance and Control of Components

(2) Methods and procedures used for the identification of released, rejected, quarantined, or unchecked incoming finished devices, components, packaging, labeling and manufacturing materials.

[(b) (4)]

[(b) (4)]

[(b) (4)]

[(b) (4)]

[(b) (4)]

E. Acceptance and Control of Components

(3) Methods/procedures used for identifying finished devices, components, labeling, packaging and manufacturing materials through all stages of production.

[(b) (4)]

46

E. Acceptance and Control of Components

(4) Methods/procedures used for identifying critical components for critical devices.

[(b) (4)]

[(b) (4)]

[(b) (4)]

[(b) (4)]

[(b) (4)]

[(b) (4)]

u)

[(b)(4)]

[(b)(4)]

[(b)(4)]

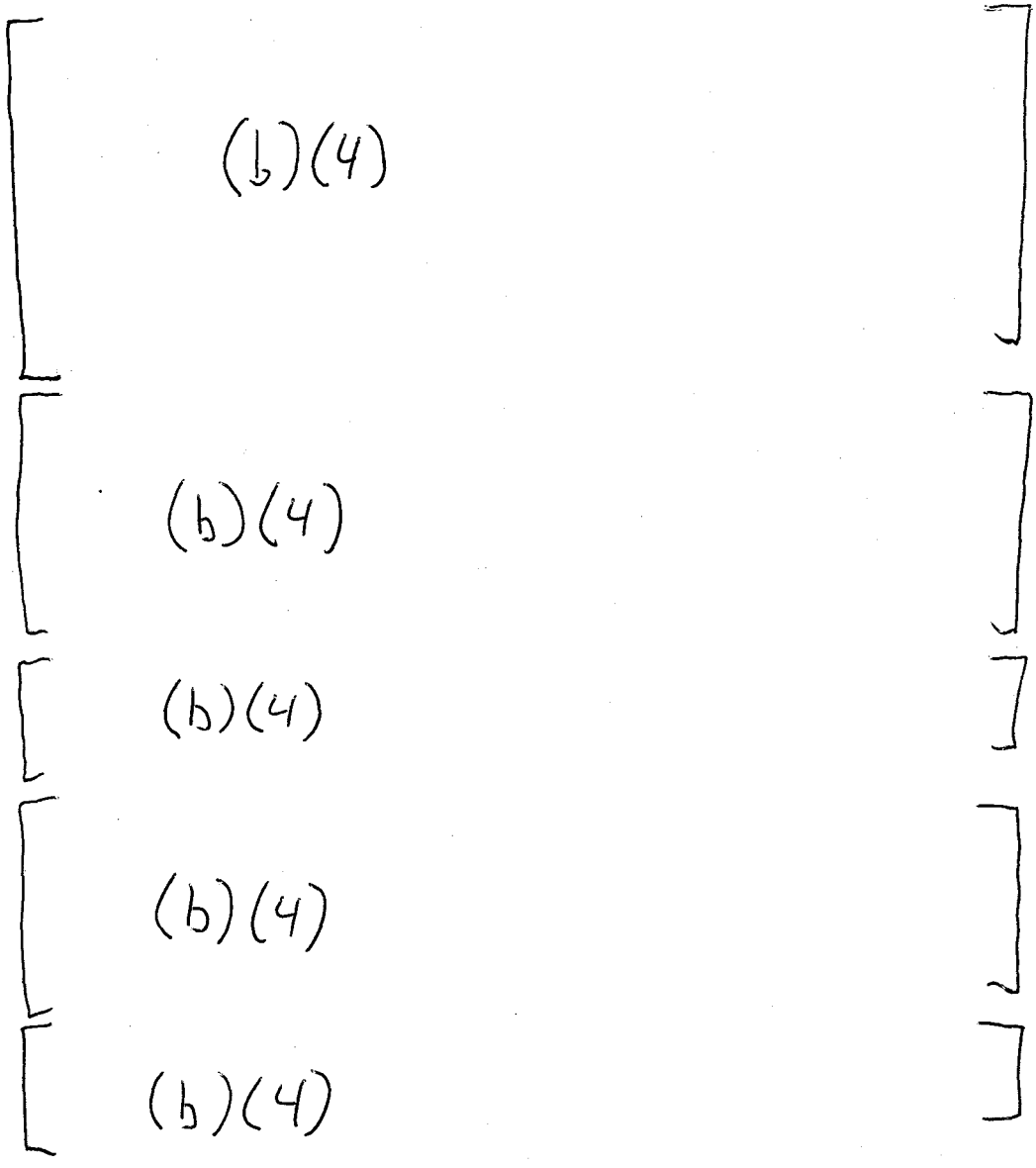
[(b)(4)]

[(b)(4)]

f

F. Production and Process Controls

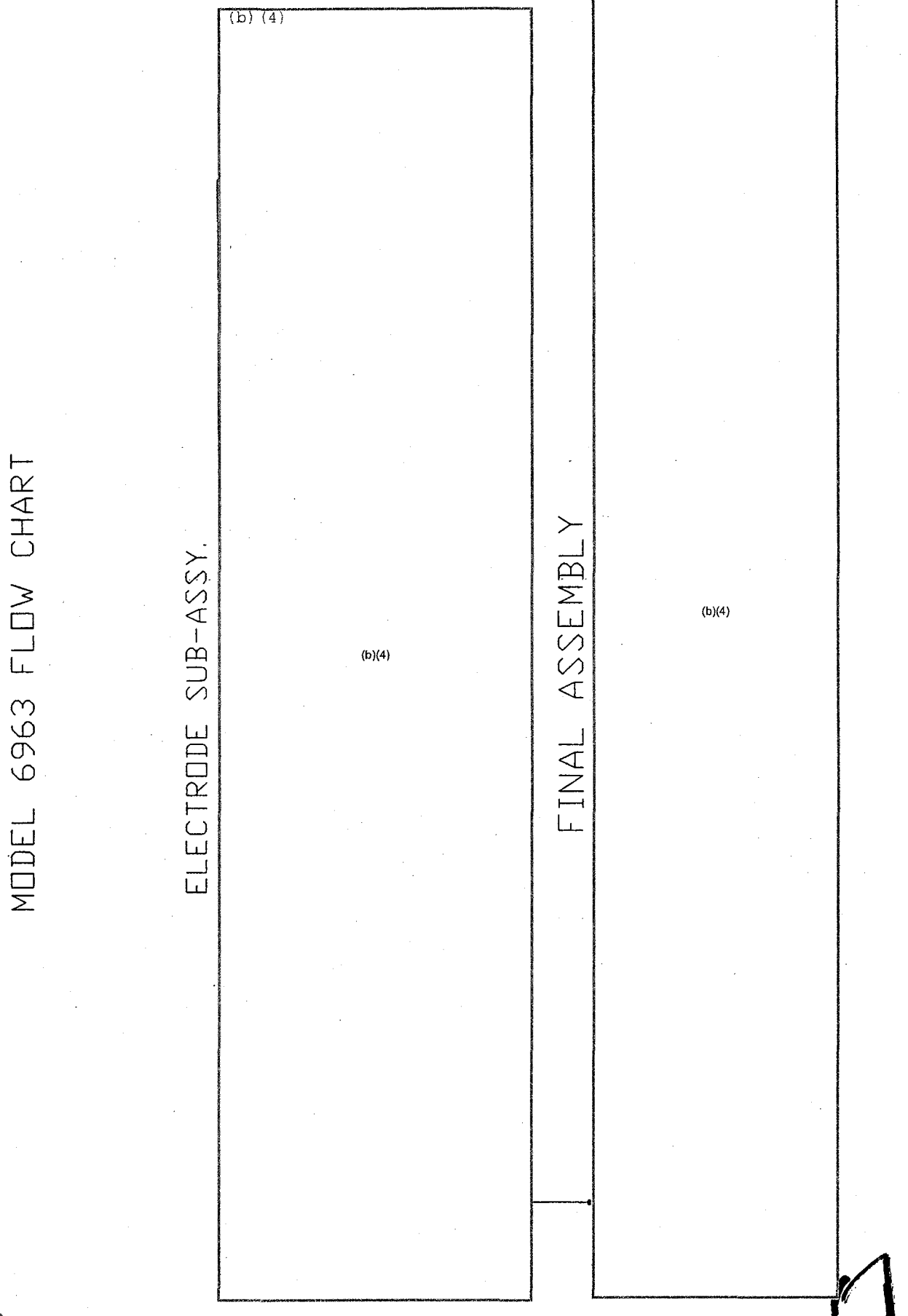
(1) Provide a flow diagram of the production process identifying all process steps.



10

MODEL 6963 FLOW CHART

ELECTRODE SUB-ASSY.



(b) (4)

(b)(4)

FINAL ASSEMBLY

(b) (4)

(b)(4)

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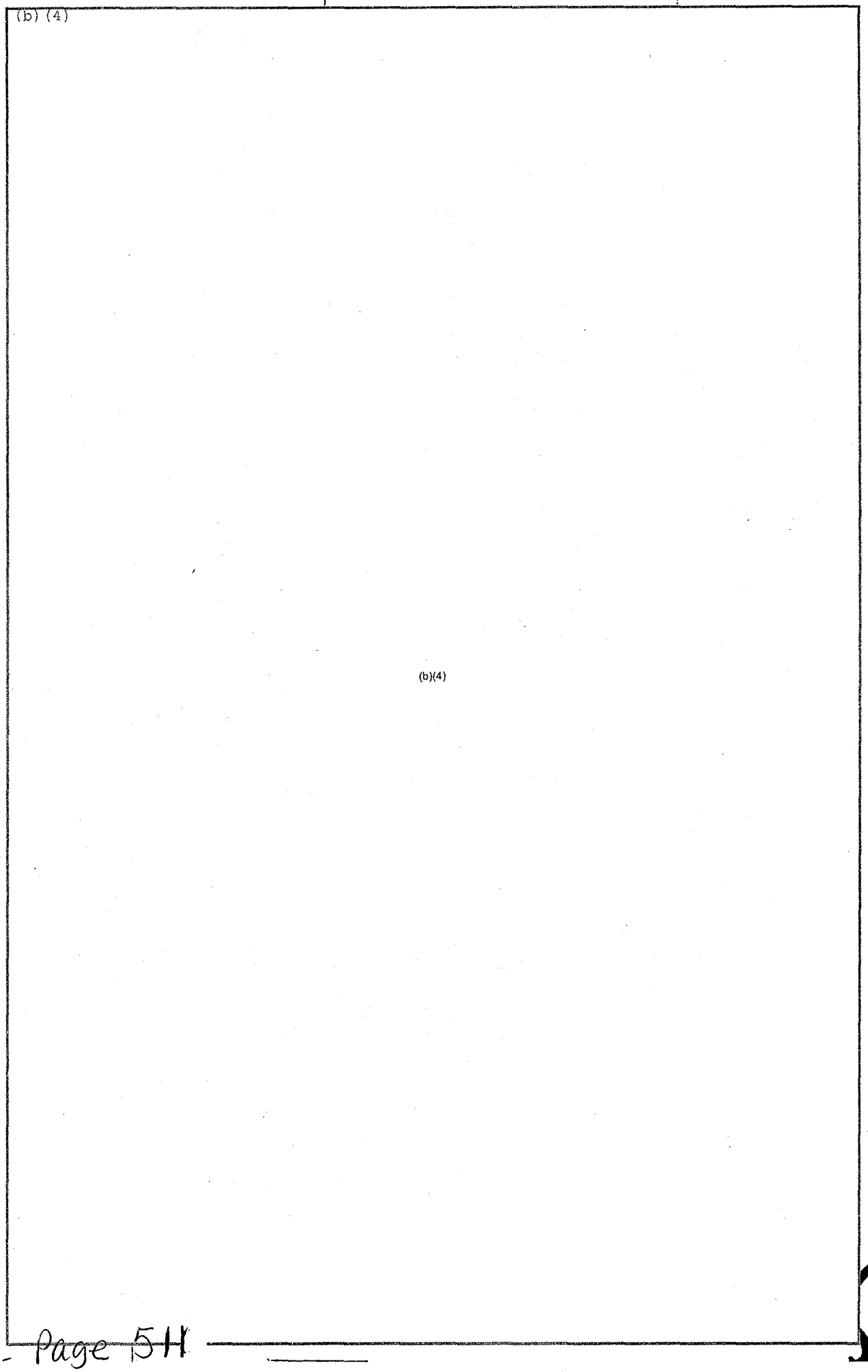
(b) (4)

MODEL 6999 WORKCELL FLOWCHART



F. Production and Process Controls

(2) Methods/procedures that define and control the manner of production and installation, including work instructions and procedures for the review and control of these instructions.

[(b)(4)]

[(b)(4)]

[(b)(4)]

[(b)(4)]

F. Production and Process Controls

(3) Identify all significant manufacturing processes and the methods and procedures used to validate, or prove, the acceptability and stability of the processes, including validation of the methods and procedures used to monitor and control the processes after validation to assure they consistently operate within acceptable process parameters.

(b)(4)

(b)(4)

(b)(4)

(b)(4)

4

[(b)(4)]

[(b)(4)]

Critical and Principle Operations for Model 6963

Title	Qual Plan	Report
(b)(4)		

TACHYARRHYTHMIA IMPLANTABLE LEAD MODEL 6963
CRITICAL AND SIGNIFICANT MANUFACTURING OPERATIONS

I. CRITICAL MANUFACTURING OPERATIONS

a.
b.
c.
d.

(b)(4)

II. SIGNIFICANT MANUFACTURING OPERATIONS

a.
b.
c.
d.
e.
f.
g.

(b)(4)

Critical and Principle Operations for Model 6999

Title	Qual Plan	Report
(b)(4)	(b)(4)	(b)(4)

Part 1 - Page 517

TACHYARRHYTHMIA IMPLANTABLE LEAD MODEL 6999
CRITICAL AND SIGNIFICANT MANUFACTURING OPERATIONS

I. CRITICAL MANUFACTURING OPERATIONS

a.
b.
c.
d.

(b)(4)

II. SIGNIFICANT MANUFACTURING OPERATIONS

a.
b.
c.
d.
e.
f.
g.
h.

(b)(4)

Medtronic

File Code:PM0001-05.92 | Page 1

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Date: 07 MAY 92 | Of 2

RICE CREEK QUALITY ASSURANCE

Type of Doc: Qualification Plan E

Family:	Model:	Topic:
Leads	6963	Equip. Qual.

Prepared By: Pedro Meregotte

Title: Connector pin crimper

Approved By:

1 SCOPE

This report impacts the assembly of Lead Model 6963 at Rice Creek.

2 PURPOSE

The purpose of this report is to qualify the crimper used to crimp the connector pin to the conductor coil.

3 BACKGROUND

This report will qualify a crimper that is used to crimp the connector pin to the conductor coil.

4 APPLICABLE DOCUMENTS

4.1 [redacted]

4.2 [redacted]

5 REQUIREMENTS

5.1 [redacted]

5.2 [redacted]

6 PROCEDURE

6.1 [redacted]

6.2 [redacted]

6 PROCEDURE (continued)

6.3 [(b) (4)]

6.4 [(b) (4)]

6.4 [(b) (4)]

6.5 [(b) (4)]

Medtronic

File Code:PM0002-6.92 | Page 1 | 46

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Date: 29 JUNE 92 | Of 2

RICE CREEK QUALITY ASSURANCE

Type of Doc: Qualification Report — E

Family:	Model:	Topic:
Leads	6963	Equip. Qual.

Prepared By: Pedro Meregotte P.M.

Title: Connector pin crimper

Approved By: MB

1 SCOPE

This report impacts the assembly of Lead Model 6963 at Rice Creek.

2 PURPOSE

The purpose of this report is to qualify the crimper used to crimp the connector pin to the conductor coil.

3 BACKGROUND

This lead is currently built in (b)(4) and manufacturing is being started in R.C. a split build. This report will qualify a crimper that is used to crimp the connector pin to the conductor coil.

4 APPLICABLE DOCUMENTS

4.1 (b)(4) (b)(4) [(b)(4)]

4.2 (b)(4) (b)(4) [(b)(4)]

4.3 (b)(4) (b)(4) [(b)(4)]

5 REQUIREMENTS

5.1 [(b)(4)]

5.2 [(b)(4)]

6 PROCEDURE

6.1 [(b)(4)]

6.2 [(b)(4)]

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6 PROCEDURE (continued)

6.3 [(b)(4)]

6.4 [(b)(4)]

6.4 [t... (b)(4)]

7 RESULTS

7.1 [(b)(4)]

7.2 [(b)(4)]

7.3 [(b)(4)]

8 CONCLUSION

8.1 [(b)(4)]

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	Date: 13 Nov 92 91	of 6 48
RICE CREEK QUALITY ASSURANCE	Type of Doc: Qualification Plan (E)	
	Family: Leads / Model: 6999, 6921S/M/L / Topic: Qual, Process	
	Prepared By: Tim Smith/ John Bremmers	
Title: MODEL 6921S, M, L AND 6999 PATCH LEADS TRANSFER	Approved By: / John Fontenas	

1 PURPOSE

The purpose of this plan is to outline the activities to be performed to qualify the 6921S, M, L and 6999 Leads Manufacturing in Rice Creek.

2 SCOPE

This plan encompasses the assembly of 6921 and 6999 leads in Rice Creek. The final packaging of these leads is not covered initially, and will be appended as that process becomes available.

3 BACKGROUND

These patch leads are currently in production at Medtronic BV. To support the initial US market requirements, additional production capacity is being added at Medtronic, Rice Creek. Plans for this tranfer call for:

3.1
3.2 (b)(4)

4 APPLICABLE DOCUMENTS

4.1 Manufacturing Transfer Plan: Tachy Patch Lead Transfer from ESTC to Rice Creek

4.2 (b) (4)
4.3
4.4
4.5
4.6
4.7
4.8 (b)(4) (b)(4)
4.9
4.10
4.11
4.12
4.13
4.14
4.15 (b) (4)
4.16 (b)(4)
4.17

5 MANIFOLD PATCH SUBASSEMBLY (b) (4) (b)(4)

5.1 EQUIPMENT AND PROCESS QUALIFICATION

5.1.1 (b)(4)

5.1.2 (b)(4)

6 ELECTRODE PATCH SUBASSEMBLY (b)(4)

6.1 EQUIPMENT AND PROCESS QUALIFICATION

6.1.1

6.1.2

(b)(4)

6.1.2.2

6.1.2.3

6.1.2.4

7 EPICARDIAL AND SUB-Q PATCH LEAD ASSEMBLY

7.1 EQUIPMENT QUALIFICATION

7.1.1 (b)(4)

7.1.1.1 Equipment to be qualified: (b)(4) (b)(4) and (b)(4)

7.1.1.2 Requirements:

7.1.1.2.1

7.1.1.2.2

(b)(4)

7.1.1.3 Sample size:
Evaluation samples (for engineering use):

Qty	(b)(4) setting
(b)(4)	(b)(4)
(b)(4)	(b)(4)
(b)(4)	(b)(4)

Qualification samples:

(b)(4) (b)(4)

7.1.2 (b)(4)

7.1.2.1 Equipment to be qualified: Press (b)(4)

7.1.2.2 Requirements:

7.1.2.2.1 (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4)

7.1.2.2.2 (b)(4)

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[(b)(4)]

7.1.2.3 Sample size:

[(b)(4)]

Qty	Pressure	[(b)(4)]
(b) (4)	(b)(4)	

[(b)(4)]

Qty	Pressure	[(b)(4)]
(b) (4)	(b)(4)	

7.1.3 [(b)(4)]

7.1.3.1 Equipment to be qualified: (b)(4) [(b)(4)] (b) (4) (b)(4)

7.1.3.2 Requirements:

7.1.3.2.1

7.1.3.2.2 (b)(4)

7.1.3.3 Sample size:

[(b)(4)]

Qty	[(b)(4)] setting
(b) (4)	(b)(4)

Qualification samples:

Pull Test (b)(4)

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Cross Section N = 2

7.1.4 [(b)(4)]

7.1.4.1 Equipment to be qualified: [(b)(4)] (b)(4)

7.1.4.2 Requirements:

[(b)(4)] (b)(4)

7.1.4.3 Sample size: (b)(4) [(b)(4)]

7.1.5 [(b)(4)]

7.2 PROCESS QUALIFICATION

7.2.1 [(b)(4)]

Model	Qty
6921S	(b)(4)
6921M	
6921L	
6999	

7.2.2 TEST PROCEDURE

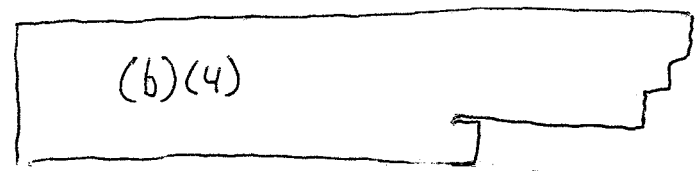
[(b)(4)]

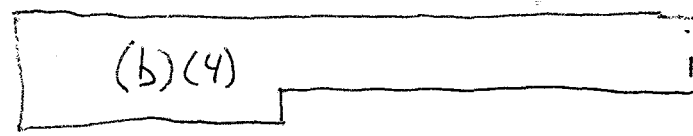
7.2.2.2 Electrical Tests

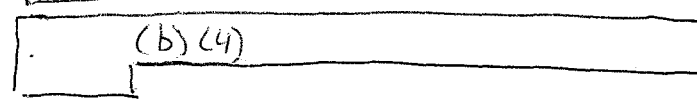
7.2.2.2.1 [(b)(4)]

Loop	6921S	6921M	6921L	6999

Inner	(b)(4)
Second	
Third	(b)(4)
Fourth	
Fifth	

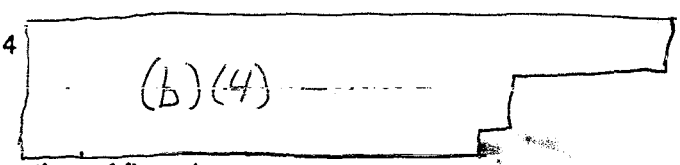
7.2.2.2.2 

7.2.2.2.3 

7.2.2.2.4 

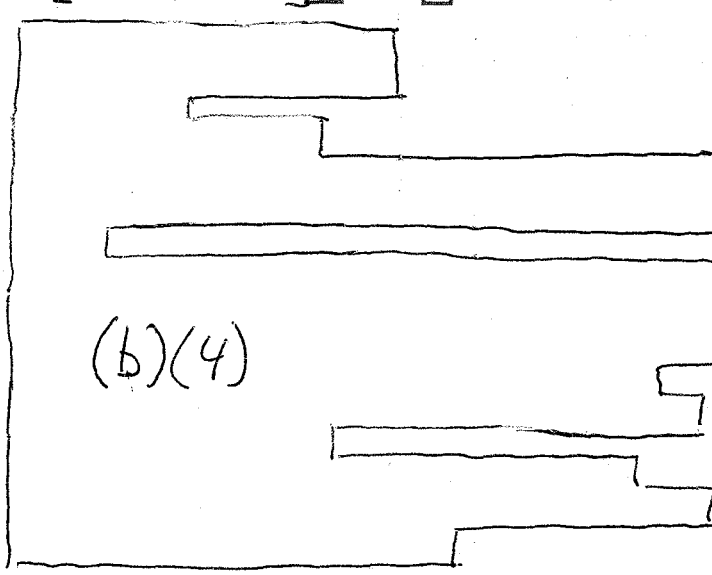
7.2.2.3 Dimensional Check

7.2.2.3.1 Measure and record the dimensions indicated on attached drawing.

7.2.2.4 

time of five minutes.

7.2.2.5 Mechanical Test - [(b)(4)] leads (b)(4)ea model) - per DA534

7.2.2.5.1 

7.2.2.5.2

7.2.2.5.3

7.2.2.5.4

7.2.2.5.5

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7.2.3 DETAIL REQUIREMENTS

7.2.3.1 [(b)(4)]

7.2.3.2 [(b)(4)]

7.2.3.3 [(b)(4)]

7.2.3.4 [(b)(4)]

(b)(4)

7.2.3.5 Verify the following critical components are traced:

7.2.3.5.1
7.2.3.5.2 (b)(4)
7.2.3.5.3

7.2.3.6 Verify the following critical operations are traced:

7.2.3.6.1
7.2.3.6.2
7.2.3.6.3 (b)(4)
7.2.3.6.4

7.2.3.7

8 End of Plan

Medtronic PSG

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D. Doyle
12/17/91
Prepared By
Date 19 DEC 91
Approved By

DESIGN ASSURANCE REPORT

54

TITLE: TEST RESULTS FOR MODEL 6921S, M, L AND 6999 PATCH LEADS TRANSFER

KEY WORDS:

File Code A:95DD1622
Project No.
Page 1 of 3

cc: (b)(6)

1.0 PURPOSE/BACKGROUND

Testing has been completed on each of Model 6921S, M, L, and 6999 patches for the purpose of qualifying build activities at Rice Creek.

2.0 SUMMARY

2.1 [(b)(4)]

2.2 [(b)(4)]

3.0 TESTS, TEST CONDITIONS, TEST SEQUENCE, AND PASS/FAIL CRITERIA

3.1 Visual and X-ray

[(b)(4)]

3.2 Dimensional measurements

[(b)(4)]

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3.3 Initial Electrical Testing per (b)(4)

(b)(4)

(b)(4) (b)(4)

(b)(4)

3.4 Thermal Shock

(b)(4)

3.5 Post-Saturation Electrical per (b)(4)

All patches were tested as in section 3.3.

(b)(4) (b)(4)

(b)(4)

3.6 Composite Pull Test per (b)(4)

(b)(4)

Distal (b)(4) (b)(4)

(b)(4)

Proximal (b)(4) (b)(4)

3.7 Connector Pulls

(b)(4)

(b)(4) (b)(4)

4.0 APPLICABLE DOCUMENTS

Manufacturing Transfer Plan:

(b)(4) (b)(4)

(b)(4) (b)(4)

SUB-Q PARTS LIST AND DRAWING

(b)(4) (b)(4)

(b)(4) (b)(4)

SUB-Q PRODUCT SPEC

(b)(4) (b)(4)

SUB-Q PL AND DRAWING

(b)(4) (b)(4)

(b)(4) (b)(4)

(b)(4)

F. Production and Process Controls

(4) Procedures used to assure that process changes are properly reviewed, approved and validated.

(b)(4)

(a) Process changes due to product specification changes:

- (b)(4)
- (b)(4)
- (b)(4)
- (b)(4)

- (b)(4)
- (b)(4)
- (b)(4)

(b) Process changes not related to product specification changes:

- (b)(4)
- (b)(4)
- (b)(4)
- (b)(4)

F. Production and Process Controls

(5) Methods and procedures used to develop, identify, distribute and maintain manufacturing and quality assurance documentation including the procedures used to authorize and qualify documentation changes.

[(b)(4)]

[(b)(4)]

[(b)(4)]

[(b)(4)]

[(b)(4)]

[(b)(4)]

1. [(b)(4)]
2.
3.
4.

[(b)(4)]

(b)(4)

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[(b)(4)]

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[(b)(4)]

[(b)(4)]

[(b)(4)]

[(b)(4)]

[(b)(4)]

[(b)(4)]

77

[(b)(4)]

F. Production and Process Controls

(6) Methods/procedures used to identify and control non-conforming finished devices, components, packaging and labeling. The description should include reprocessing procedures and controls, and procedures used to investigate, identify, and correct causes of non-conformance.

[(b)(4)]

[(b)(4)]

[(b)(4)]

[(b)(4)]

Reprocessing Procedures and Controls

[(b)(4)]

(b)(4)

(b)(4)

(b)(4)

(b)(4)

90

F. Production and Process Controls

(7) Methods/procedures used to identify critical operations for critical devices.

A critical operation is defined as "Any operation in the manufacture of a critical device which, if improperly performed, may be reasonably expected to cause the failure of a critical device or to affect its safety or effectiveness" [21 CFR 820.3(g)].

Factors that are considered when critical operations are identified are as follows:

- [(b)(4)]
- [(b)(4)]
- [(b)(4)]

[(b)(4)]

- [(b)(4) specifications.]
- [(b)(4)]
- [(b)(4)]
- [(b)(4)]

- [(b)(4)]
- [(b)(4)]
- [(b)(4)]
- [(b)(4)]
- [(b)(4)]
- [(b)(4)]
- [(b)(4)]
- [(b)(4)]

G. Packaging and Labeling Control

(1) Methods/procedures used to assure that labeling received and used in production is acceptable for its intended use and to assure that there are no labeling mixups during storage and labeling operations.

[(b)(4)]

[(b)(4)]

[(b)(4)]

[(b)(4)]

[(b)(4)]

[(b)(4)]

[(b)(4)]

QA

G. Packaging and Label Control

(2) Methods/procedures used to assure that packaging will protect the device during normal processing, handling, storage and distribution

(b)(4)

(b)(4)

4

a

H. Holding, Distribution and Installation

(B)(4)

(B)(4)

(B)(4)

(B)(4)

(B)(4)

(B)(4)

(B)(4)

(B)(4)

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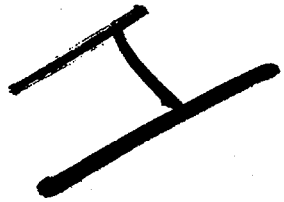
H. Holding, Distribution and Installation

[(B)(4)

(B)(4)

(B)(4)

(B)(4)



I. Device Evaluation

(1) Methods/procedures used for establishing acceptance criteria and assuring that finished devices meet approved specifications before release.

(B)(4)

(B)(4)

Finished Device Inspection Procedures

(B)(4)

(B)(4)

(B)(4)

(B)(4)

(B)(4)

(B)(4)

I. Device Evaluation

(2) Methods/procedures used to investigate product that fails to meet acceptance criteria, including assuring that corrective action is implemented and the records are maintained.

[(B)(4)]

[(B)(4)]

[(B)(4)]

[(B)(4)]

[(B)(4)]

(B)(4)

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(B)(4)

(B)(4)

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(B)(4)

I. Device Evaluation

(B)(4)

(B)(4)

(B)(4)

(B)(4)

(B)(4)

(B)(4)

(B)(4)

(B)(4)

[redacted]

5

J. Records

(1) Methods/procedures used for the establishment, use and maintenance of the Device History Record. Provide copies of the records which make up the Device History Record, e.g., routing forms, data sheets, and batch records.

(B)(4)

(B)(4)

(B)(4)

(B)(4)

(B)(4)

98

(B)(4)

(B)(4)

(B)(4)

(B)(4)

(B)(4)

(B)(4)

Mec onic

Microfilm Access No.

TRACEABILITY CARD

DATA

(b)(4)

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Medtronic

Microfilm Access No.

TRACEABILITY CARD

DATA

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TRACEABILITY CARD

JOB

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(b)(4)

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TRACEABILITY CARD

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TRACEABILITY CARD

JOB

Microfilm Access No.

(b)(4)

(b)(4)

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TRACEABILITY CARD

DATA

Microfilm Access No.

(b)(4)

Part 1 - Page 564

(b)(4)

(b)(4)

Medtronic

TRACEABILITY CARD

Microfilm Access No.

JOB

(b)(4)

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TRACEABILITY CARD

DATA

(b)(4)

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(b)(4)

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Medtronic

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TRACEABILITY CARD

DATA

Microfilm Access No.

(b)(4)

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Microfilm Access No.

TRACEABILITY CARD

JOB

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(b)(4)

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Medtronic

Microfilm Access No.

TRACEABILITY CARD

TRAVELER (PEEL TEST)

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(b)(4)

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TRACEABILITY CARD

JOB

Microfilm Access No.

(b)(4)

(b)(4)

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TRACEABILITY CARD

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JOB

Microfilm Access No.

(b)(4)

Part 1 - Page 57

(b)(4)

(b)(4)

Medtronic

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TRACEABILITY CARD

BATCH

Microfilm Access No.

(b)(4)

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Medtronic

TRACEABILITY CARD

BATCH

Microfilm Access No.

Part 1 - Page 513

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Medtronic

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TRACEABILITY CARD

BATCH _____

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TRACEABILITY CARD

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JOB

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TRACEABILITY CARD

DATA

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(b)(4)

(b)(4)

J. Records

(2) Methods/procedures used to establish and maintain the Device Master Record (DMR) and to control changes to the DMR.

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

. . . . .

(b)(4)

Device Records

(b)(4)

[(6)(4)

]

J. Records

(3) Complaint receiving and processing procedures, including the methods/procedures used to assure that all complaints received are properly reviewed, evaluated and, when necessary, investigated. Provide copies of records used in the complaint processing program and the complaint processing procedures used

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Definitions

(b)(4)

Complaints are defined as such by Medtronic as follows:

1. (b)(4)
2. (b)(4)
3. (b)(4)
4. (b)(4)
5. (b)(4)
6. (b)(4)
7. (b)(4)

Procedure

1. (b)(4)
2. (b)(4)
3. (b)(4)

4. [redacted]

5. [redacted]

6. [redacted]

7. [redacted]

8. [redacted]

9. [redacted]

10. [(b)(4)

]

11. [(b)(4),

y.]

Copies of documents (forms) used in the complaint program and complaint processing are provided on the following pages.

(Report from field) MEDTRONIC CONFIDENTIAL

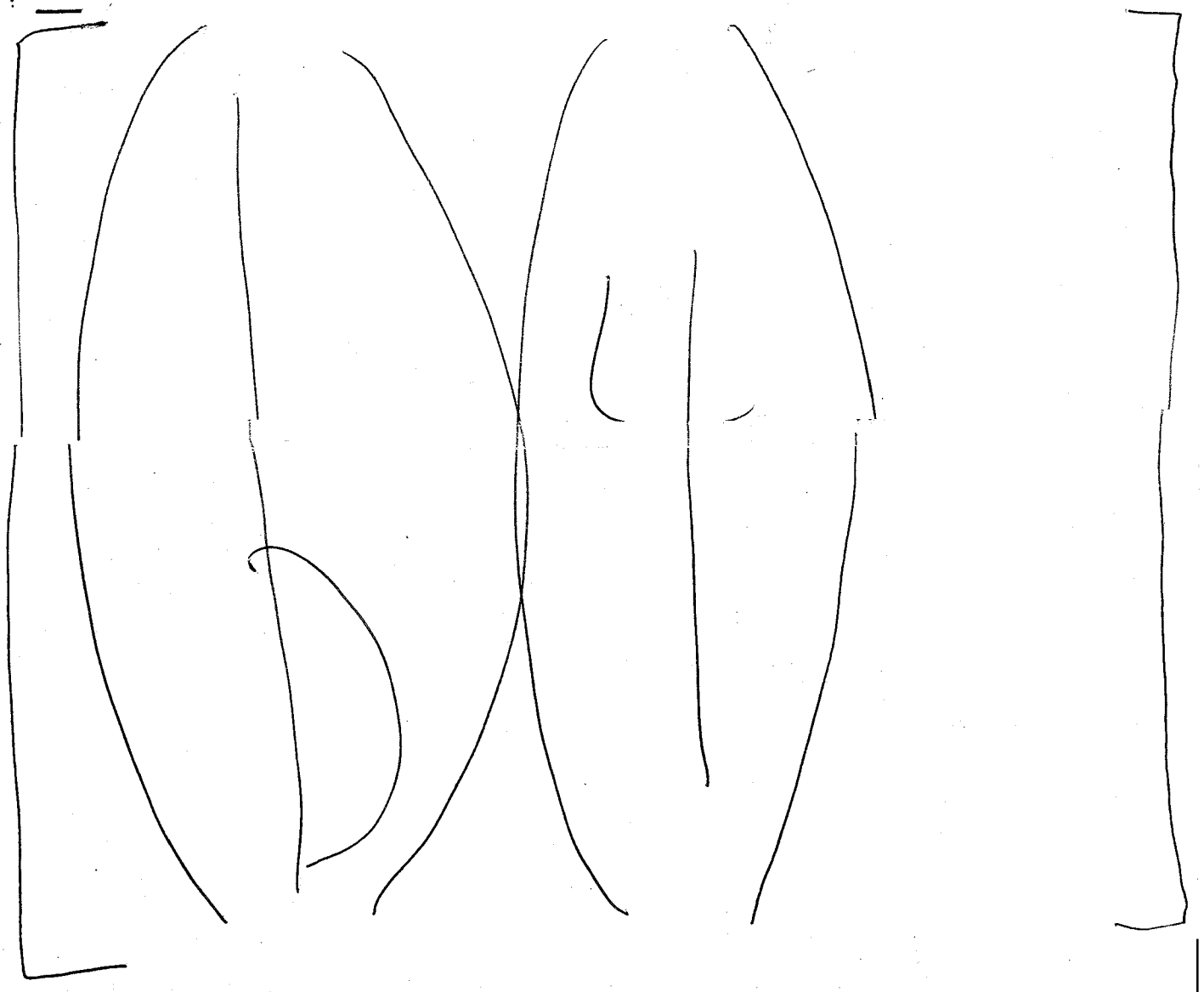
Medtronic

MEDTRONIC COMPLAINT REPORT

Date: 104

COMPLAINANT

PATIENT



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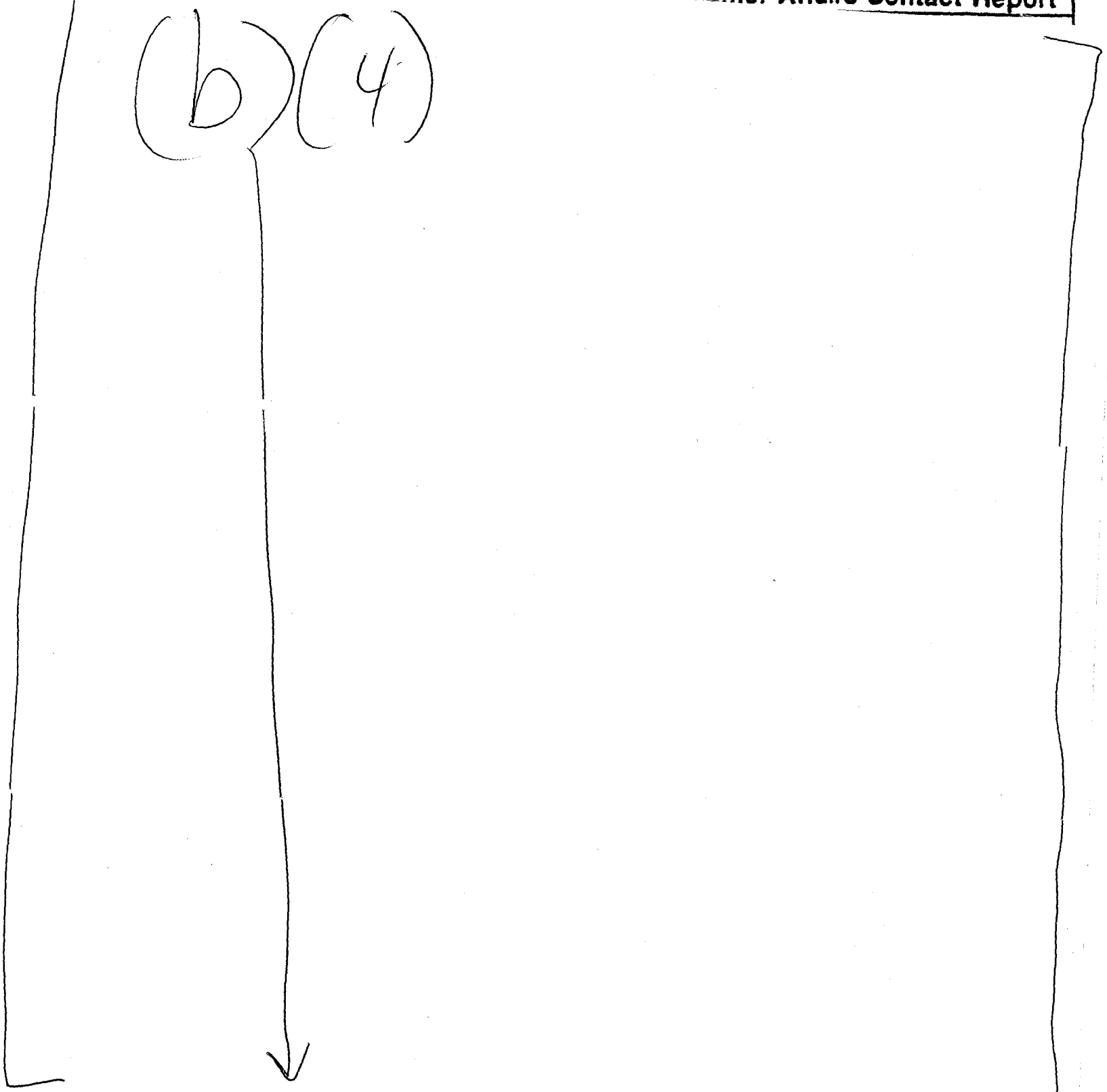
(b)(4)



Medtronic

Medtronic, Inc.
000 Central Avenue, N.E.
Minneapolis, MN 55432
Tel Phone: (800) 328-2518

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REMOVED PRODUCT INFORMATION REPORT

Instructions: Use this form to report your experience with a Medtronic product or when returning a device for evaluation. Back of original form may be used to further explain clinical experience. This information is for warranty consideration, Medical Device Reporting, and performance assessment.

107

PLEASE CLEAN/GAS STERILIZE PRODUCT BEFORE RETURNING DEVICE TO THE MANUFACTURER

CUSTOMER INFORMATION

Physician Names

Patient Name

Date of Implant | Date of Explant

Hospital

Street Address

City | State | Zip

DIAGNOSTIC REASON FOR PACING (Check all that apply)

- ☐ Mobitz II 2° Block
- ☐ Complete A-V Block
- ☐ Sinus Bradycardia
- ☐ Intrinsic Rate of 30 bpm or Less
- ☐ Sinus Brady-Tachy
- ☐ SSS
- ☐ Tachyarrhythmias
- ☐ A-F Slow Vent. Response
- ☐ Multifascicular Block
- ☐ Diagnostic Other _____

PULSE GENERATOR INFORMATION

Model No. _____

Serial No. _____

Status:
- ☐ Replaced (Note Replacement Below)
- ☐ Not Replaced
- ☐ Attempted Implant/ Not Used

PULSE GENERATOR EXPERIENCE

- ☐ Elective Replacement Indicator (Battery depletion)
- ☐ Elective Replacement
- ☐ Programming Difficulty
- ☐ Telemetry Difficulty
- ☐ Sensing Difficulty
- ☐ No Output
- ☐ Infection
- ☐ Erosion
- ☐ Muscle Stimulation
- ☐ System Upgrade
- ☐ Other, please explain _____

Programmed Parameters While Implanted (Prior to ERI):

	Pulse Mag. (V) atrial	Pulse Mag. (V) vent.	Pulse Width (ms) atrial	Pulse Width (ms) vent.	Sensitivity (mV) atrial	Sensitivity (mV) vent.	AV Interval (ms)	Pulse Interval (bpm)	Mode* (select from below)
acute (date _____)									
chronic (date _____)									
[illegible] (date _____)									

*Mode Selections: AAI VVI VVIR DVI DVIR DDD DDDR Other _____

NOTE: INTERROGATE AND INCLUDE PROGRAMMER TELEMETRY PRINTOUT.

VENTRICULAR LEAD INFORMATION

Model No. _____

Serial No. _____

Status:
- ☐ Reused
- ☐ Repositioned
- ☐ Replaced (Note Replacement Below)
- ☐ Capped
- ☐ Removed
- ☐ Unipolarized
- ☐ Not Implanted/Not Used

VENTRICULAR LEAD EXPERIENCE

Chronic Threshold Measurements:

Pacing output _____ (volts)

current _____ (mA)

Sensing _____ (mV)

Resistance _____ (ohms)

- ☐ Elective
- ☐ Infection
- ☐ Erosion
- ☐ Non-capture
- ☐ Other, please explain: _____
- ☐ Sensing Difficulty
- ☐ Positioning Difficulty
- ☐ Apparent Fracture

ATRIAL LEAD INFORMATION

Model No. _____

Serial No. _____

Status:
- ☐ Reused
- ☐ Repositioned
- ☐ Replaced (Note Replacement Below)
- ☐ Capped
- ☐ Removed
- ☐ Unipolarized
- ☐ Not Implanted/Not Used

ATRIAL LEAD EXPERIENCE

Chronic Threshold Measurements:

Pacing output _____ (volts)

current _____ (mA)

Sensing _____ (mV)

Resistance _____ (ohms)

- ☐ Elective
- ☐ Infection
- ☐ Erosion
- ☐ Non-capture
- ☐ Other, please explain: _____
- ☐ Sensing Difficulty
- ☐ Positioning Difficulty
- ☐ Apparent Fracture

IF DEVICE RELATED MEDICAL COMPLICATION OR DEATH, PLEASE DESCRIBE: _____

NOTE: INCLUDE ALL PERTINENT MEDICAL RECORDS, INCLUDING EKG's, WHICH DOCUMENT THE REPORTED EXPERIENCE.

REPLACEMENT DEVICE INFORMATION

Pulse Generator:

Model No. _____

Serial No. _____

VENTRICULAR LEADS Model No.	VENTRICULAR LEADS Serial No.	ATRIAL LEADS Model	ATRIAL LEADS Serial No.

FOLLOW-UP INFORMATION (Indicate the name, address, and phone number of the person who can provide additional information.)

Name _____ Area Code _____ Phone _____

Address _____ City _____ State _____ Zip Code _____

If you have a complaint, please specify: _____

Evaluation Report completed by: ☐ Medtronic employee | Date

Thank you for providing us with this information. If you have any further questions or comments, please contact Medtronic's Customer Service Department at (800) 328-251

186971-001 Original - Medtronic Consumer Affairs Copy - Hospital Copy - Medtronic Representative Med Fm 2261 Aug

Medtronic

Instructions. Use this form to report your experience with a Medtronic product or when return or analysis. This information is necessary and will expedite processing for warranty c... ...n.

MEDTRONIC CONFIDENTIAL

Please indicate model and serial numbers of the device(s) involved: Pulse Generator	Lead(s) →	Model No.:	Serial No.:
Model No.:	Serial No.:	Model No	Serial No.:

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GENERAL INFORMATION

Physician		Hospital		
Patient Name		Street Address		
Date of Implant	Date of Explant	City	State	Zip

CLINICAL INFORMATION

NOTE: Please include all pertinent medical records including EKG's.

Reported Experience:

- ☐ Elective Replacement
- ☐ Patient Expired
- ☐ Infection
- ☐ Erosion
- ☐ Battery Depletion
- ☐ Rate Change ____ bpm to ____ bpm
- ☐ No Output
- ☐ Noncapture
- ☐ Oversensing
- ☐ Undersensing
- ☐ Programming Difficulty
- ☐ Positioning Difficulty
- ☐ High Threshold Readings
- ☐ Fractured Lead
- ☐ Stylet Difficulty
- ☐ Other (please explain):
- ☐ Visual Irregularity: _____

Reported experience was observed ☐ Continuously ☐ Intermittently

Pacing Mode while implanted: ☐ DDD ☐ VVI ☐ DVI ☐ _____

Programmed Parameters While Implanted:

Pulse magnitude: _____ (volts) Pulse Width: _____ Pulse Interval (Rate): _____

Sensitivity: _____ Refractory: _____ A-V Interval: _____

Lead Status: ☐ Reused ☐ Repaired ☐ Unipolarized ☐ Repositioned ☐ Replaced ☐ Capped

REPLACEMENT INFORMATION

If replaced, indicate replacement device(s). Pulse Generator	Lead(s) →	Model No.:	Serial No.:
Model No.:	Serial No.:	Model No.:	Serial No.:

FOLLOW—UP INFORMATION

Please indicate the name, address and phone number of the person to receive follow-up information:

Name	Area Code	Phone
Address		
City	State	Zip

If you have a complaint, please specify:

Evaluation Report completed by	Date.

179921-001 White-Medtronic Yellow-Customer Med Fm 2261 Oct 85

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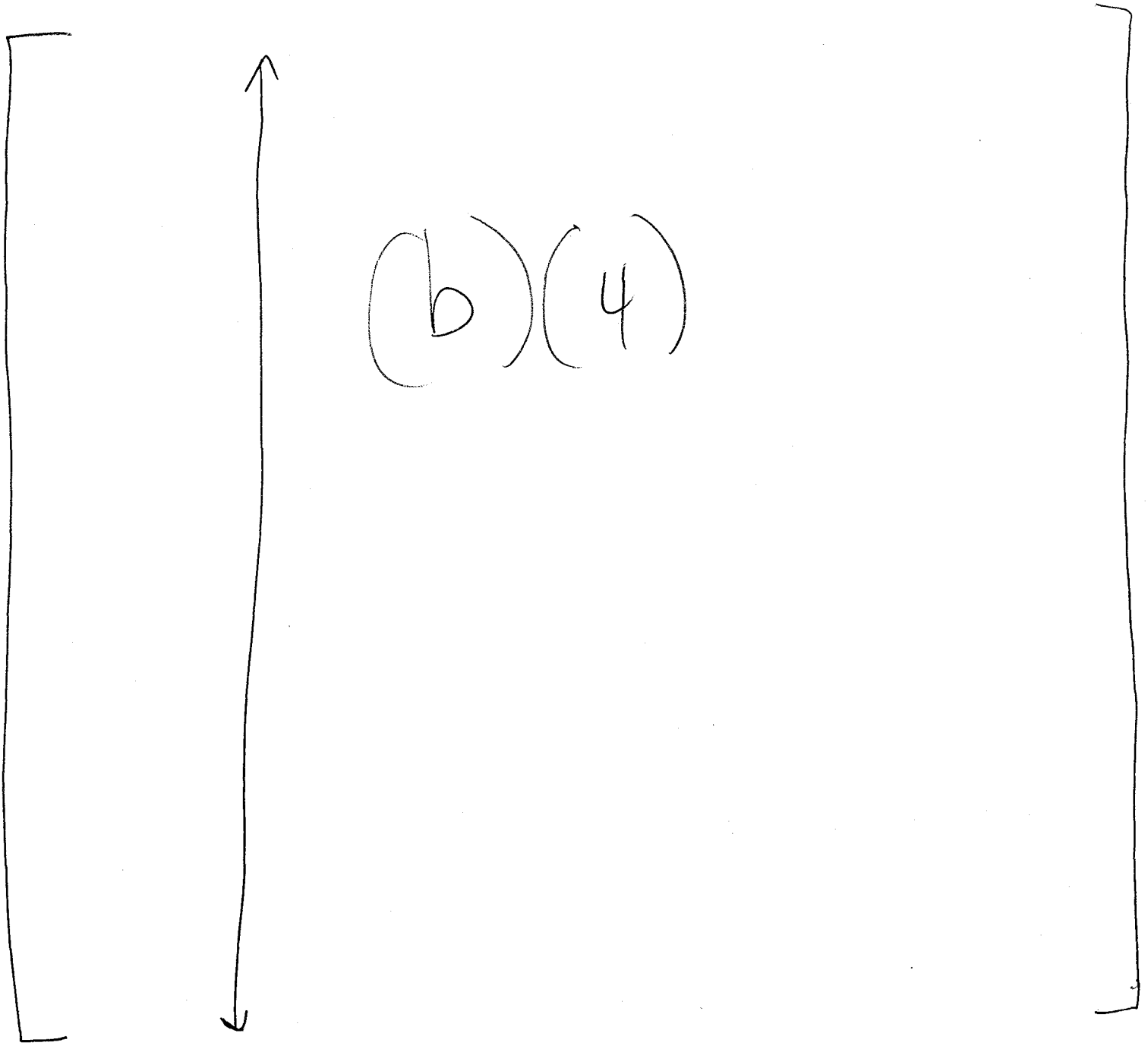
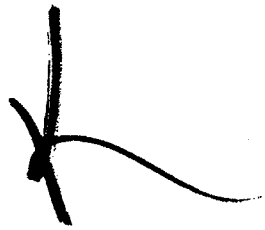
TO EXPOSE ADHESIVE, REMOVE LINER. TO EXPOSE ADHESIVE, REMOVE LINER. TO EXPOSE ADHESIVE, REMOVE LINER. TO EXPOSE ADHESIVE, REMOVE LINER.

COMPLAINT SUMMARY INPUT



A-EX.csi



K. Sterile Devices

(1) Methods/procedures for release for distribution, e.g., sterility testing, parametric release, and process control release. Provide copies of all finished device testing procedures.

(b)(4)

Copies of the following finished device test procedures are provided at the end

1. (b)(4) (b)(4) al

2. (b)(4) (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

a) Sterilization Equipment Qualification

(b)(4)

(b)(4)

(b)(4)

b) Biological Qualification; D-Value Testing

(B)(4)

(B)(4)

(B)(4)

(B)(4)

(B)(4)

(B)(4)

(B)(4)

(B)(4)

(B)(4)

(b)(4)

Product Sample	Inoculation Level	D-Value
(B)(4) (b)(4)	(b)(4)	

(b)(4)

(b)(4)

c) Bioburden

(b)(4)

(B)(4)

(B)(4)

(B)(4)

[(B)(4)

[(B)(4)

[(B)(4)

d) Sterilization Parameters

[(B)(4)

[(B)(4)

[(B)(4)

[(B)(4)

Table I

Nominal Sterilization Process Parameters (Rice Creek)

Prevacuum	(b) (4)
Prehumidity	
EO Gas Pressure[1]	
Chamber Temperature	
Chamber Cold Spot Temp.	
Air Displacement	(b)(4)
EO Exposure Time	
Post Vacuum	
Post Vacuum Flushes	
Humidity	
Aeration	

[1] Ethylene oxide is a (b) (4) (b)(4) mix; (b) (4) (b)(4)

K. Sterile Devices

(2) Methods/procedures to indicate whether the packaging materials have been challenged to assure they are microbially retentive, and that the seal(s) maintains sterility.

Packaging materials for Medtronic Model 6999 Lead consist of an inner and outer Tyvek/polyethylene/Mylar pouch; the inner pouch, containing the product, is heat-seal closed. This inner pouch is placed into a larger, outer pouch, which is also heat-seal closed.

The packaging materials for the Medtronic Model 6963 Lead consist of a PVC tray, Tyvek lid and [(b)(4)] adhesive.

Microbial challenge testing has been performed on the PVC packaging and has demonstrated that this package configuration provides an efficient barrier to maintain the sterility of the contents when subjected to extremely vigorous microbial stress conditions.

Test samples of the PVC tray with Tyvek lid and (B)(4) adhesive were aged (b)(4) months (post-sterilization) prior to testing. Prior to microbial challenge testing, samples were subjected to (B)(4)

[(B)(4)

[(B)(4)

[(B)(4)

Medtronic

STERILIZATION TECHNICAL SERVICES PROCEDURE

MEDTRONIC CONFIDENTIAL

2-220 117

TITLE: STERILITY MONITORING

ISSUE NUMBER	DESCRIPTION OF CHANGE	APPROVAL SIGNATURES	DATE OF APPROVAL
(b)(4), (b)(6)			

(b)(4), (b)(6)

Medtronic

MEDTRONIC CONFIDENTIAL

STERILIZATION TECHNICAL SERVICES PROCEDURE

NUMBER: 2-220

TITLE: STERILITY MONITORING

ISSUE NUMBER	DESCRIPTION OF CHANGE	APPROVAL SIGNATURES	DATE OF APPROVAL
(b)(4), (b)(6)			

(b)(4), (b)(6)

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STS 2-220

PROCEDURE TITLE: STERILITY MONITORING

1.0 **SCOPE:**

1.1 Sterility monitoring of biological indicators for Sterilization Quarantine Release, Sterilization Certification and Reverification Tests.

2.0 **PURPOSE:**

2.1 To establish and document the procedure for testing the biological indicators used for monitoring dry heat, Gamma Radiation, Steam and Ethylene Oxide Sterilization.

3.0 **APPLICABLE DOCUMENTS:** (Current Revisions)

3.1 (B)(4)

3.2 (B)(4)

3.3 (B)(4)

3.4 (B)(4)

3.5 (B)(4)

3.5.1 (B)(4)

3.5.2 (B)(4)

3.5.3 (B)(4)

3.5.4 (B)(4)

3.5.5 (B)(4)

3.5.6 (B)(4)

3.5.7 (B)(4)

3.5.8 (B)(4)

3.5.9 (B)(4)

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3.6 The following Sterilization Services Procedures: (Current revisions).

3.6.1 (B)(4)

3.6.2 (B)(4)

3.6.3 (B)(4)

3.6.4 (B)(4)

3.6.5 (B)(4)

3.6.6 (B)(4)

3.6.7 (B)(4)

3.6.8 (B)(4)

3.7 (B)(4)

4.0 **APPARATUS/TEST EQUIPMENT:**

4.1 (b)(4)

4.2

4.3

4.4 (b)(4)

4.5

4.6

4.7

4.8

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4.9 (b)(4)

4.10

4.11

4.12

4.13

5.0 **PROCEDURE FOR PREPARATION OF TEST MEDIA:**

5.1 Prepare (b)(4) per Section 5.5 of (b)(4)

6.0 **STERILITY MONITORING FOR STERILIZATION QUARANTINE RELEASE:**

6.1 The Retrieval of Biological Indicators.

6.1.1 (B)(4)

6.1.2 (B)(4)

6.2 Labeling of Test Containers.

6.2.1 (B)(4)

6.2.1.1 (b)(4) (B)(4)

6.2.1.1.1 (B)(4)

6.2.1.1.2 (B)(4)

6.2.1.1.3 (B)(4)

6.2.1.2 [(B)(4)

6.2.1.2.1 [(B)(4)

6.2.1.3 [(B)(4)

6.2.1.3.1 [(B)(4)

6.2.1.4 [(B)(4)

6.2.1.4.1 [(B)(4)

6.2.2 [(B)(4)

6.2.2.1 [(B)(4) ch

6.2.2.1.1 See 6.2.1.1.1 thru 6.2.1.1.3.

6.2.2.1.2 See 6.2.1.1.2

6.2.2.2 [(B)(4)

6.2.2.3 [(B)(4)

6.2.2.3.1 [(B)(4)

6.2.2.3.2 [(B)(4)

6.2.2.4 [(B)(4)

NOTE: (b)(4)

6.2.3 [(b)(4)]

6.2.3.1 (b)(4)

NOTE: (b)(4)

6.2.3.2 (b)(4)

6.2.3.3 [(b)(4)]

6.3 Transferring of Biological Indicators to Media.

6.3.1 (b)(4)

6.3.2 (b)(4)

6.3.3 (b)(4)

6.3.4 (b)(4)

6.3.5 (b)(4)

6.3.6 (b)(4)

6.3.7 [(b)(4)]

6.3.7.1 (b)(4)

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NOTE: (b)(4)

6.3.7.2 (b)(4)

6.3.7.2.1 (b)(4)

6.3.7.3 (b)(4)

6.3.7.4 (b)(4)

6.3.7.5 (b)(4)

6.3.7.6 (b)(4) (b)(b)(4)

6.3.7.7 (b)(4)

6.3.7.8 (b)(4)

6.3.7.9 (b)(4)

6.3.7.9.1 (b)(4)

6.3.7.9.2 (b)(4)

6.3.7.10 (b)(4)

6.3.7.10.1 (b)(4)

6.3.7.10.2 (b)(4)

6.3.7.10.3 (b)(4)

6.3.7.11 (b)(4)

6.4 Recording the results.

6.4.1 (b)(4)

(b)(4)

6.4.2 (b)(4)

6.4.2.1 (b)(4)

6.4.2.1.1 (b)(4)

6.4.2.2 (b)(4)

6.4.3 (b)(4)

6.4.3.1 (b)(4)

6.4.4 (b)(4)

6.4.4.1 (b)(4)

126

6.4.4.2 (b)(4)

6.4.4.2.1 (b)(4)

6.4.4.2.2 (b) (4) (b)(4)
(b)(4)

6.4.4.3 (b)(4)

NOTE: (b)(4)

6.4.5 (b)(4)

6.4.5.1 (b)(4)

6.4.5.2 (b)(4)

6.4.6 (b)(4)

127

6.4.6.1 (b)(4)

6.4.6.2 (b)(4)

6.4.6.3 (b)(4)

6.4.6.3.1 (b)(4)

6.4.6.3.2 (b)(4)

NOTE: (b)(4)

6.4.6.4 (b)(4)

6.4.6.4.1 (b)(4)

6.4.7 (b)(4)

6.4.8 (b)(4)

6.5 Disposal of the Media.

6.5.1 (b)(4)

6.5.1.1 (b)(4)

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6.5.1.2 (b)(4)

7.0 **STERILITY MONITORING FOR STERILIZATION CERTIFICATION, AND REVERIFICATION:**

7.1 The Retrieval of Test Samples.

7.1.1 (b)(4)

7.1.1.1 (b)(4)

7.2 Preparation of Testing Materials.

7.2.1 (b)(4)

7.2.2 (b)(4)

7.2.3 (b)(4)

7.3 Test Procedure

7.3.1 (b)(4)

7.3.2 (b)(4)

7.3.3 (b)(4)

7.3.4 (b)(4)

7.3.4.1 (b)(4)

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7.3.4.1.1 (b)(4)

7.3.4.2 (b)(4)

7.3.4.2.1 (b)(4)

7.3.5 (b)(4)

7.3.5.1 (b)(4)

7.3.5.1.1 (b)(4)

7.3.5.1.2 (b)(4)

7.3.5.1.3 (b)(4)

7.3.6 (b)(4)

7.3.6.1 (b)(4) (b)(4) (b)(4) (b)(4)

7.3.6.2 (b)(4) (b)(4) (b)(4)

7.3.6.3 (b)(4) (b)(4) (b)(4)

7.3.6.4 (b)(4) (b)(4) (b)(4)

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7.4 Recording the Test Results.

7.4.1 (b)(4)

7.4.1.1 (b)(4)

7.4.1.2 (b)(4)

7.4.1.3 (b)(4)

7.4.1.4 (b)(4)

7.4.2 (b)(4)

7.4.2.1 (b)(4)

7.4.3 (b)(4)

7.4.3.1 (b)(4)

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7.4.3.2 (b) (4) (b)(4)

7.5 Disposal of the Media.

7.5.1 (b)(4)

7.5.1.1 (b)(4)

7.5.2 (b)(4)

7.5.3 (b)(4)

7.5.4 (b)(4)

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STERILIZATION TECHNICAL SERVICES PROCEDURE

NUMBER: 2-222

TITLE: STERILIZATION QUARANTINE RELEASE

MEDTRONIC CONFIDENTIAL

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ISSUE NUMBER	DESCRIPTION OF CHANGE	APPROVAL SIGNATURES	DATE OF APPROVAL
(b)(4), (b)(6)			

(b)(4), (b)(6)

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STERILIZATION TECHNICAL SERVICES PROCEDURE

NUMBER: 2-222

MEDTRONIC CONFIDENTIAL

TITLE: STERILIZATION QUARANTINE RELEASE

133

ISSUE NUMBER	DESCRIPTION OF CHANGE	APPROVAL SIGNATURES	DATE OF APPROVAL
(b)(4), (b)(6)			

(b)(4), (b)(6)

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INSTRUCTION TITLE: STERILIZATION QUARANTINE RELEASE

1.0 SCOPE:

1.1 To cover quarantine releases of all sterile lots submitted to Sterilization Technical Services for sterility monitoring.

2.0 PURPOSE:

2.1 To establish and document the procedures used in the release of quarantined sterilized product.

3.0 APPLICABLE DOCUMENTS: (Current Revisions)

3.1 [redacted] (b)(4)

3.2 [redacted] (b)(4)

3.3 [redacted] (b)(4)

3.4 [redacted] (b)(4)

3.5 [redacted] (b)(4)

3.6 [redacted] (b)(4)

3.7 [redacted] (b)(4)

3.8 [redacted] (b)(4)

3.9 [redacted] (b)(4)

4.0 APPARATUS OR TEST EQUIPMENT:

4.1 [redacted] (b)(4)

5.0 PROCEDURES - ETHYLENE OXIDE STERILIZATION:

5.1 [redacted] (b)(4)

5.1.1 [redacted] (b)(4)

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5.1.1.1 (b)(4)

5.1.2 (b)(4)

5.1.2.1 (b)(4)

5.1.2.1.1 (b)(4)

5.1.2.1.1.1 (b)(4)

5.1.2.1.1.2 (b)(4)

5.1.2.1.1.2.1 (b)(4)

5.1.2.2 (b)(4)

5.1.3 (b)(4) If

136

5.1.3.1 (b)(4)

5.1.3.1.1 (b)(4)

5.1.3.2 (b)(4)

5.1.3.3 (b)(4)

5.1.3.4 (b)(4)

5.1.4 (b)(4)

PROCEDURE FOR COMPLETION OF QUARANTINE RELEASE FORM

5.2 (b)(4)

(b)(4)

5.2.1 (b)(4)

5.2.2 (b)(4)

5.2 (b)(4)

5.2.4 (b)(4)

5.2.5 (b)(4)

5.2.6 (b)(4)

5.2.6.1 (b)(4)

5.2.6.2 (b)(4) A137

5.2.7 (b)(4)

5.2.8 (b)(4)

5.2.8.1 (b)(4)

5.2.8.2 (b)(4)

5.2.9 (b)(4)

5.2.9.1 (b)(4)

5.2.9.2 (b)(4)

5.2.10 Data Retention

5.2.10.1 (b)(4)

5.3 (b)(4)

5.3.1 (b)(4)

5.3.1.1 (b)(4)

[(B)(4)] CONFIDENTIAL 138

5.3.1.2 [(B)(4)]

5.3.1.3 [(B)(4)]

5.3.2 [(B)(4)]

5.3.3 [(B)(4)]

5.3.3.1 [(B)(4)]

5.3.3.2 [(B)(4)]

5.3.4 [(B)(4)]

5.3.4.1 [(B)(4)]

5.3.4.2 [(B)(4)]

5.3.5 [(B)(4)]

5.3.5.1 [(B)(4)]

5.3.5.2 [(B)(4)]

5.3.6 Data Retention.

5.3.6.1 [(B)(4)]

K. Sterile Devices

(3) Pyrogenicity studies which have been conducted on the device, if applicable. Also, indicate whether each lot will be tested, and provide a copy of the test procedure.

[(B)(4)

[(B)(4)

[(B)(4)

a. [(B)(4)

b. [(B)(4)

c. [(B)(4)

[(B)(4)

4WTULY

Medtronic

STERILIZATION TECHNICAL SERVICES PROCEDURE

NUMBER: 2-226

TITLE: DETECTION AND QUANTITATION OF ENDOTOXIN

MEDTRONIC CONFIDENTIAL 140

ISSUE NUMBER	DESCRIPTION OF CHANGE	APPROVAL SIGNATURES	DATE OF APPROVAL
(b)(4), (b)(6)			

(b)(4), (b)(6)

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STERILIZATION TECHNICAL SERVICES PROCEDURE

NUMBER: 2-226 141

TITLE: DECTECTION AND QUANTITATION OF ENDOTOXIN

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ISSUE NUMBER	DESCRIPTION OF CHANGE	APPROVAL SIGNATURES	DATE OF APPROVAL
(b)(4), (b)(6)			

(b)(4), (b)(6)

MEDTRONIC CONFIDENTIAL

PROCEDURE TITLE: DETECTION AND QUANTITATION OF ENDOTOXIN

1.0 SCOPE:

1.1 To detect and quantitate endotoxin levels through use of the Limulus Amebocyte Lysate gel-clot test.

2.0 PURPOSE:

2.1 To establish and document a standard method of conducting the LAL gel-clot test including materials preparation, reagent handling, and device extraction procedures for the detection and quantitation of endotoxin.

3.0 APPLICABLE DOCUMENTS: (Current Editions)

3.1 [(B)(4)]

3.2 [(B)(4)]

3.3 [(B)(4)]

3.3.1 [(B)(4)]

3.3.2 [(B)(4)]

3.3.3 [(B)(4)]

3.3.4 [(B)(4)]

3.4 The United States Pharmacopeia; Current Revision.

3.5 FDA Draft Guidelines, "Detection and Quantitation of Endotoxin."

4.0 APPARATUS OR TEST EQUIPMENT:

4.1 (b)(4)

4.2

(b)(4)

4.3

4.4

4.5 (b) (4)

4.6

4.7

4.8

4.9

4.10

4.11

4.12

4.13

(b)(4)

4.14

4.15

4.16

4.17

4.18

4.19

4.20

4.21

4.22

4.23

4.24 (b) (4)

4.25

4.26

(b)(4)

4.27

4.28

4.29

5.0 PROCEDURE:

5.1 Glassware preparation

5.1.1 (b)(4)

5.1.2 (b)(4)

5.1.3 (b)(4)

(b) (4) (b)(4)

5.2 Preparation and handling of endotoxin standards.

5.2.1 (b) (4) (b)(4)

5.2.2 (b)(4)

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5.2.2.1 [(b)(4)]

5.2.2.1.1 [(b)(4)]

5.2.2.2 [(b)(4)]

5.2.2.3 [(b)(4)]

5.2.3 [(b)(4)]

5.2.3.1 [(b)(4)]

5.2.3.2 [(b)(4)]

5.2.3.3 [(b)(4) (b) (4)]

5.2.3 [(b)(4)]

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TABLE 1

Dilution	Endotoxin Used	*SSEI/SWEI Used	Concentration
(b)(4)	(b)(4)		

(b)(4) [(b)(4)]

5.2.3.5 [(b)(4)]

5.2.3.6 [(b)(4)]

5.3 [(b)(4)]

5.3.1 [(b)(4)]

5.3.2 [(b)(4)]

5.3.3 [(b)(4)]

5.3.3.1 [(b)(4)]

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5.3.3.2 [(b)(4)]

5.3.3.3 [(b)(4)]

5.4 Sample preparation and considerations.

5.4.1 [(b)(4)]

5.4.1.1 [(b)(4)]

5.4.1.2 [(b)(4)]

5.4.1.3 [(b)(4)]

5.4.1.4 [(b)(4)]

5.4.1.5 [(b)(4)]

MEDTRONIC CONFIDENTIAL

5.4.1.6 [(b)(4)]

5.4.1.7 [(b)(4)]

5.4.1.8 [(b)(4)]

5.5 Conducting the LAL gel-clot test.

5.5.1 Testing requirements

5.5.1.1 [(b)(4)]

5.5.1.2 [(b)(4)]

5.5.1.3 [(b)(4)]

5.5.2 [(b)(4)]

5.5.2.1 [(b)(4)]

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5.5.2.2 [(b)(4)]

5.5.2.3 [(b)(4)]

5.5.2.4 [(b)(4)]

5.5.2.5 [(b)(4)]

5.5.2.5.1 [(b)(4)]

5.5.2.6 [(b)(4)]

5.5.2.7 [(b)(4)]

5.5.2.7.1 [(b)(4)]

5.5.2.8 [(b)(4)]

5.5.2.9 (b)(4)

5.5.2.10 (b)(4)

5.5.2.11 (b)(4)

5.5.2.12 (b)(4)

5.5.2.13 (b)(4)

5.6 Results

5.6.1 (b)(4)

i (b)(4)

5.6.2 (b)(4)

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5.6.3 [(b)(4)

[(b)(4)

5.6.3.1 [(b)(4)

5.6.3.2 [(b)(4)

5.6.3.3 [(b)(4)

5.6.4 [(b)(4)

DETECTION OF SAMPLE ENDOTOXIN

Page____of____ Date_____ Employee #_____

Temperature In_____Out_____

MEDTRONIC CONFIDENTIAL 152

TEST ID			
SAMPLE ID			NEGATIVE CONTROL
			NEGATIVE CONTROL
			NEGATIVE CONTROL

(b)(4)

ENGINEER

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(ML5)

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K. Sterile Devices

(4) If ethylene oxide is used as the sterilization method, methods/procedures for the aeration time, the test method to detect EO residues, the frequency of testing, and the release criteria. Provide copies of all procedures and data.

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

ORIGINAL

Medtronic

STERILIZATION TECHNICAL SERVICES PROCEDURE

NUMBER: 1-119

MEDTRONIC CONFIDENTIAL

154

TITLE: STERILANT RESIDUE ANALYSIS

ISSUE NUMBER	DESCRIPTION OF CHANGE	APPROVAL SIGNATURES	DATE OF APPROVAL
(b)(4), (b)(6)			

(b)(4), (b)(6)

MEDTRONIC CONFIDENTIAL 155

TITLE: Sterilant Residue Analysis

1.0 SCOPE:

Procedure for Product Aeration Certification and on-going Sterilant Residue Monitoring.

2.0 PURPOSE:

To document the procedure used for the preparation, coordination of sterilization, aeration, and extraction of test samples and the recording of test results.

3.0 APPLICABLE DOCUMENTS:

(b)(4)

4.0 APPARATUS OR TEST EQUIPMENT:

4.1 (b)(4)

4.2 (b)(4)

4.3 (b)(4)

4.4 (b)(4)

MEDTRONIC CONFIDENTIAL

5.0 (b)(4)

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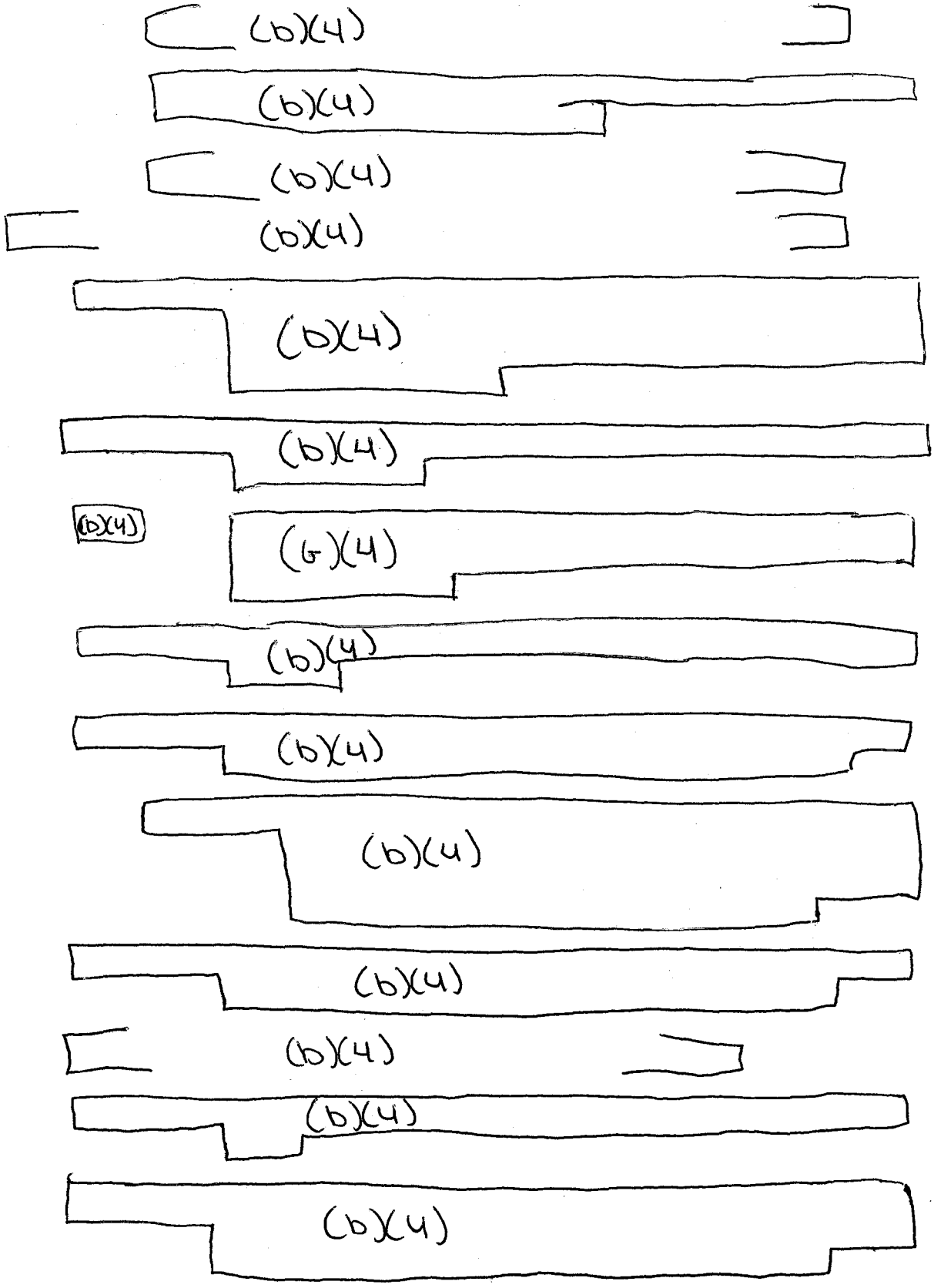
157



MEDTRONIC CONFIDENTIAL 158

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MEDTRONIC CONFIDENTIAL

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(b)(4)

(b)(4)

(b)(4)

(b)(4)

R1

MEDTRONIC CONFIDENTIAL 161

6.0 PROCEDURE FOR ON-GOING STERILANT RESIDUE MONITORING:

[(b)(4)]

[(b)(4)]

[(b)(4)]

[(b)(4)]

[(b)(4)]

[(b)(4)]

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N 7/91

STERILANT RES : MONITORING LOG

Sample Analyzed	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4) %	(b)(4) % Cl	(b)(4)

MEDTRONIC CONFIDENTIAL

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MEDTRONIC CONFIDENTIAL

ETHYLENE OXIDE RESIDUE WORKSHEET

(b)(4)

Sample No.	
	(b)(4)
TOTAL	

[(b)(4)]

[(b)(4)]

Whole Page Redaction

(b)(4)

Medtronic

QUALITY ASSURANCE INSTRUCTION

Number: 9-0810

uction Type: CHEMICAL QUALITY ASSURANCE ENGINEERING

ction Title: Residue EtO in Sterilized Product

Issue Number	Approving Employee's Title	Approving Employee's Name	Approving Employee's Signature	Date of Approval	Issue or Change Description
(b)(4), (b)(6)					

(b)(4), (b)(6)

Medtronic **QUALITY ASSURANCE INSTRUCTION** Number: 9-0810 ~~166~~

Instruction Type	Chemical Quality Assurance Engineering
Instruction Title	Residue ETO In Sterilized Product

Issue Number	Approving Employee's Title	Approving Employee's Name	Approving Employee's Signature	Date of Approval	Issue or Change Description
(b)(4), (b)(6)					

(b)(4), (b)(6)

MEDTRONIC CONFIDENTIAL 167

TITLE: STERILANT RESIDUE

1.0 Scope

1.1 This procedure pertains to all sterilized devices and/or material sterilized with ethylene oxide.

2.0 Purpose

This procedure describes the method to be used for analyzing the amount of residual ethylene oxide, ethylene chlorohydrin and ethylene glycol in ETO sterilized products.

3.0 Applicable Documents

3.1 (b)(4)

3.2 (b)(4) [(b)(4)]

4.0 Apparatus and Reagents

4.1 (b)(4) [(b)(4)] (b)(4)

4.2 (b)(4) [(b)(4)]

4.3 [(b)(4)]

4.4 [(b)(4)]

4.5 [(b)(4)]

4.6 [(b)(4)]

4.7 [(b)(4)]

4.8 [(b)(4)]

4.9 [(b)(4)]

4.10 (b)(4)

4.11 [(b)(4)] (b)(4)

4.12 [(b)(4)]

4.13 [(b)(4)]

5.0 Procedure

[(b)(4)]

[(b)(4)]

[(b)(4)] [(b)(4)]

[(b)(4)]

[(b)(4)]

[(b)(4)]

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[(b)(4)]

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OVEN PROGRAM

OVEN PROGRAM

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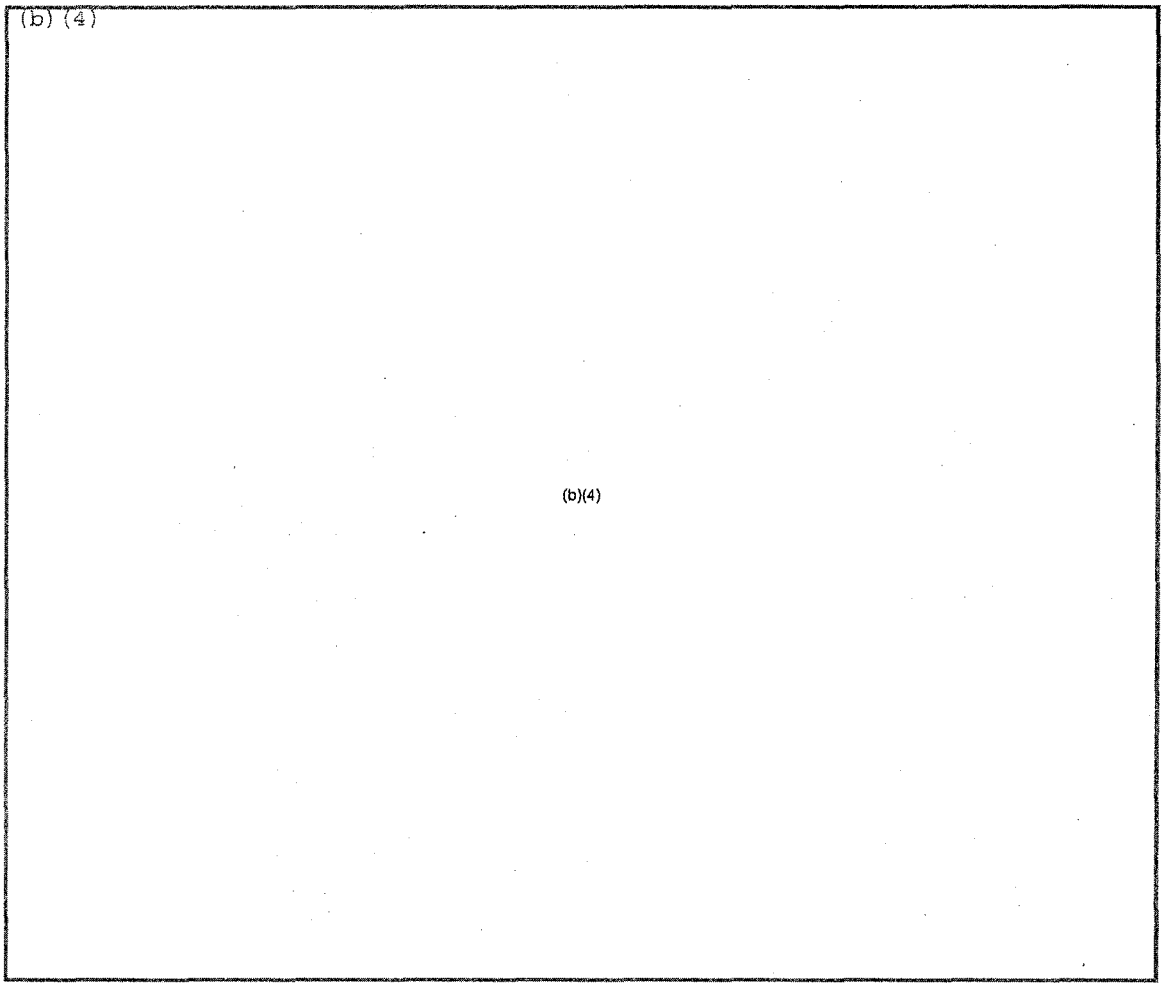
nED DETECTOR & SIGNALS

(b)(4)



L. Devices Containing Software

Software is not applicable to the manufacture of the Model 6963 and 6999 leads.

LABELING

194

TECHNICAL MANUAL

TRANSVENE™-SVC Unipolar, Endocardial, Coronary Sinus or Superior Vena Cava Lead for Cardioversion and Defibrillation

MODEL 6963

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DESCRIPTION AND INTENDED USE

The Medtronic® TRANSVENE™-SVC Model 6963 Unipolar, Endocardial, Coronary Sinus or Superior Vena Cava Lead features an electrode for the delivery of cardioversion and defibrillation therapies. It is intended for long-term use in the coronary sinus or superior vena cava and is designed to be used only with a Medtronic Implantable PCD™ Device along with at least one other lead, such as the TRANSVENE™-RV Model 6966 Tripolar, Endocardial, Screw-In, Ventricular Lead.

Silicone insulation surrounds the low resistance conductor coil and the coil electrode is a platinum alloy. The lead also has a 6.5 mm connector.

The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

CONTENTS OF PACKAGE

The leads are supplied sterile. Each package contains:

- 1 TRANSVENE™-SVC lead with anchoring sleeve, stylet, and stylet guide
- 1 vein lifter
- Extra stylets
- Product literature

CONTRAINDICATIONS

There are no known contraindications for this lead.

WARNINGS

Do not attempt to use this lead with a non-Medtronic Implantable Cardioverter/Defibrillator device. An implanted lead forms a direct, low-resistance current path to the myocardium. Therefore, use only battery-powered equipment during lead implantation and testing to protect against fibrillation that may be caused by alternating currents. Line-powered equipment used in the vicinity of the patient must be properly grounded. Lead connector pins must

be insulated from any leakage currents that may arise from line-powered equipment.

See also the section titled "General Warnings".

PRECAUTIONS

Necessary Hospital Equipment

Defibrillating equipment should be kept nearby for immediate use during the acute lead system testing, implantation procedure, or whenever arrhythmias are possible or intentionally induced during post-implant testing.

Inspecting the Package

Carefully inspect the package before opening. If the container, the package, or the lead appear to have been damaged, do not use the lead. Return the damaged lead to your Medtronic representative.

Handling the Lead

Leads should be handled with great care at all times. Any **severe bending, kinking, stretching, or handling with surgical instruments may cause permanent damage to the lead.**

Lead insulators attract small particles such as lint and dust. Therefore, protect the lead from materials shedding these substances. Handle the lead with sterile surgical gloves that have been rinsed in sterile water or equivalent.

Do not immerse leads in mineral oil, silicone oil, or any other liquid.

Using an Anchoring Sleeve

Use an anchoring sleeve with all leads to secure the lead from moving and to protect the lead insulation and conductor coil from damage caused by tight ligatures.

Chronic Repositioning

Chronic repositioning of the lead may be difficult because of the fibrotic tissue development. However, if a lead must be removed or repositioned, proceed with extreme caution. Return all removed or unused leads or portions thereof to Medtronic.

See additional cautions in the section titled "Suggested Implantation Procedure."

10

POTENTIAL COMPLICATIONS

The potential complications related to the use of transvenous leads include, but are not limited to, the following patient-related conditions that can occur during and following lead insertion: fibrillation or other arrhythmias, conduction disturbances, loss of contractility, air embolism, cardiac perforation, heart wall rupture, cardiac tamponade, infection, and tissue necrosis.

Other potential complications related to the lead include, but are not limited to, the following: lead dislodgement, lead conductor fracture, and insulation failure.

ENSURING PRODUCT INTEGRITY

Carefully inspect the package before opening. It is not recommended that you use the product after its expiration date.

If the integrity of the package has been compromised prior to the product expiration date, place the contents in a gas-permeable bag and resterilize it with ethylene oxide as described below.

CAUTION: Use ethylene oxide only.

The process should not exceed temperatures of 55° C (125° F). Allow proper aeration of ethylene oxide residues prior to implantation. Use some acceptable method to determine sterilizer effectiveness, such as a biological indicator.

Due to the variability between sterilizers, precise sterilization instructions cannot be provided. Contact your sterilizer manufacturer for more information regarding sterilization procedures.

SUGGESTED IMPLANTATION PROCEDURE

General Instructions

The implantation procedure generally includes using a stylet guide, stylets, and vein lifter; selecting an insertion site; positioning the lead; taking electrical and defibrillation efficacy measurements; anchoring the lead; and connecting the lead to the pulse generator.

Some implantation techniques vary according to physician preference and the patient's anatomy or physical condition. The techniques for selecting an insertion site, using a stylet guide or a stylet, positioning a lead, and anchoring a lead,

described below suggest one or two possible versions, while more may exist.

Opening the Package

While lifting the lead out of the package, make sure that the anchoring sleeve does not slide off the distal end of the lead.

Using the Stylet Guide and Stylets

The lead is packaged with the stylet guide attached to the connector pin and a stylet already inserted. If the stylet guide has been removed, replace it by gently pushing it as far as possible onto the connector pin (Figure 1).

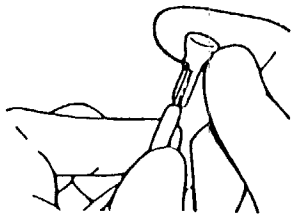


Figure 1. Stylet guide attachment.

A stylet provides additional stiffness and controlled flexibility for maneuvering the lead into position. Stylets vary in stiffness for different lead and stylet flexibility. Each stylet knob is etched with the stylet diameter and length.

If a stylet is not already in the lead, insert a stylet through the stylet guide and into the lead body. If a slight curve is needed for the stylet, refer to instructions in the section titled "Positioning a Lead in the Coronary Sinus or Superior Vena Cava."

CAUTION: To avoid damage to the lead or body tissue, do not use excessive force or surgical instruments to insert a stylet into the lead. When handling a stylet, avoid overbending, kinking, or blood contact.

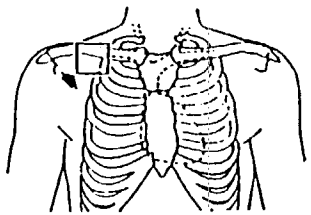
CAUTION: Repeated insertions of a stylet increase the chance that blood may accumulate on it, which may cause difficulty in passing the stylet through the lead and may cause damage to the lead.

Selecting an Insertion Site

The lead may be inserted by venotomy through several different venous routes, including the right or left cephalic vein or the external or internal jugular vein. In general, a left venous entry site will aid in maneuvering the lead into the coronary sinus orifice.

CAUTION: If insertion is done via a subclavian approach, the lead should be positined far laterally to avoid clamping the lead body between the clavicle and the first rib. Clamping the lead may eventually cause the conductor to fracture, may cause damage to the insulation, or may cause other damage to the lead. This may result in complications such as loss of detection, loss of pacing therapies, or loss of cardioversion./defibrillation therapy. Certain anatomical abnormalities, such as thoracic outlet syndrome, may also precipitate pinching andf subsequent fracture of the lead. If significant resistance is encountered during a subclavian stick implant procedure, do not force the lead by adjusting patient's posture (i.e., raising the arm or putting a towel behind the person's back) to facilitate the passage of the lead. In such cases it is recommended that an alternate venous entry site be used.

Use fluoroscopy to facilitate accurate lead placement.



Using a Vein Lifter

A vein lifter facilitates lead introduction. Insert its tapered end into the incised vein and gently push the lead tip underneath and into the vein (Figure 2). During insertion of the lead into the vein, make sure the anchoring sleeve does not slide off the distal end of the lead.

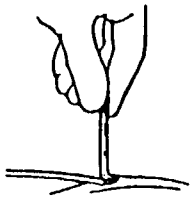


Figure 2. Using the vein lifter.

CAUTION: Avoid placing the lead under extreme tension or angulation to prevent lead dislodgement and possible lead fracture. **Do not grip the lead with surgical instruments.**

Positioning a Lead in the Coronary Sinus or Superior Vena Cava

For added control in maneuvering the lead tip, the distal end of the lead may be slightly curved by inserting a gently curved stylet as shown in Figure 3. A possible angle of curvature is illustrated in Figures 4 and 5.

CAUTION: To avoid damage to the stylet, do not use a sharp object to impart a curve to the distal end (Figure 3).

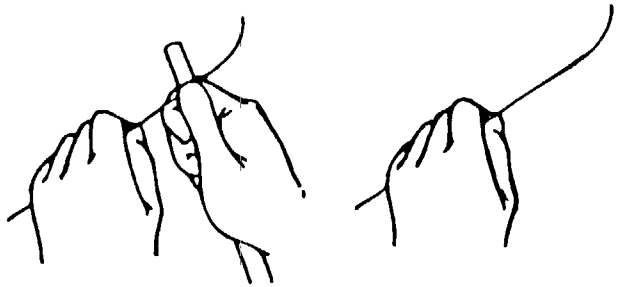


Figure 3. Imparting a curve to the stylet.

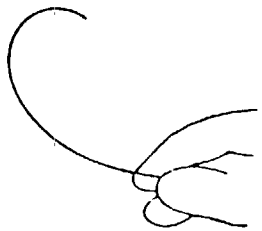


Figure 4. Bend the stylet into a gentle spiral. This gives the lead a gentle curve upward, to the left, and posterior.

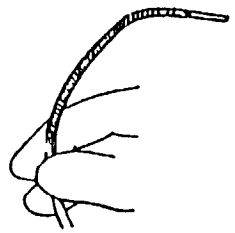


Figure 5. The curve in the stylet is designed to facilitat passage of the lead across the superior surface of the tricuspid valve. The second bend helps to position the lead to the left and posterior toward the coronary sinus ostium.

The electrode may be placed in either the coronary sinus or the superior vena cava using either the venotomy method or the percutaneous lead introducer method.

If placing the electrode in the coronary sinus, advance the lead into the right atrium and rotate the curved stylet to manipulate the tip over the tricuspid valve. Move the tip medially and posteriorly to the coronary sinus ostium and advance the lead into the coronary sinus. Continue advancing the lead through the coronary sinus as far as desired.

Do not advance the TRANSVENE™-SVC electrode to the apex as this would not allow sufficient distance between it and other defibrillation electrodes.

If the lead goes through the tricuspid valve opening, retract the lead with a gentle posterior rotation and then advance it toward the coronary sinus ostium.

If the electrode is to be placed in the superior vena cava, advance the tip such that the distal portion of the electrode is approximately 3 to 5 cm proximal to the superior vena cava—right atrial junction.

The electrode for the TRANSVENE™-SVC must be as far as possible from other defibrillation electrodes. Also, the cardiac mass between the electrodes should be as large as possible. Insufficient separation between the electrodes may result in reduced defibrillation efficacy.

Accurate positioning of the electrode is essential for defibrillation efficacy. Use fluoroscopy (P-A and lateral position) to ensure that the distal end of the electrode is properly positioned in the superior vena cava or is lodged in the coronary sinus with the proximal end of the electrode advanced beyond the coronary sinus ostium.

The patient should have x-rays taken every six months to verify the integrity of the PCD™ system.

Taking Electrical and Defibrillation Efficacy Measurements

Refer to the clinical protocol for recommended procedures and values.

Anchoring the Lead

Use the anchoring sleeve to secure the lead from moving and to protect the lead insulation and conductor coil from damage caused by tight ligatures.

Anchor the lead with nonabsorbable sutures.

The TRANSVENE™-SVC uses the triple groove anchoring sleeve illustrated in Figure 6.

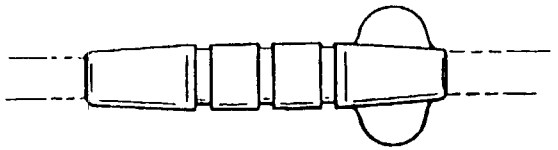


Figure 6. The triple groove anchoring sleeve.

With a triple groove anchoring sleeve, generally two or three of the grooves may be used with the following procedure (Figure 7 or 8).

The triple groove anchoring sleeve is already situated on the lead. Partially insert the anchoring sleeve into the vein.

Use the most distal suture groove to secure the anchoring sleeve to the vein.

Use the middle groove to secure the anchoring sleeve to the fascia and lead. First, create a base by looping a suture through the fascia underneath the middle groove and tying a knot. Continue by firmly wrapping the suture around the middle groove and tying a second knot.

Use the third and most proximal groove to secure the anchoring sleeve to the lead body.

Alternatively, only two of the three grooves on the anchoring sleeve may be used to tie down the lead. In that case, follow the anchoring procedure for the distal and middle groove (Figure 8).

CAUTION: Do not use the anchoring sleeve tabs for suturing.

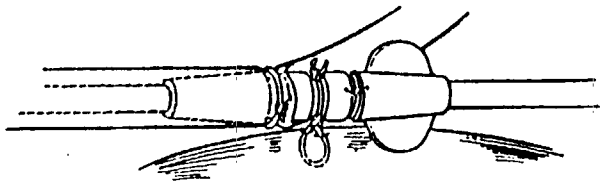


Figure 7. Triple groove anchoring sleeve secured to the lead and fascia using three grooves.

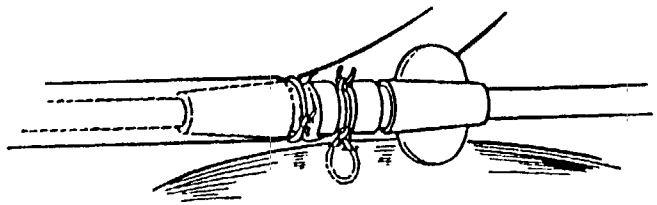


Figure 8. Triple groove anchoring sleeve secured to the lead and fascia using two grooves.

Tie the sutures securely but gently to prevent damage to the anchoring sleeve.

CAUTION: Do not secure the ligatures so tightly that they damage the vein or lead. **Do not tie a ligature directly to the lead body** (Figure 9). During anchoring, take care to avoid dislodging the lead tip.

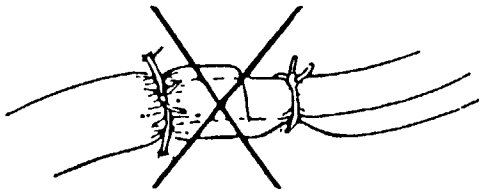


Figure 9. Do NOT secure the sutures too tightly and do NOT tie a suture to the lead body.

Connecting the Lead to a Tachyarrhythmia Device

Before tunneling the lead connector, record each lead's serial number along with the function of the lead. Tunnel the lead subcutaneously to the pulse generator pocket. A tunneling tool may be used to pull all the leads through to the pocket area. Refer to Figures 10a and 10b for instructions and illustrations showing lead connections to the Medtronic® PCD™ Tachyarrhythmia Control Device Model 7217B.

Insert the lead connector into the connector block. Refer to the tachyarrhythmia control device technical manual for the use of setscrews and setscrew tools.

Before closing the pocket, verify sensing, pacing, and defibrillation efficacy.

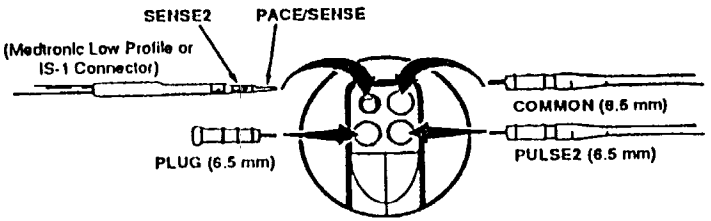
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillating Electrodes	Endocardial Two-Electrode System Connection Diagram
Medtronic® Model 7217B PCD™ Device	2	**PACE/SENSE, SENSE2** Insert the Pace/Sense lead connector of the TRANSVENE™-RV into the PACE/SENSE, SENSE2 port. **COMMON** Insert the unipolar lead connector of the TRANSVENE™-RV, -SVC, or -SQ into the COMMON port.  **PULSE1** Insert the connector plug packaged with the pulse generator into the PULSE1 port. **PULSE2** Insert the lead connector of either the TRANSVENE™-RV, -SVC, or -SQ lead into the PULSE2 port.

Figure 10a. Connections for endocardial and subcutaneous leads (single pulse) into the Medtronic® PCD™ Tachyarrhythmia Control Device Model 7217B or 7217IB.

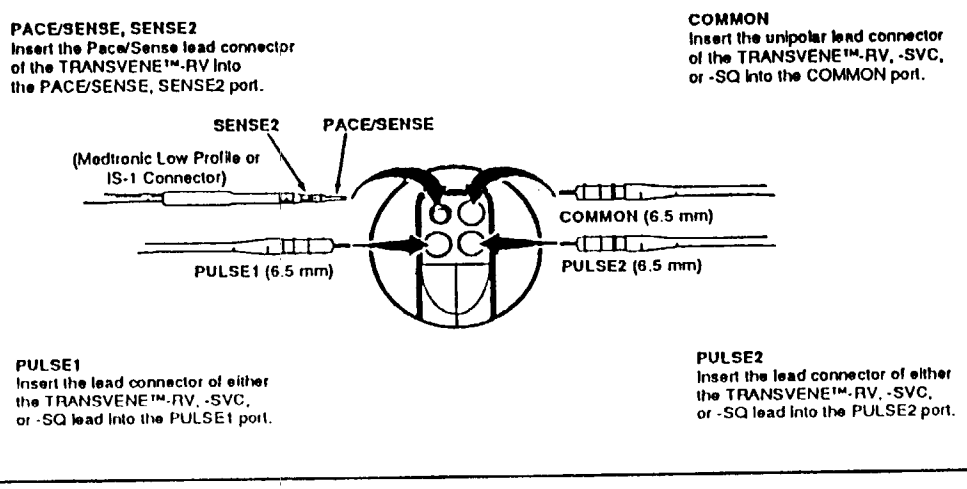
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillating Electrodes	Endocardial Three-Electrode System Connection Diagram
Medtronic® Model 7217B PCD™ Device	3	

Figure 10b. Connections for endocardial and subcutaneous leads (simultaneous or sequential pulse) into the Medtronic® PCD™ Tachyarrhythmia Control Device Model 7217B or 7217IB.

CAUTION: Always remove the stylet before connecting the lead to the pulse generator. Failure to remove the stylet may result in lead failure.

CAUTION: To prevent undesirable twisting of the lead body, wrap the excess lead length loosely under the pulse generator and place both into the subcutaneous pocket (Figure 11). Ensure that the leads and adaptor do not leave the pulse generator at an acute angle. Sharp angles place undue stress on the lead conductor and insulation.

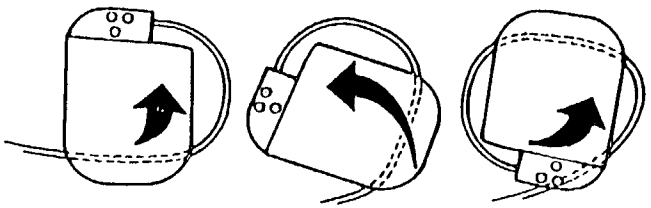


Figure 11. While rotating the pulse generator, loosely wrap the excess lead length and place it under the pulse generator.

CAUTION: When placing the pulse generator and leads into the subcutaneous pocket:

- Do NOT coil the lead. Coiling the lead can twist the lead body and may result in lead dislodgement (Figure 12).
- Do NOT grip the lead or pulse generator with surgical instruments.

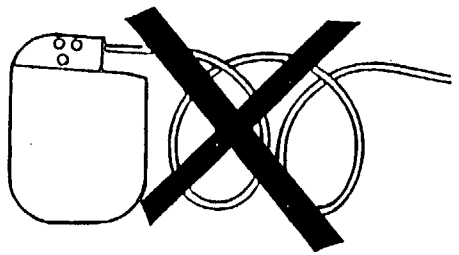


Figure 12. Do not coil the lead body.

After implantation, monitor the patient's electrocardiogram continuously. If a lead dislodges, it usually occurs during the immediate postoperative period.

SPECIFICATIONS (Nominal)

PARAMETER	MODEL 6963
Polarity	Unipolar
Chamber	Coronary Sinus/Superior Vena Cava
Fixation	None. Tip Lodges in the Coronary Sinus or is placed in the Superior Vena Cava
Length	Lead: 110 cm Electrode: 5.0 cm
Connector	6.5 mm
Material	Conductor Coil: MP35N Alloy Insulator: Silicone Electrode: Platinum Alloy Coil

PARAMETER	MODEL 6963
Electrode Surface Area	90 mm2
Diameter	Body: 1.7 mm Electrode Tip: 2.3 mm
Lead Introducer (recommended size)	8.0 French
Configuration	Electrode: Coiled, 48 turns per inch Conductor: Multifilar
Unipolar Resistance	3.3 ohms (110 cm)

GENERAL WARNING

Medtronic® implantable leads are implanted in the extremely hostile environment of the human body. Leads are necessarily very small in diameter and must still be very flexible, which unavoidably reduces their potential performance or longevity. Leads may fail to function for a variety of causes, including, but not limited to: medical complications, body rejection phenomena, allergic reaction, fibrotic tissue, or failure of leads by breakage or by breach of their insulation covering. In addition, despite the exercise of all due care in design, component selection, manufacture, and testing prior to sale, leads may be easily damaged before, during, or after insertion by improper handling or other intervening acts. Consequently, no representation or warranty is made that failure or cessation of function of leads will not occur or that the body will not react adversely to the implantation of leads or that medical complications (including perforation of the heart) will not follow the implantation of leads or that the lead will, in all cases, restore adequate cardiac function.

For complete warranty information, see the accompanying card enclosed in the package.

MEDTRONIC® DEFIBRILLATION LEAD DISCLAIMER OF WARRANTIES

THIS MEDTRONIC® TRANSVENE™-SVC MODEL 6963 PERMANENT IMPLANTABLE DEFIBRILLATION LEAD (THE "LEAD") HAS BEEN MANUFACTURED UNDER CAREFULLY CONTROLLED CONDITIONS TO ASSURE ITS QUALITY AND RELIABILITY. HOWEVER, BECAUSE MEDTRONIC HAS NO CONTROL OVER CONDITIONS UNDER WHICH THE LEAD IS USED, MEDTRONIC PROVIDES THE FOLLOWING DISCLAIMER:

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EUROPE
Medtronic Europe
Immeuble Myron
6, avenue E. van Nieuwenhuyse
B-1160, Brussels
Belgium
Telephone: (32) 2-676 08 11

ASIA–PACIFIC
Japan
Medtronic Asia-Pacific
Shuwa Kioi-cho Park Bldg, 5F
3-6, Kioi-cho, Chiyoda-ku
Tokyo 102
Japan
Telephone: (81) 3-3230-2919

Australia
Medtronic Australasia Pty. Ltd.
22 Clarke Street
Crows Nest, Sydney, N.S.W., 2065
Australia
Telephone: (61) 2-437-6066

Asia
Medtronic International Ltd.
2002 CC Wu Building
308 Hennessey Road, Wanchai
Hong Kong, B.C.C.
Telephone: (852-5) 891-4068

LATIN AMERICA
Medtronic, Inc.
450 Fairway Drive
Suite 103
Deerfield Beach, FL 33441
U.S.A.
Telephone: (305) 428-8556

NORTH AMERICA
Canada
Medtronic of Canada, Ltd.
6733 Kitimat Road
Mississauga, Ontario L5N 1W3
Canada
Telephone: (416) 826-6020
Toll-free: 1-800-268-5346
(24-hour consultation service)

United States
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432
U.S.A.
Telephone: (612) 574-4000
Toll-free: 1-800-328-2518
(24-hour consultation service)

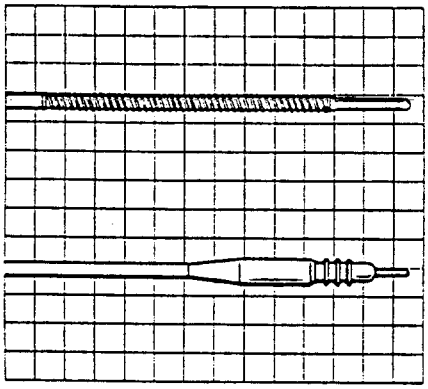
Medtronic

March 1992
UC9002088aEN 195421-002

Medtronic

TRANSVENE™-SVC 6963

Unipolar Connector (6.5 mm)/Connecteur Unipolaire (6,5 mm)/Unipolarer Konnektor (6,5 mm)/Conector Monopolar (6,5 mm)/Connettore Monopolare (6,5 mm)



Serial Number	Use Before
Numéro de Série	Utiliser Avant
Seriennummer	Zu Implantieren vor dem
Número de Serie	Fecha de Caducidad
Numero di Serie	Data di Scadenza

Sterile Lot Number	Sterilization Date
Lot de Stérilisation No.	Date de Stérilisation
Sterilisationsnummer	Sterilisationsdatum
Lote Estéril Número	Fecha de Esterilización
Numero di Lotto Sterile	Data di Sterilizzazione

Lead Length:
Longueur de la Sonde:
Länge der Elektrode:
Longitud del Electrodo:
Lunghezza dell'Elettrocatetere:

Sterilization Validity Period:	4 Years
Durée de Validité de Stérilisation:	4 Ans
Wirksamkeit der Sterilisation:	4 Jahre
Periodo de Validez de la Esterilización:	4 Años
Periodo di Validità della Sterilizzazione:	4 Anni

Contents: One lead with silicone insulation, accessories and product literature
Contenu: Une sonde avec isolant en silicone, accesoires et documentation relative au produit
Inhalt: Eine Elektrode mit Silikonisolation, Zubehör und Produktbeschreibung
Contenido: Un electrodo con aislante de Silicona, Accesorios y literatura del producto
Contenuto: Un elettrocatetere con isolante in silicone, accesson e letteratura del prodotto

CAUTION: Federal Law (U.S.A.) restricts this device to sale by or on the order of a physician.
ATTENTION: La réglementation américaine (FDA) n'autorise la vente de ce produit que sur prescription médicale.
ACHTUNG: Ein US-Bundesgesetz schränkt den Verkauf dieses Produkts an Ärzte oder auf Anordnung durch einen Arzt ein.
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ATTENZIONE: La legge Federale (U.S.A.) limita la vendita di questo prodotto esclusivamente ai medici o su richiesta d'un medico.

The contents (STERILE) of the inner package have been sterilized by ethylene oxide gas.
Le contenu (STERILE) du paquet interne a été stérilisé au gaz d'oxyde d'éthylène.
Der Inhalt (STERIL) der inneren Verpackung ist in Äthylenoxydgas sterilisiert.
El contenido (ESTERILE) del paquete interior ha sido esterilizado con gas óxido de etileno.
Il contenuto (STERILE) della confezione interna è stato sottoposto a sterilizzazione con gas ossido di etilene.

STORAGE: Store below 40° C/104° F
STOCKAGE: Au-dessous de 40° C/104° F
LAGERUNG: Unter 40° C/104° F
ALMACENAMIENTO: Por debajo de 40° C/104° F
IMMAGAZZINAGGIO: Al di sottodi 40° C/104° F

Shelf Box Label for Model 6963 Lead

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TRANSVENE™-SVC 6963

Unipolar Connector (6.5 mm)/Connecteur Unipolaire (6,5 mm)/Unipolarer Konnektor (6,5 mm)/Conector Monopolar (6,5 mm)/Connettore Monopolare (6,5 mm)

Serial Number Numéro de Séne Seriennummer Número de Serie Numero di Serie	Use Before Utiliser Avant Zu Implantieren vor dem Fecha de Caducidad Data di Scadenza
Sterile Lot Number Lot de Stérilisation No. Sterilisationsnummer Lote Estéril Número Numero di Lotto Sterile	Sterilization Date Date de Stérilisation Sterilisationsdatum Fecha de Esterilización Data di Sterilizzazione
Non Reusable Usage Unique Nicht wiederverwendbar Interior Desechable Non Riusabile	Lead Length: Longueur de la Sonde: Länge der Elektrode: Longitud del Electrodo: Lunghezza dell'Elettrocatetere:

Contents: One lead with silicone insulation and accessories
Contenu: Une sonde avec isolant en silicone et Accesoires
Inhalt: Eine Elektrode mit Silikonisolation und Zubehör
Contenido: Un electrodo con aislante de Silicona y Accesorios
Contenuto: Un elettrocatetere con isolante in silicone e accessori

Sterilization: Ethylene oxide gas
Stérilisation: Gaz d'oxyde d'éthylène
Sterilisation: Äthylenoxydgas
Esterilización: Gas óxido de etileno
Sterilizzazione: Gas ossido di etilene

CAUTION: Federal Law (U.S.A.) restricts this device to sale by or on the order of a physician.
ATTENTION: La règlementation américaine (FDA) n'autorise la vente de ce produit que sur prescription médicale.
ACHTUNG: Ein US-Bundesgesetz schränkt den Verkauf dieses Produkts an Ärzte oder auf Anordnung durch einen Arzt ein.
PRECAUCION: Las Leyes Federales (EE.UU) restringen la venta de este dispositivo únicamente a médicos o por prescripción médica.
ATTENZIONE: La legge Federale (U.S.A.) limita la vendita di questo prodotto esclusivamente ai medici o su richiesta d'un medico.

The contents of this package is **STERILE.**
Le contenu de ce paquet est **STERILE.**
Der Inhalt dieser Packung ist **STERIL.**
El contenido de este envoltorio está **ESTERIL.**
Il contenuto de questa confezione è **STERILE.**

If the package is damaged or opened see the Technical Manual for information.
Si l'emballage est endommagé ou ouvert voir le manuel technique pour information.
Im Falle einer beschädigten oder geöffneten Packung Gebrauchsanweisung beachten.
Si el paquete ha sido dañado o abierto, ver el Manual Técnico para información.
Se la confezione è danneggiata o aperta vedere il Manuale Tecnico per le informazione relative.

Sterile Pack Label for Model 6963 Lead

TECHNICAL MANUAL

The TRANSVENE™-SQ Unipolar, Subcutaneous, Oval Patch Lead for Cardioversion and Defibrillation

MODEL 6999

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DESCRIPTION AND INTENDED USE

The Medtronic® TRANSVENE™-SQ Model 6999 Unipolar, Subcutaneous, Oval Patch Lead is designed for the delivery of cardioversion and defibrillation therapies. It is intended for long-term use with an implantable tachyarrhythmia control device such as the Medtronic Model 7217B PCD™ device along with at least one complementary defibrillating lead and a pacing/sensing lead, such as the TRANSVENE™-RV Model 6999; a third defibrillating lead, such as the TRANSVENE™-SVC Model 6963, may also be used.

The lead features platinum alloy electrode coils and a low–resistance metal-alloy conductor coil. Helical coils partially embedded into the silicone patch act as the electrode for cardioversion and defibrillation pulses. The lead also has a 6.5 mm unipolar connector.

There are 3 nodes on one side of the patch, and 2 nodes at the junction of the lead body and patch electrode. These nodes are intended to mark the insulated side of the patch electrode.

The lead has application for patients in whom implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

CONTENTS OF PACKAGE

The leads are supplied sterile. Each package contains:

- 1 TRANSVENE™-SQ lead
- Product literature

CONTRAINDICATIONS

There are no known contraindications for this lead.

WARNINGS

Do not attempt to use this lead with a non-Medtronic Implantable Cardioverter/Defibrillator device. Use only battery-powered equipment during lead implantation and testing to protect against fibrillation that may be caused by alternating currents. Line-powered equipment used in the vicinity of the patient must be properly grounded. Lead connector pins must be insulated from any leakage currents that may arise from line-powered equipment.

See also the General Warnings section.

PRECAUTIONS

Necessary Hospital Equipment

External defibrillating equipment should be kept nearby for immediate use during the acute lead system testing, implantation procedure, and whenever arrthythmias are possible or intentionally induced during post-implant testing.

Inspecting the Package

Carefully inspect the package before opening. If the container, the package, or the lead appear to have been damaged, do not use the lead. Return the damaged lead to your Medtronic representative.

Handling the Lead

Leads should be handled with great care at all times. **Any severe bending, kinking, stretching, or handling with surgical instruments may cause permanent damage to the lead.**

Lead insulators attract small particles such as lint and dust. Therefore, to minimize contamination, protect the lead from materials shedding these substances. Handle the lead with sterile surgical gloves that have been rinsed in sterile water or equivalent.

Do not immerse leads in mineral oil, silicone oil, or any other liquid.

Positioning the Lead

Implant the lead electrode with the exposed coil side toward the heart. This can be verified by ensuring that the side of the patch with the nodes is facing away from the heart. If the insulation side is placed toward the heart, current from a tachyarrhythmia control device may not be adequate to treat a detected tachyarrhythmia. Place sutures through the outer 8 mm of the polyester mesh. Do not suture over the electrode coils, as sutures could fracture the coils. It is recommended that 4 sutures be used to secure each patch electrode.

See additional cautions in the section on Suggested Implantation Procedure.

Potential Complications

The potential complications related to the use of subcutaneous patch leads include, but are not limited to, the following patient-related conditions: serous fluid accumulation around

the patch; infection; and bleeding after placement, after repositioning, or if sutures tear out.

Other potential complications related to the lead and the programmed parameters of the tachyarrhythmia device include, but are not limited to, the following:

Complications	Possible Effects
Displacement, lead insulation or conductor fracture, poor connection to the tachyarrhythmia device	Intermittent or continuous loss of defibrillation or cardioversion therapy. *
Electrode Fracture	Intermittent or continuous loss of defibrillation or cardioversion therapy.*
Threshold Elevation	Loss of defibrillation or cardioversion therapy.*

* Loss of defibrillation or cardioversion therapy efficacy may occur due to lead displacement or fracture. Therefore, the patient's ECG should be monitored during the hospital stay. If such a loss occurs, check X rays for lead displacement or fracture.

ENSURING PRODUCT INTEGRITY

Carefully inspect the package before opening. It is not recommended that you use the product after its expiration date.

If the integrity of the package has been compromised prior to the product expiration date, place the contents in a gas-permeable package and resterilize it with ethylene oxide as described below.

CAUTION: Use ethylene oxide only.

The process should not exceed temperatures of 55° C (125° F). Allow proper aeration of ethylene oxide residues prior to implantation. Use some acceptable method to determine sterilizer effectiveness, such as a biological indicator.

Due to the variability between sterilizers, precise sterilization instructions cannot be provided. Contact your sterilizer manufacturer for more information regarding sterilization procedures.

POSITIONING A SUBCUTANEOUS PATCH LEAD

The recommended starting position for the TRANSVENE™-SQ subcutaneous patch lead is along the left chest near the left heart. The patch may be repositioned, if necessary, to meet the implant defibrillation efficacy criteria outlined in the following section. The subcutaneous patch may be placed subcutaneously, submuscularly, or directly on the periosteum of the ribs.

CAUTION: **The patch must be placed such that the nodes are facing away from the heart.**

TAKING ELECTRICAL AND DEFIBRILLATION EFFICACY MEASUREMENTS

In order to demonstrate reliable defibrillation efficacy, it is recommended that ventricular fibrillation be initiated and successfully terminated three out of four times at a stored ouput energy of 18 joules or less.

Recommended Pacing/Sensing Measurements at Implant
(when using a pacing system analyzer)

Measurements Required	Acute Lead System	Chronic Lead System
Capture threshold	≤ 1.5 V - epicardial	≤ 3.0 V
(at 0.5 ms pulse width)	≤ 1.0 V - endocardial	≤ 3.0 V
Impedance	200 - 800 ohms	200 - 800 ohms
Filtered R-wave amplitude	≥ 5 mV (during sinus rhythm)	≥ 3 mV (during sinus rhythm)
Slew rate	≥ 0.75 V/s	≥ 0.45 V/s

Initial electrical measurements may deviate from the recommendations because of acute cellular trauma. If this occurs, wait five to fifteen minutes and repeat the testing procedure. Values may vary depending upon lead type, pulse generator settings, cardiac tissue condition, and drug interactions. If electrical measurements do not stabilize to acceptable levels, it may be necessary to reposition the lead and repeat the testing procedure.

For more information on obtaining electrical measurements, consult the technical manual supplied with the testing device.

CONNECTING THE LEAD TO A TACHYARRHYTHMIA CONTROL DEVICE

Before tunneling the lead connector, record each lead's serial number along with the function of the lead. Tunnel the lead connector subcutaneously to the pulse generator pocket. A tunneling tool may be used to pull all the leads through to the pocket area. Use of a chest tube is suggested in tunneling the lead connector to the pulse generator to prevent damage to the lead.

Refer to Figures 1a and 1b for instructions and illustrations showing lead connections to the Medtronic® PCD™ Tachyarrhythmia Control Device Model 7217B.

Insert the lead connector into the connector block. Refer to the tachyarrhythmia control device technical manual for the use of set screws and wrenches.

Before closing the pocket, verify sensing, pacing, and defibrillation efficacy.

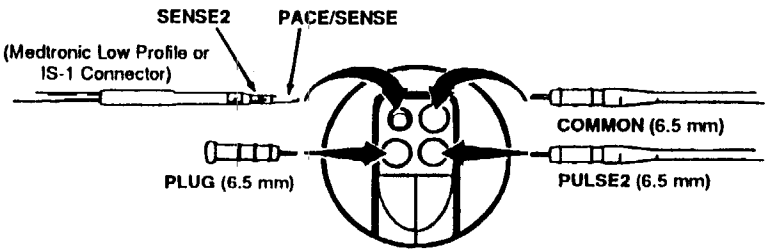
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillating Electrodes	Endocardial Two-Electrode System Connection Diagram
Medtronic® Model 7217B PCD™ Device	2	**PACE/SENSE, SENSE2** Insert the Pace/Sense lead connector of the TRANSVENE™-RV into the PACE/SENSE, SENSE2 port. **COMMON** Insert the unipolar lead connector of the TRANSVENE™-RV, -SVC, or -SQ into the COMMON port.  **PULSE1** Insert the connector plug packaged with the pulse generator into the PULSE1 port. **PULSE2** Insert the lead connector of either the TRANSVENE™-RV, -SVC, or -SQ lead into the PULSE2 port.

Figure 1a. Connections for endocardial and subcutaneous leads (single pulse) into the Medtronic® PCD™ Tachyarrhythmia Control Device Model 7217B.

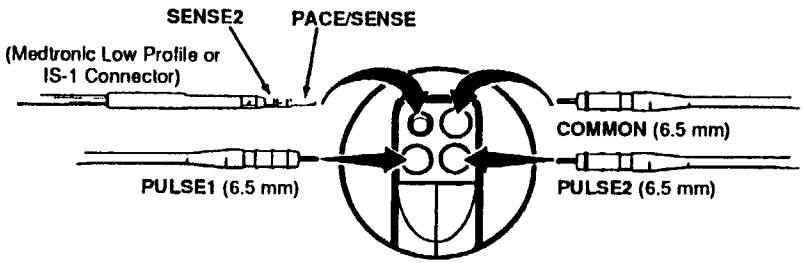
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillating Electrodes	Endocardial Three-Electrode System Connection Diagram
Medtronic® Model 7217B PCD™ Device	3	**PACE/SENSE, SENSE2** Insert the Pace/Sense lead connector of the TRANSVENE™-RV into the PACE/SENSE, SENSE2 port. **COMMON** Insert the unipolar lead connector of the TRANSVENE™-RV, -SVC, or -SQ into the COMMON port.  **PULSE1** Insert the lead connector of either the TRANSVENE™-RV, -SVC, or -SQ lead into the PULSE1 port. **PULSE2** Insert the lead connector of either the TRANSVENE™-RV, -SVC, or -SQ lead into the PULSE2 port.

Figure 1b. Connections for endocardial and subcutaneous leads (simultaneous or sequential pulse) into the Medtronic® PCD™ Tachyarrhythmia Control Device Model 7217B.

CAUTION: To prevent undesirable twisting of the lead body, wrap the excess lead length loosely under the pulse generator and place both into the subcutaneous pocket (Figure 2). Ensure that the leads do not leave the pulse generator at an acute angle. Sharp angles place undue stress on the lead conductor and insulation.

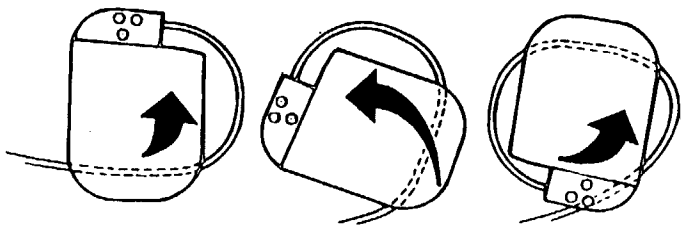


Figure 2. While rotating the pulse generator, loosely wrap the excess lead length and place it under the pulse generator.

CAUTION: When placing the pulse generator and leads into the subcutaneous pocket:

Do NOT coil the lead. Coiling the lead can twist the lead body and may result in lead dislodgement (Figure 3).

Do NOT grip the lead or pulse generator with surgical instruments.

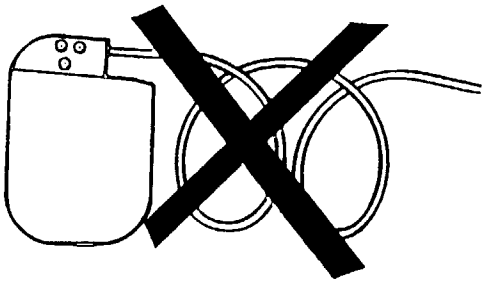


Figure 3. Do not coil the lead body.

After implantation, monitor the patient's electrocardiogram continuously. If a lead dislodges, it usually occurs during the immediate postoperative period.

SPECIFICATIONS (Nominal)

PARAMETER	MODEL 6999
Polarity	Unipolar
Fixation	Sutures (may be placed through the outer 8 mm of the patch body)
Lead Body Length	50 cm
Connector	6.5 mm
Material	Conductor Coil: Multifilar MP35N Alloy Insulator: Silicone Rubber Electrode: Platinum Alloy Coil

PARAMETER	MODEL 6999
Lead Body Diameter	2.5 mm
Patch Dimensions	6.1 cm x 9.1 cm
Number of Electrode Coils	4
Silicone Patch Area	50.1 cm2
Area Enclosed by Outermost Coil	40.0 cm2
DC Resistance	1.2 ohms

GENERAL WARNING

Medtronic® implantable leads are implanted in the extremely hostile environment of the human body. Leads are necessarily very small in diameter and must still be very flexible, which unavoidably reduces their potential performance or longevity. Leads may fail to function for a variety of causes, including, but not limited to: medical complications, body rejection phenomena, allergic reaction, fibrotic tissue, or failure of leads by breakage or by breach of their insulation covering. In addition, despite the exercise of all due care in design, component selection, manufacture, and testing prior to sale, leads may be easily damaged before, during, or after insertion by improper handling or other intervening acts. Consequently, no representation or warranty is made that failure or cessation of function of leads will not occur or that the body will not react adversely to the implantation of leads or that medical complications will not follow the implantation of leads or that the lead will, in all cases, restore adequate cardiac function.

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EUROPE
Medtronic Europe
Immeuble Myron
6, avenue E. van Nieuwenhuyse
B-1160, Brussels
Belgium
Telephone: (32) 2-676 08 11

ASIA–PACIFIC
Japan
Medtronic Asia-Pacific
Shuwa Kioi-cho Park Bldg, 5F
3-6, Kioi-cho, Chiyoda-ku
Tokyo 102
Japan
Telephone: (81) 3-3230-2919

Australia
Medtronic Australasia Pty. Ltd.
22 Clarke Street
Crows Nest, Sydney, N.S.W., 2065
Australia
Telephone: (61) 2-437-6066

Asia
Medtronic International Ltd.
2002 CC Wu Building
308 Hennessey Road, Wanchai
Hong Kong, B.C.C.
Telephone: (852-5) 891-4068

LATIN AMERICA
Medtronic, Inc.
450 Fairway Drive
Suite 103
Deerfield Beach, FL 33441
U.S.A.
Telephone: (305) 428-8556

NORTH AMERICA
Canada
Medtronic of Canada, Ltd.
6733 Kitimat Road
Mississauga, Ontario L5N 1W3
Canada
Telephone: (416) 826-6020
Toll-free: 1-800-268-5346
(24-hour consultation service)

United States
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432
U.S.A.
Telephone: (612) 574-4000
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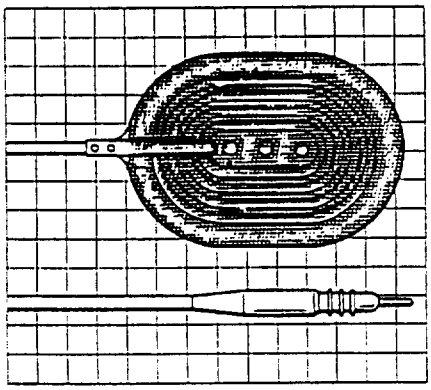
Medtronic

TRANSVENE™-SQ 6999

Unipolar Connector (6.5 mm)/Connecteur Unipolaire (6,5 mm)/Unipolarer Konnektor (6,5 mm)/Conector Monopolar (6,5 mm)/Connettore Monopolare (6,5 mm)



Serial Number	Use Before
Numéro de Série	Utiliser Avant
Seriennummer	Zu Implantieren vor dem
Número de Serie	Fecha de Caducidad
Numero di Serie	Data di Scadenza

Sterile Lot Number	Sterilization Date
Lot de Stérilisation No.	Date de Stérilisation
Sterilisationsnummer	Sterilisationsdatum
Lote Estéril Número	Fecha de Esterilización
Numero di Lotto Sterile	Data di Sterilizzazione

Lead Length:
Longueur de la Sonde:
Länge der Elektrode:
Longitud del Electrodo:
Lunghezza dell'Elettrocatetere:

Sterilization Validity Period:	4 Years
Durée de Validité de Stérilisation:	4 Ans
Wirksamkeit der Sterilisation:	4 Jahre
Periodo de Validez de la Esterilización:	4 Años
Periodo di Validità della Sterilizzazione:	4 Anni

Contents: One lead with Silicone Insulation and Product Literature.
Contenu: Une Sonde avec Isolant en Silicone et Documentation Relative au Produit.
Inhalt: Eine Elektrode mit Silikonisolation und Produktbeschreibung.
Contenido: Un Electrodo con Aislante de silicona y Literatura del Producto.
Contenuto: Un Elettrocatetere con Isolante in Silicone e Letteratura del Prodotto.

CAUTION: Federal Law (U.S.A.) restricts this device to sale by or on the order of a physician.
ATTENTION: La règlementation américaine (FDA) n'autorise la vente de ce produit que sur prescription médicale.
ACHTUNG: Ein US-Bundesgesetz schränkt den Verkauf dieses Produkts an Ärzte oder auf Anordnung durch einen Arzt ein.
PRECAUCION: Las Leyes Federales (EE.UU) restringen la venta de este dispositivo únicamente a médicos o por prescripción médica.
ATTENZIONE: La legge Federale (U.S.A.) limita la vendita di questo prodotto esclusivamente ai medici o su richiesta d'un medico.

The contents (STERILE) of the inner package have been sterilized by ethylene oxide gas.
Le contenu (STERILE) du paquet interne a été stérilisé au gaz d'oxyde d'éthylène.
Der Inhalt (STERIL) der inneren Verpackung ist in Äthylenoxydgas sterilisiert.
El contenido (ESTERILE) del paquete interior ha sido esterilizado con gas óxido de etileno.
Il contenuto (STERILE) della confezione interna è stato sottoposto a sterilizzazione con gas ossido di etilene.

STORAGE: Store below 40° C/104° F
STOCKAGE: Au-dessous de 40° C/104° F
LAGERUNG: Unter 40° C/104° F
ALMACENAMIENTO: Por debajo de 40° C/104° F
IMMAGAZZINAGGIO: Al di sottodi 40° C/104° F

Shelf Box Label for Model 6999 Lead

37

Medtronic

TRANSVENE™-SQ 6999

Unipolar Connector (6.5 mm)/Connecteur Unipolaire (6,5 mm)/Unipolarer Konnektor (6,5 mm)/Conector Monopolar (6,5 mm)/Connettore Monopolare (6,5 mm)

Serial Number Numéro de Série Seriennummer Número de Serie Numero di Sene	Use Before Utiliser Avant Zu Implantieren vor dem Fecha de Caducidad Data di Scadenza
Sterile Lot Number Lot de Stérilisation No. Sterilisationsnummer Lote Estéril Número Numero di Lotto Sterile	Sterilization Date Date de Stérilisation Sterilisationsdatum Fecha de Esterilización Data di Sterilizzazione
Non Reusable Usage Unique Nicht wiederverwendbar Interior Desechable Non Riusabile	Lead Length: Longueur de la Sonde: Länge der Elektrode: Longitud del Electrodo: Lunghezza dell'Elettrocatetere:

Contents: One lead with silicone insulation.
Contenu: Une Sonde avec isolant en silicone.
Inhalt: Eine Elektrode mit Silikonisolation.
Contenido: Un Electrodo con aislante de Silicona.
Contenuto: Un Elettrocatetere con isolante in silicone.

Sterilization: Ethylene oxide gas
Stérilisation: Gaz d'oxyde d'éthylène
Sterilisation: Äthylenoxydgas
Esterilización: Gas óxido de etileno
Sterilizzazione: Gas ossido di etilene

CAUTION: Federal Law (U.S.A.) restricts this device to sale by or on the order of a physician.
ATTENTION: La réglementation américaine (FDA) n'autorise la vente de ce produit que sur prescription médicale.
ACHTUNG: Ein US-Bundesgesetz schränkt den Verkauf dieses Produkts an Ärzte oder auf Anordnung durch einen Arzt ein.
PRECAUCION: Las Leyes Federales (EE.UU) restringen la venta de este dispositivo únicamente a médicos o por prescripción médica.
ATTENZIONE: La legge Federale (U.S.A.) limita la vendita di questo prodotto esclusivamente ai medici o su richiesta d'un medico.

The contents of this package is **STERILE.**
Le contenu de ce paquet est **STERILE.**
Der Inhalt dieser Packung ist **STERIL.**
El contenido de este envoltorio está **ESTERIL.**
Il contenuto de questa confezione è **STERILE.**

If the package is damaged or opened see the Technical Manual for information.
Si l'emballage est endommagé ou ouvert voir le manuel technique pour information.
Im Falle einer beschädigten oder geöffneten Packung Gebrauchsanweisung beachten.
Si el paquete ha sido dañado o abierto, ver el Manual Técnico para información.
Se la confezione è danneggiata o aperta vedere il Manuale Tecnico per le informazione relative.

Sterile Pack Label for Model 6999 Lead

AA
PEDB
DCRND

P J015/S000

5-Nov-1992

fax

FROM:	LETTER DATE	LOGIN DATE	DUE DATE
MEDTRONIC INC. ATTN: JENNIFER M. MARRONE 7000 CENTRAL AVENUE, N.E. MINNEAPOLIS,, MN 554323576	11/04/92	11/05/92	/ /
	DOCUMENT: PMA	CONTROL # P920015/S000 AMENDMENT	

SUBJECT:
MEDTRONIC(R) TRANSVENE LEAD SYSTEM

	OFFICE	DATE REFERRED
3 COPIES OF VOLUME 1	~~OK~~ H	11/5/92
____ COPIES OF VOLUME ____	DCRND	11/13/92
____ COPIES OF VOLUME ____		
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____ COPIES OF VOLUME ____		

Medtronic

Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576
Telephone: (612) 574-4000
Cable: Medtronic Telex: 29-0598
FAX: (612) 574-4879

P920015/AC2V1

November 4, 1992

Office of Device Evaluation
PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

Re: Amendment to Premarket Approval Application for the Medtronic® Multiprogrammable Tachyarrhytmia Control System with Non-thoracotomy Cardioversion and Defibrillation Electrodes. i.e., the PCD™ Transvene System, Lead Models 6963, 6966 and 6999 (Document Control Number P920015)

The purpose of this letter is to clarify the intent of the amendment to the PMA application for the Medtronic Transvene Lead System submitted on October 26, 1992.

The cover letter to that submission stated the purpose was to obtain approval to manufacture the Model 6963 CS/SVC and the Model 6999 SQ leads at the Rice Creek facility. These leads are currently manufactured at the Kerkrade facility for which approval was requested in the PMA. If approved, Medtronic intends to manufacture the 6963 and 6999 at both the Rice Creek and Kerkrade facilities.

Should additional information be required, please contact the undersigned.

Sincerely,

MEDTRONIC, INC.

C. Whitacre

Chip Whitacre
Product Regulation Manager
Cardiac Pacing Business
(612) 574-8556
(612) 574-6424 FAX

RECEIVED
NOV 10 4 1
FDA/CDRH/ODE/DMC

2

DCRND

P9 015/S000 9-Jul-1993

MPC

FROM:	LETTER DATE	LOGIN DATE	DUE DATE
MEDTRONIC INC. ATTN: JENNIFER M. MARRONE 7000 CENTRAL AVENUE, N.E. MINNEAPOLIS,, MN 554323576	07/08/93	07/09/93	/ /
	DOCUMENT: PMA	CONTROL # P920015/S000 AMENDMENT	

SUBJECT:
MEDTRONIC(R) TRANSVENE LEAD SYSTEM

	OFFICE	DATE REFERRED
23 COPIES OF VOLUME 1	~~CK~~	7/9/93
____ COPIES OF VOLUME ____	DCRND	7/12/93
____ COPIES OF VOLUME ____		
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Part 1 - Page 696

1

Medtronic

Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576
Telephone: (612) 574-4000
Cable: Medtronic Telex: 29-0598
FAX: (612) 574-4879

RECEIVED
JUL 93 10 4 9
FDA/CDRH/ODE/DHC

July 8, 1993

Office of Device Evaluation
PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

Acc'd

Re: Addendum to PMA Amendment to Transvene, P920015, Appendix I

The following additional information is provided as an Addendum to the June 11, 1993 PMA Amendment to the Transvene PMA application, P920015.

- Chronic pace/sense information of those patients (N = 113) that did not experience a spontaneous or induced episode after prehospital discharge, see Patients Followed For 6 Months or More; Device Experience.
- Spontaneous and induced episode information over time (at 3 month intervals), see Spontaneous and Induced Episodes.
- More detailed analysis of explanted leads (e.g., presented by each lead model), see Explanted Transvene Leads.
- Further detail on actuarial survival, see One Year Actuarial Survival.
- Lead dislodgment information specific to the total number of leads in the population, see Lead Dislodgments.
- Returned device information, patient 94244, see Returned Device, Patient 94244.
- Status of Medtronic [(b)(4)] lead reliability, see Medtronic [(b)(4)] Lead Reliability.

y

The existence of this PMA Amendment and the data and other information it contains are confidential, and the protection afforded to such confidential information by 18 USC 1905 and other applicable laws is hereby claimed.

Twenty copies of this PMA Amendment are provided. Should additional information be required by the Agency, please contact the undersigned.

Sincerely yours,

MEDTRONIC, INC.

Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
(612) 574-4688
(612) 574-6424 FAX

Attachment

Patients Followed For 6 Months or More; Device Experience

Of the patients followed for 6 months or more, 544 had an induced or spontaneous episode at the pre-hospital discharge or later (544/657 = 82.8%). Therefore, there were 113 patients that have not have a chronic episode. However, all of these patients had PACE/SENSE parameters tested at a chronic follow-up except for 1 patient (PACE/SENSE parameters are assessed at each follow-up as an assurance that the integrity of the lead system has not been compromised). This patient was last tested at the 3 month follow up (b)(4) (b)(4) pacing threshold and (b)(4) (b)(4) At the 6 month follow-up PACE/SENSE parameters were not performed and at the 12 month follow-up testing was not possible due to high intrinsic sinus rate.

Table 1 contains a distribution of the follow-up periods where the PACE/SENSE parameters were captured for these 113 patients.

Follow-up Period	Number of Patients
3 mo	1
6 mo	29
9 mo	25
12 mo	28
15 mo	11
18 mo	5
21 mo	4
24 mo	1
27 mo	3
other	6
Total	113

Table 1: Distribution of Follow-up periods where PACE/SENSE parameters were obtained for 113 patients

Table 2 contains the mean pacing threshold values for the 113 patients obtained at follow-up.

PCD Transvene System Mean Pacing Thresholds and EGM values Obtained at Last Known Follow-up for 113 patients					
Variable	# of Pts	Mean	Std Dev	Min	Max
(b)(4)	102	(b)(4)			
	6				
	113				

Table 2: Pacing Thresholds and EGM at last known follow-up for 113 patients

Spontaneous and Induced Episodes

Figure 1 shows the distribution over time of all spontaneous and induced episodes for **all 757** patients. What this figure presents is that by the 3 month follow-up, 59.5% of the patients have had either an induced or spontaneous episode, by the 6 month follow-up, 70.3% of the patients have had either a spontaneous or induced episode and by the 12 month follow-up, 78.9% have had a spontaneous or induced episode. This graph was also completed for those patients with 6 months or greater of follow-up (657) and is presented in Figure 2. This figure shows that by the 3 month follow-up, 60.7% of the patients have had either an induced or spontaneous episode, by the 6 month follow-up, 72.9% have had either a spontaneous or induced episode and by the 12 month follow-up 82.8% have had an induced or spontaneous episode.

Part 1 - Page 703

PCD TRANSVENE LEAD SYSTEM

DISTRIBUTION OF SPONTANEOUS AND INDUCED EPISODES

CUMULATIVE % OF PATIENTS WITH EPISODES

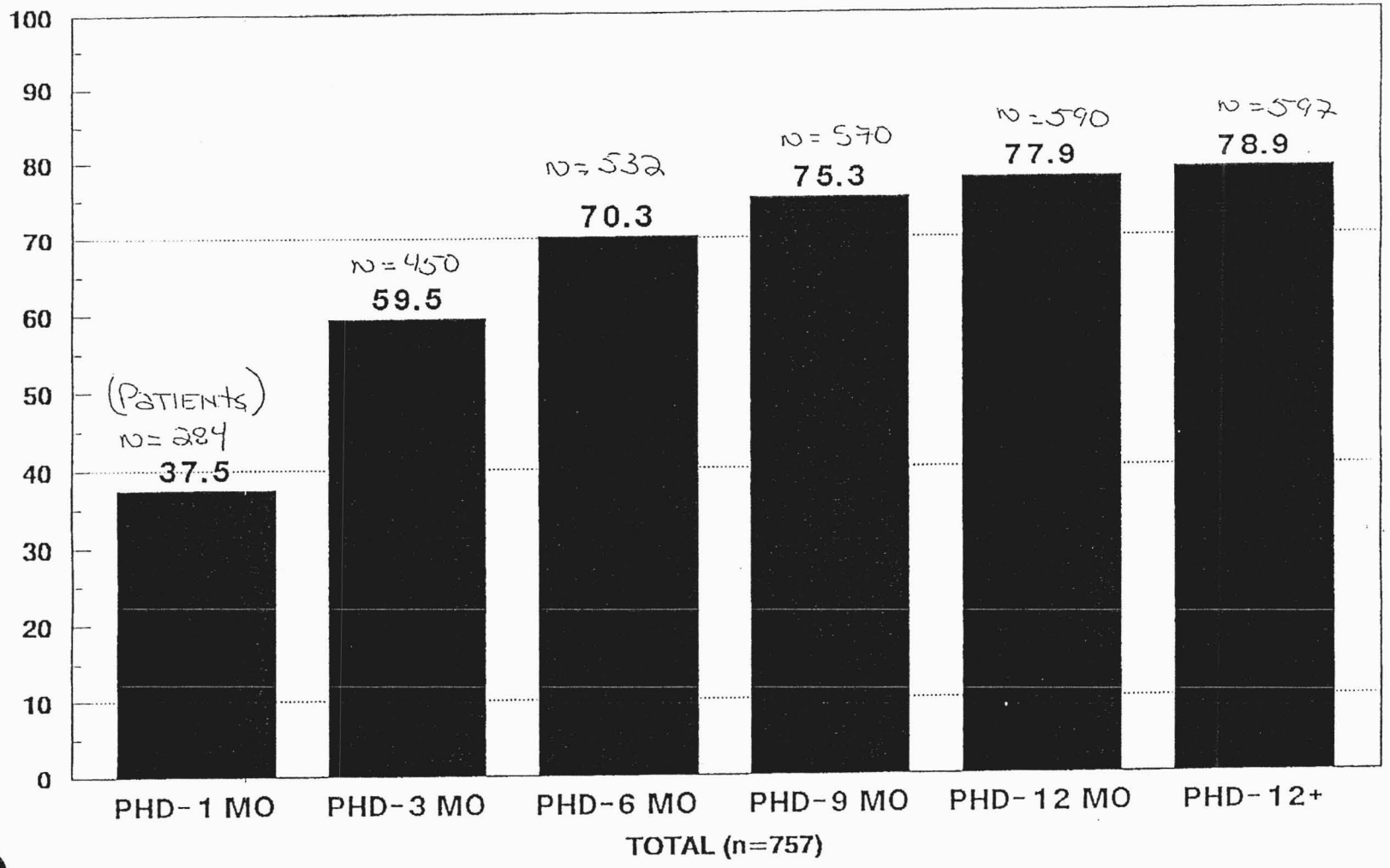

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Figure 1

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Part 1 - Page 7 of 14

PCD TRANSVENE LEAD SYSTEM

DISTRIBUTION OF SPONTANEOUS AND INDUCED EPISODES

PATIENTS WITH 6+ MONTHS OF FOLLOW-UP

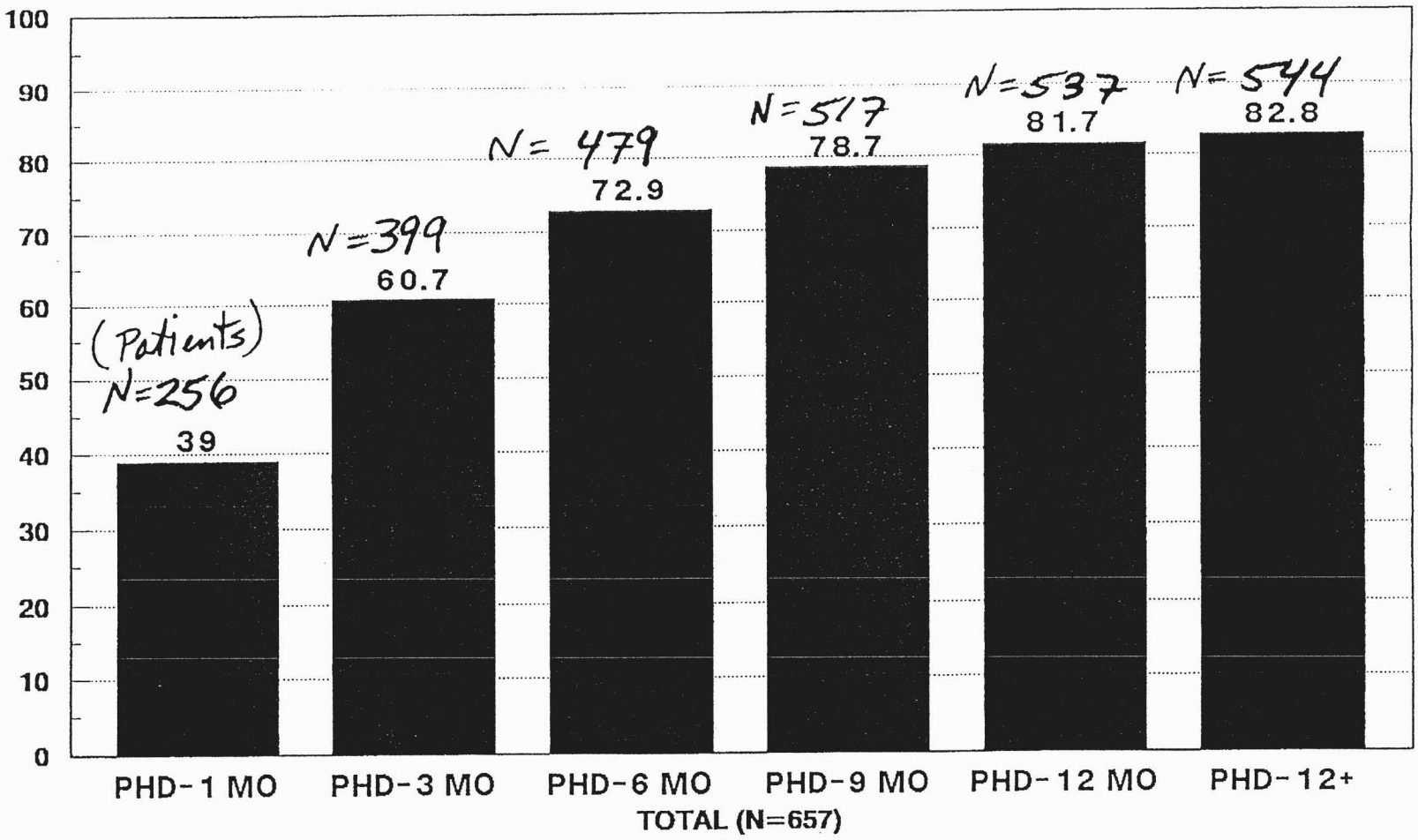

Figure 2

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Explanted Transvene Leads

The investigational plan requests that if the patient expires during the course of the clinical study, or if the PCD and associated leads are explanted for any other reason, that the entire system be returned to Medtronic for analysis. Table 1 provides an overview of the number of PCD devices explanted, the reason for explant, the number received for analysis, and the number of lead systems (either in part or the entire lead system) returned for analysis.

PCD Transvene System Reasons for PCD Device Explant and Lead Systems Returned n = 762			
Reason for Explant	# of PCD's Explanted	# PCD Received for analysis	# of lead systems returned for analysis
Patient Death	22	17	13
Infection	22	10	7
Cardiac Transplant	9	5	3
Low Battery Voltage	1	1	0
PCD Performance Issue	4	4	2
L23	1	1	0
Lead Issues	4	4	4
Total	63	42	29

Table 1 Reasons for PCD Device Explant and Lead Systems Returned - 2/1/93

Patient Death:

There were 51 reported patients deaths and 22 PCD devices explanted. Seventeen have been received at Medtronic for analysis, of which 13 included the entire or part of the lead system.

Table 2 contains a breakdown of the leads received by model number from the 13 lead systems returned for analysis.

PCD Transvene System Explanted Leads returned due to Patient Death			
# of Systems Returned	Model 6884/6966/SP2100	Model 6881/6963	Model 6895/6999
13	(b)(4) (b)(4)		

Table 2: Explanted Leads returned due to patient death

The analysis of these leads indicated that the leads were within specification.

Infection:

There were 22 devices explanted due to infection. (b)(4) have been received at Medtronic for analysis, of which 7 included the entire or part of the lead system.

Table 3 contains a breakdown of the leads received by model number from the 7 lead systems returned for analysis.

PCD Transvene System Explanted Leads returned due to Infection			
# of Systems Returned	Model 6884/6966/SP2100	Model 6881/6963	Model 6895/6999
7	(b)(4) (b)(4)		

Table 3: Explanted Leads returned due to infection

The analysis of these leads indicated that the leads were within specification.

Heart Transplant:

There were 9 devices explanted due to heart transplants. (b)(4) devices have been received at Medtronic for analysis, of which 3 included the entire or part of the lead system.

Table 4 contains a breakdown of the leads received by model number from the 3 lead systems returned for analysis.

PCD Transvene System Explanted Leads returned due to Heart Transplants			
# of Systems Returned	Model 6884/6966/SP2100	Model 6881/6963	Model 6895/6999
3	(b)(4)		

Table 4: Explanted Leads returned due to heart transplants

The analysis of these leads indicated that the leads were within specification.

PCD Device Performance Issues:

There were 4 devices explanted due to PCD device performance issues. These issues are explained in detail in the Complication/Observation section II.E.2 "Early Device Explant". All 4 devices have been received at Medtronic for analysis, of which 2 included the entire or part of the lead system.

Table 5 contains a breakdown of the leads received by model number from the 2 lead systems returned for analysis.

PCD Transvene System Explanted Leads returned due to PCD Device Issues			
# of Systems Returned	Model 6884/6966/SP2100	Model 6881/6963	Model 6895/6999
2	(b)(4)		

Table 5: Explanted Leads returned due to PCD Device Issues

The analysis of these leads indicated that the leads were within specification.

Lead Issues:

There were 4 devices explanted due to heart transplants. All 4 devices have been received at Medtronic for analysis, of which all 4 included the entire or part of the lead system.

Table 6 contains a breakdown of the leads received by model number from the 4 lead systems returned for analysis.

PCD Transvene System Explanted Leads returned due to Lead Issues			
# of Systems Returned	Model 6884/6966/SP2100	Model 6881/6963	Model 6895/6999
4	(b)(4) (b)(4)		

Table 6: Explanted Leads returned due to Lead Issues

The analysis of these leads indicated that the leads were within specification with the exception of 1 Model 6966 that was removed due to lead fracture attributed to subclavian crush phenomena. This fracture is described in detail (patient 96442) in the Complications/Observation section II.D.4 "Lead Related" events.

One Year Actuarial Survival

Projected one year survival calculations for the various death classifications are provided in Table IB4-2. **The actuarial projections include perioperative deaths only in the calculation of one year survival from death due to all causes (shown in the row labelled Overall).** The perioperative death rate defined as deaths which occurred within thirty days of implant was 0.7% (5/757) which is considerably less than the perioperative mortality for the PCD System with Epicardial leads (5.3% - 39/742). Included in this table are the projected one year survival calculations for patients who ultimately received a PCD Transvene System (n = 757) and all patients that were screened for a PCD Transvene System (n = 897) regardless of implant outcome. The outcome of the 897 patients screened for a PCD Transvene System are described more fully in section IC2.

PCD Transvene System One Year Actuarial Survival		
	Received a Transvene System (N = 757)	Screened for a Transvene System (n = 897)
Sudden Cardiac Death	99.5%	99.5%
Non-Sudden Cardiac	96.2%	96.6%
All Cardiac	95.8%	96.1%
Noncardiac	98.1%	98.4%
Perioperative	0.7%	1.6%
Overall	93.3%	92.9%

Table IB4-2: PCD Transvene System - One Year Actuarial Survival - 2/1/93

The positive impact of the PCD Transvene System on patient mortality is clearly obvious from this analysis. The sudden cardiac death survival rate in this patient group is 99.5% for those in the patient group that received a Transvene System and 99.4% for those who were screened for a Transvene System. This is a marked improvement when compared with the reported survival of similar patient groups treated with drug therapy alone.

Lead Dislodgments

Table 1 contains the number of lead dislodgements categorized by type of lead dislodged. This table also provides the total number of leads implanted for each type of lead. For example, there were 24 RV lead dislodgements that were categorized as a complication out of 757 RV leads implanted. Therefore, the incidence of RV lead dislodgement is 3.2% (24/757).

PCD Transvene System Reported Complications/Observations Lead Dislodgements		
Category	Complications	Observations
	Num (% of Pts)	Num (% of Pts)
RV Lead Dislodgement (757 RV leads implanted)	24/757 (3.2%)	1/757 (0.1%)
CS Lead Dislodgement (261 CS lead implanted)	22/261 (8.4%)	4/261 (1.5%)
SVC Lead Dislodgements (535 SVC leads implanted)	45/535 (8.4%)	7/535 (1.3%)
Total Number of Lead Dislodgements	91	12

Table 1: PCD Transvene System: Lead Dislodgements - 2/1/93

Returned Device for Patient 94244

All devices that were explanted due to patient death have been analyzed and were found to be within specification. Therefore, for patient 94244, the device (b)(4) was within specification.

Final interrogation of the device showed that since discharge from the hospital the patient had experienced an additional 23 episodes of spontaneous VT and 1 episode of spontaneous VF. In the case of VT, 22 episodes were successfully treated by VT Therapy #1 (Burst) and one episode required VT Therapy #4 (b)(4) The episode of VF was successfully reverted by VF Therapy #1 (b)(4)

The last episode detected by the PCD Device was VT and the cycle length of the episode was 480 ms. VT Therapy #1 (Burst) successfully terminated this episode.

The investigator classified this patient death as perioperative and sudden cardiac. The relationship of the death to the implanted PCD Transvene System was classified as unknown. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

Medtronic Polyurethane Lead Reliability

The following information is presented in order to provide an overall assessment and support of polyurethane lead reliability, specifically as it relates to the tachyarrhythmia application for which the Model 6966 (6884) lead is intended.

Background on Brady Pacing Lead Experiences

Medtronic utilizes two systems to monitor performance of its brady pacing leads. The analysis of returned product is used to identify lead failure mechanisms. However, it cannot be used to estimate clinical performance since all leads/lead segments are not explanted or returned. Clinical performance is monitored through our Chronic Lead Study (CLS), a multi-center study currently involving eleven representative U.S. Clinical centers and over 20,000 leads. Lead performance in the CLS is presented as actuarial survival from clinical complications resulting in lead explants or abandonment. Specific complication criteria have been established[1]. Since all leads are not explanted it is not always possible to relate a clinical complication to a specific failure mechanism and not all complications are associated with lead failure.

The primary failure mechanisms for brady pacing leads are conductor fracture and insulation failure. Conductor fractures are primarily associated with the widely accepted "Subclavian Stick" implant procedure using percutaneous lead introducers. Leads implanted by this procedure can be clamped and crushed between the first rib and clavicle, leading to fracture of the conductor, and sometimes, insulation failures as well. Bipolar leads are more susceptible to this failure mechanism than unipolar leads because of their larger lead body diameter. Crush fractures tend to occur primarily during the first two years post implant.

For leads with polyurethane insulation, the primary insulation failure mechanisms are Environmental Stress Cracking (ESC) and Metal Ion Oxidation (MIO); both tend to occur starting about 2 years post implant. Bipolar leads tend to be more susceptible to insulation failure than unipolar leads.

ESC is associated with stress on the lead either induced during manufacture or via implant procedure. Newer generation Medtronic leads have greater ESC resistance due to improvements in design, manufacturing processes and materials.

MIO is an oxidative degradation of polyurethane insulation. The reaction is catalyzed by metal ions released by the corrosion of the conductor coils. To reduce the potential for MIO, newer Medtronic lead designs have applied a sputtered coating of platinum to the conductor coils. Also, (b)(4) polyurethane tends to be more resistant to MIO than (b)(4). Medtronic has used an accelerated oxidation environment, Solution A, to evaluate MIO and potential factors that can minimize its occurrence.

A table depicting the frequency of these failure mechanisms (conductor fractures, MIO and ESC) for brady leads, Models 4004/M and 4058/M, follows this response. As shown, conductor fracture due to crush is the predominate failure mode. See table, Failure Mechanisms, following this discussion.

The Model 4004/M is a bipolar lead incorporating (b)(4) polyurethane and platinum coating. As of February 28, 1993, survival probability of the Models 4004/4004M is 97.0 ± 1.7% at 36 months[1]. Crush fracture is the primary source of lead failures to date, with rates comparable to that of earlier bipolar lead designs.

Over the past several months Medtronic and FDA have had numerous discussions about the occurrences of failure associated with MIO in the Model 4004/M lead. As of February 28, 1993, Returned Product Analyses has identified 22 MIO failures out of approximately (b)(4) leads implanted (.030%). MIO failures in previous lead designs tend to predominate in 3 areas: proximally in the pacemaker pocket, medially in the clavicular region, and distally near the ring electrode. With Models 4004/M, platinum sputter coating appears to reduce the occurrence of MIO proximally and medially. The majority of the MIO failures (20 of 22) occurred distally. Distal failure occurs between the ring electrode and the AV valve and appear to be related to flexing of the lead associated with ventricular contractions.

Initial Solution A testing was conducted under static conditions and gave no indication of this failure mechanism. Currently testing is underway to develop a dynamic Solution A test to study factors affecting this failure mechanism and potential corrective actions. To date, we have been able to induce failures and are conducting experiments to understand contributing factors.

Some common features to both brady and tachy leads are the (b)(4) conductor coil, coaxial coil design, polyurethane insulation (b)(4) and platinum alloy electrode material. Like the 6966 lead, the Models 4016A, 4058/M and 4024 also have platinum coating on the conductor coil and (b)(4) as the inner insulation. Individual lead differences include the electrode fixation mechanisms, i.e., screw-in helix versus tines and the (b)(4) versus (b)(4) insulation usage. Using (b)(4) insulation provides more stiffness, and greater resistance to insulation failure, whereas (b)(4) provides for greater ease of handling.

The brady lead most similar to the 6966 lead is the 4016A. Both have (b)(4) (b)(4) as the inner(most) insulation, (b)(4) for the middle/outer insulations, distal screw-in fixation mechanisms, similar French (introduction) sizes and virtually identical insulation dimensions. Only the coil dimensions vary slightly.
The 4058/M lead is also very similar to the 4016A; the only substantive change is the introduction size, 9 French. Model 4016A and 4058/M leads have shown excellent clinical performance; for the 4016A actuarial survival is 98.2% at three years (b)(4) implants) and for the 4058/M actuarial survival is 99.7% at three years (b)(4) implants)[1].

The 6966 lead has a larger body diameter than the brady leads. This is to be expected given the tripolar coaxial design of the lead. Given the larger French size of the 6966, it is more susceptible to crush between the clavicle and rib than the smaller French leads. Lead fracture due to crush in this area is, however, a recognized failure mechanism for all transvenous leads implanted via subclavian insertion, (brady or tachy leads). This is vigorously addressed in product labeling (lead technical manuals) and includes appropriate cautions about the use of the procedure.

Also, the larger diameter of the 6966 lead body and presence of a defibrillation coil electrode proximal to the distal pace/sense ring of the 6966 lead imparts more stiffness to it than the brady leads. Hence, there is less lead body movement below the valve when the 6966 is implanted in the right ventricle as compared to a brady lead. This was clearly evident in the videotape comparing the in-vivo flexing of both a brady and tachy lead (presented in FDA/Medtronic meeting of February 18, 1993). Decreased flexing of the 6966 lead below the valve is our basis for expecting flex-related MIO will not be a significant failure mechanism of the 6966 lead.

Analysis of Transvene Model 6966 Lead and Clinical Presentation

The Model 6966 tripolar tachy lead is comparatively less flexible than brady leads. Therefore, distal MIO as evident in a very small percent (.030%) of brady 4004/4004M leads is not necessarily indicative of a similar occurrence in the 6966 lead. A videotape illustrating the clinical flex performance differences between brady and tachy leads was presented during the FDA/Medtronic meeting on February 18.

Analysis of the Model 6966 lead, as it relates to the potential for MIO, indicates that it would be more likely to occur on the middle versus the outer or innermost insulations. Lead failure due to MIO typically is found on the inner insulation on returned bipolar brady leads. Therefore, this failure mechanism is not expected to significantly affect the (b)(4) outer insulation of the 6966 lead. Should MIO occur on the outer insulation of the 6966 lead, the net effect would be an increased defibrillation electrode surface area. This would not be expected to significantly affect system performance. Additionally, the more resistant properties of (b)(4) (to MIO), of the 6966 innermost insulation, are expected to further reduce the potential for MIO (99.7% survival Model 4058/M at three years)[1].

For the Model 6966 lead, should the middle, (b)(4) insulation fail, it would likely present initially as an intermittent short (as is more typical with brady leads) and can progress over time if not identified and treated, to a hard (direct) short. These could manifest initially as oversensing, and ultimately as integrated bipolar sensing, respectively (intermittent versus hard short). In the case of a hard short of the middle insulation, specifically, shorting the pacing tip to the common defibrillation electrode, an integrated bipolar sensing system is created. In this type of system, sensing occurs between the unipolar pacing tip and the common defibrillation electrode

(versus standard bipolar sensing between the pace/sense tip and the ring electrodes). This type of sensing system is identical to the CPI Endotak configuration, currently in clinical trials, and also to Medtronic's historic Transvene RV lead, the Model SP2100 lead. These type of integrated systems have been shown to be clinically acceptable. Note that (b)(4) Model SP2100 leads were implanted at the start of the Transvene clinical study. There have been no observations or reported problems related to the SP2100 lead performance. (Data from the SP2100 lead have been incorporated in the clinical experience analysis reported in this PMA application.)

Intermittent sensing could result in oversensing, if the detection criteria are also met, and this could result in delivery of inappropriate, i.e., not needed, therapies. This can be considered a "safe failure" given the system would "err" by oversensing (versus undersensing) and the patient could receive an unnecessary therapy. Also, patients are instructed to report therapies to their physicians; this facilitates identification of any inappropriate therapy.

Recently, a Model 6884[2] lead was explanted after 27 months when the patient received a heart transplant. The lead was fully functional at explant, however, returned product analysis has indicated the presence of some MIO in the clavicular region. Transvene leads, like brady leads, are implanted by subclavian insertion and are susceptible to being crushed between the clavicle and first rib. As indicated above, with brady leads this can result in conductor fractures, insulation failures or both. Detailed analysis of this lead follows this discussion.

It should be noted that MIO is only one potential failure mechanism of implantable leads. As discussed, others include fracture due to crush in the area of subclavian insertion, environmental stress cracking due to stresses the in-vivo environment may impart to the lead and lead dislodgement.

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[1] Medtronic Product Performance Report, February 1993.

[2] The Model 6884 lead is the earlier version of the Model 6966 lead and differs only in the connector pin configuration; the 6884 has a 3.2 mm, high voltage connector pin and the 6966 has a 6.5 mm, high voltage connector pin. Otherwise the leads are the same.

Transvene Clinical Assessment Experience

Given over 2000 worldwide Transvene patients implanted to date, ranging from zero to forty months implant duration, there have been no reports of undersensing, insulation failures, or oversensing that could not be managed via reprogramming. Furthermore, the benefits of Transvene implantation are dramatically apparent from the perspective of perioperative mortality, 0.7 percent for Transvene versus 5.3 percent for epicardial implants. Transvene survival from SCD is 99.5 percent and overall survival is 93.3 percent at one year. Additionally, Transvene implants, on average, require 8 days in hospital versus 11 days for an epicardial system; a significant cost savings. In summary, the benefits of the Transvene system performance clearly surpass the potential for MIO, or other potential failure mechanisms, in the 6966 lead.

Conclusions

Although Medtronic cannot assure that MIO or other lead failure mechanisms will not occur in the Model 6966 lead, the actual benefits of the Transvene system, as previously discussed, would appear to exceed the potential risk due to MIO. Analysis shows that the potential for MIO to occur in the 6966 lead would result in a "safe failure." Note that preclinical and animal testing cannot completely simulate the long-term implant environment, thereby eliminating all potential for lead failures in-vivo. This was recognized by Congress in implementing the Postmarket surveillance provision in the Safe Medical Device Act of 1990. It is clear that postmarket surveillance mechanisms, e.g., returned product analysis and chronic lead monitoring, are more appropriate mechanisms for evaluating and managing potential failure mechanisms of implantable cardiac leads.

FAILURE MECHANISMS

(CLINICAL/ELECTRICAL FAILURES FROM RETURN PRODUCT ANALYSIS)

(b)(4)

(b)(4)

FAILURE MECHANISMS

(CLINICAL/ELECTRICAL FAILURES FROM RETURN PRODUCT ANALYSIS)

MECHANISM	MODEL 4004/4004M	MODEL 4058/4058M
MIO	(b)(4)	
% of Implants		
ESC		
% of Implants		
Crush		
% of Implants		

(b)(4)

FTIR-ATR

FTIR spectra were obtained for a control area (no MIO) of the inner tubing and the cracked area of the tubing. Relative ratios of key bonds were calculated using the absorption intensities. These ratios indicated that the ether segments were oxidized in the (b)(4)(b)(4) which is characteristic of MIO. In addition, peaks appeared, indicative of carboxylic acids or esters (oxidation byproducts).

Discussion

Contrary to the initial dimensional analysis of this lead that indicated the area of MIO was located to the clavicular region of implant, review of the patient's X-rays revealed that the heart was significantly enlarged due to the advanced disease state. Subsequently, a significant portion of the insulated lead body was located in the heart, including the portion with cosmetic MIO. Typically, 20 cm proximal of the tip electrode approximates the clavicular region.

Consistent with our previous analysis of MIO relative to the 6884/6966 lead, the observed MIO did not, in any way, affect the clinical performance of this lead. Patient data analysis shows that the implanted lead system, inclusive of the 6884 lead, performed appropriately. Of six spontaneous VT/VF episodes reported (4VT/2VF), all were appropriately detected and treated via the implanted PCD Transvene system.

In addition, the presence of MIO on the middle insulation is not entirely unexpected (reference February 18, 1993, Medtronic/FDA meeting). If the middle insulation had been degraded to the point of electrically shorting the sensing ring (middle conductor coil) to the common defibrillation electrode (middle coil), an integrated bipolar sensing system would, in essence, be created. In this type of system, sensing occurs between the unipolar pacing tip and the common defibrillation electrode, versus standard, or true, bipolar sensing between the pace/sense tip and the ring electrodes. This type of sensing system is identical to the CPI Endotak configuration, as well as Medtronic's earlier design of a Transvene RV lead, i.e., the Model SP2100. These types of integrated systems have been shown to be clinically acceptable. Note that canine testing of a shorted, RV cardioversion/defibrillation lead, indicated that this type of failure does not result in the lack of therapy delivery.

If the innermost insulation had degraded such that the pacing tip electrode shorted, this could manifest as intermittent sensing of the brady pace/sense function of the lead. This type of anomalous system performance is expected to be observed at follow-up sessions, given the frequent monitoring of patients (every three months) or as necessary when the patient experiences VT/VF episodes or anything unusual. Similar to brady pacing patients, problems related to pace/sense performance are typically observed at the time of follow-up (pace/sense threshold measurements are

standard follow-up procedure for both brady and tachy lead systems) and/or when the patient reports to his/her physician for any unusual events, e.g., intermittent pacing/sensing.

The extensive dilatation of the right ventricle in which this lead was implanted resulted in a large portion of insulated lead body being in the right ventricle, as opposed to primarily just the cardioversion/defibrillation electrode coil. Subsequently, this lead may have been subject to more flexing in the heart than what is typical for the RV lead. Note: this was demonstrated in the videotape that was presented to FDA at the February 18, 1993, Medtronic/FDA meeting.

Clinical data from brady pacing leads indicates that the portion of the lead subject to the flexing motion in the heart may be related to the occurrence of MIO in brady lead bodies. Brady pacing leads, proximal to the tip/ring electrodes are subject to more flexing motion, relative to a cardioversion/defibrillation RV lead, while contained in the heart. On the other hand, cardioversion/defibrillation leads, like the 6884/6966, are comprised of a comparatively stiff portion proximal to the tip/ring electrode. This length of defibrillation electrode, 5 cm, appears to flex less than a typical brady pacing lead while in the heart, as a result of greater stiffness. However, in the extremely hypertrophic heart, as was the case with this particular RV lead, the lead may be subject to more flexing, similar to that of a brady pacing lead.

Conclusions

As noted, Medtronic cannot assure that MIO, or other lead failure mechanisms will not occur in the 6884/6966 lead. However, one should consider the actual benefits of the lead versus the potential for MIO occurrence. Specifically, clinical data to date for the Transvene system show that one year actuarial survival from SCD is 99.5 percent and the average hospital stay for Transvene implant is only seven days (versus ten for an epicardial system)*. Regarding the potential for MIO occurrence, analysis shows this would result in a bipolar integrated sensing system, or in an intermittent pace/sense system. Integrated sensing has been shown to be clinically acceptable, and intermittent pacing/sensing is assessed as part of standard follow-up procedures. Additionally, with postmarket surveillance mechanisms in place, such as returned product analysis and chronic lead monitoring, Medtronic is well positioned to appropriately evaluate and manage potential failure mechanisms of implantable cardiac leads. We are committed to these surveillance mechanisms in the interest of delivering optimal implantable technology products to the health care market.

*Values are lower than those reported February 1993 due to increased follow-up data.

AA
PEDO
ORLND

P9 015/S000

13-Oct-1993

for

FROM:	LETTER DATE	LOGIN DATE	DUE DATE
MEDTRONIC INC. ATTN: JENNIFER M. MARRONE 7000 CENTRAL AVENUE, N.E. MINNEAPOLIS,, MN 554323576	10/11/93	10/12/93	/ /
	DOCUMENT: PMA	CONTROL # P920015/S000 AMENDMENT	

SUBJECT:
MEDTRONIC(R) TRANSVENE LEAD SYSTEM

	OFFICE	DATE REFERRED
4 COPIES OF VOLUME 1	~~CK~~ H	10/13/93
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MEMORANDUM

From: Doris Terry (HFZ-450)
To: File # P920015
Subject: Medtronic Transvene System
Date: October 28, 1993
Office: DCRND/ODE

The manufacturer responded to our approvable letter of September 23, 1993. In addition, the manufacturer mentioned that a follow-up inspection is scheduled for October 18, 1993 (the PMA application might be amended to provide inspection information). The manufacturer also stated that there are no new data from the clinical study of the Medtronic Transvene System which could impact safety and effectiveness.

Deficiency # 1

The manufacturer modified the labeling to include the following: diagrams for proper insertion and the final position of the leads; defibrillation efficacy data for the different lead configurations and polarity combinations (including sequential and simultaneous discharges); information and/or recommendations regarding implantation techniques and testing methods; information regarding implanting in patients who do not have a 10 Joule safety margin; information aimed at reducing the incidence of infection; instructions stressing the importance of pausing between VF inductions; information regarding the expected change in defibrillation thresholds; guidance regarding permanent pacemaker separation from the Transvene leads (RV and SVC/CS); a statement which emphasizes the need for x-rays and pace threshold testing; information regarding techniques for placing the leads via the cephalic vein; and an explanation regarding the necessity for explant and return of the leads upon the patient's death.

The manufacturer provided the requested data. No concerns about how the data are presented in the labeling.

Deficiency # 2

The manufacturer modified the labeling to include warnings which pertain to the following: use of the Sub-Q patch lead on the pericardium or epicardium; language regarding the use of dual anchoring sleeves; and information regarding extensive inductions during implant.

No significant concerns about the warnings as written.

Deficiency # 3

We told the manufacturer that the indications and contraindications for use of the Medtronic Transvene Lead System should be identical to the PCD Epicardial System with certain exceptions. The exact language which states, "The safety and

effectiveness of the PCD...", was not used. However, the proposed language is acceptable. The indications as written are acceptable. It should be noted that the contraindication proposed by the manufacturer, "The Transvene Lead System is contraindicated for use in any system other than a Medtronic implantable tachyarrhythmia control device system for which it has been tested," will not be included in the labeling as a contraindication. The manufacturer was informed of our decision in a phone conversation. They agreed to remove the contraindication, and will send documentation confirming our agreement.

The manufacturer also satisfactorily responded to the requests which consisted of the following: placing an identifying mark to distinguish nonthoracotomy leads from thoracotomy leads; reporting warning and precautions separately and providing a copy of the Patient's Manual.

I also told the manufacturer that the Warnings and Precautions should be included in the labeling according to our Blue Book Memorandum of March, 8. 1991 (manufacturer has a copy). We reviewed the manual and found that caution statements within the context of the manuals should also be included on the list of precautions. They agreed to revise their labeling to include the referenced cautions on the list.

Recommendation

The manufacturer modified the labeling as requested. Formal documentation pertaining to the warnings and precautions and the removal of the requested contraindication will be submitted. In the interim, faxed information will be sent confirming their agreement, as we discussed, regarding those concerns.

Approval of the referenced PMA application.

Medtronic

Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576
Telephone: (612) 574-4000
Cable: Medtronic Telex: 29-0598
FAX: (612) 574-4879

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FDA/CDRH/ODE/DMC

October 11, 1993

Office of Device Evaluation
PMA Documentation Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

Re: PMA Amendment to the Medtronic® TRANSVENE® Lead System
(Document Control Number P920015) /AC2V1
Response to FDA Approvable Letter of September 23, 1993

The purpose of this PMA Amendment is to respond to FDA's letter dated September 23, 1993 (reference Attachment A).

Responses to all items described in FDA's letter are provided in Attachment B.

Copies of the final proposed labeling (technical manuals and package labels) for the TRANSVENE® lead system (reference Attachment C) and the PCD® Device (reference Attachment D) are provided. (Note: The PCD® Technical Manual is synonymous with the term Physician's Manual.)

In addition, consistent with item #4 of FDA's Approvable letter, a copy of the PCD® Patient's Manual, "Restoring the Rhythms of Life", is included (reference Attachment E).

As indicated in FDA's letter, Transvene® approval remains subject to compliance with applicable GMP regulations. A follow-up inspection to the pre-PMA approval inspection is scheduled for October 18, 1993. If necessary, we will amend the PMA to include additional information at that time.

Via this Amendment, we are also informing the Agency that there is no new safety and effectiveness information learned about the device (system) from the ongoing clinical study that could reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling.

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Three copies of this submission are provided in accordance with 21 CFR Part 814.44(e)(2). It contains confidential and commercial trade secret information and we request that it be given the maximum protection provided by the law. If additional information is required, please contact Dennis Connolly at (612) 574-4696.

Sincerely,

MEDTRONIC, INC.

Charles H Swanson for

Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business Unit
(612) 574-4688
(612) 574-6424 FAX

Attachment

Table of Contents

Attachment A: Deficiency Letter

Attachment B: Responses to Approvable Letter

Attachment C: TRANSVENE® Technical Manuals and Package Labeling

Attachment D: PCD® Technical Manual

Attachment E: PCD® Patient Manual "Restoring the Rhythms of Life"

A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

Ms. Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

SEP 23 1993

RE: P920015
Medtronic● Transvene● Lead System
Filed: April 1, 1992
Amended: August 27, September 21, October 27 and November 5, 1992,
March 29, June 2, 14, and July 9, 1993

Dear Ms. Marrone:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA). The Circulatory System Devices Panel which also reviewed your PMA, recommended to CDRH at the August 2, 1993, panel meeting that the PMA be considered approvable. CDRH is pleased to inform you that the PMA is approvable subject to your submission of the following:

1. The labeling should be modified to include the following directions for use:

   a. diagrams which demonstrate the proper insertion technique and final anatomic position of the intravascular leads and the Sub-Q patch;

   b. defibrillation efficacy data on the different lead configurations, various polarity combinations and sequential versus simultaneous discharges;

   c. information and/or recommendations regarding specific implantation techniques and methods of testing the different configurations. For example, when is it recommended to use a two-lead configuration versus a three-lead configuration, when to implant in the superior vena cava (SVC) versus the coronary sinus (CS), and how the most advantageous position of the Sub-Q patch is determined;

   d. information or recommendations, based on your experience, regarding implantation in patients who do not have at least a 10 Joule safety margin;

   e. information aimed at reducing the incidence of infection;

   f. instructions stressing the importance of pausing between inductions of ventricular fibrillation (VF) at the time of implantation for at least a specified period of time in order to

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decrease morbidity and mortality. The comments and the pause duration suggested should be based on the experience of the primary investigators in your study;

g. information regarding the change in defibrillation thresholds that one may expect with time as based on the experience of your investigators in your study;

h. guidance and techniques for separating permanent pacemaker leads from the Transvene● leads to minimize the interaction between the two devices, and diagnostic methods which can be employed at implant or predischarge to confirm the absence of adverse interaction;

i. a statement which emphasizes the need for x-rays and pace/sense threshold testing at follow-up to check for lead dislodgement (x-rays should be done at 3-month intervals for 1 year);

j. information regarding techniques for placing the leads via the cephalic vein when possible; and

k. an explanation regarding the necessity for explant and return of the leads upon the patient's death.

2. The labeling should be modified to include the following warnings:

a. a statement that the Sub-Q patch lead is not for use on the pericardium or epicardium, because it is too inflexible to be used as such;

b. stronger and more specific language regarding the use of dual anchoring sleeves on the right ventricle (RV), SVC, and CS leads. Based on the experience of your investigators, please describe the techniques used to fixate the lead at the insertion into the vein to minimize dislodgment; and

c. information which states that after extensive VF inductions at implant testing with the nonthoracotomy lead system, serious consideration should be given to delaying the thoracotomy for at least 2 days. Please include a statement which states that the clinical data showed that when a thoracotomy was performed immediately after testing, the perioperative mortality rate was increased from 0.7 to 9.3 percent.

3. In addition you should note the following:

a. The indications and contraindications for use of the Medtronic● Transvene● Lead System must be identical (except for certain modifications which pertain to the Transvene● Leads and those described below) to those for the PCD™ Epicardial System. Please change your second indication to read: Poorly tolerated,

sustained ventricular tachycardia and/or fibrillation which recurs spontaneously or can be induced despite the best antiarrhythmic drug therapy. Please also include the following statement in your indications section:

Note: The clinical outcome of hemodynamically stable, sustained VT patients is not fully known. The safety and effectiveness of the PCD● Transvene System in this subgroup of VT patients has not been determined.

b. The technical manuals for the Transvene● Leads must state that the leads are for use together as a system. The labeling (where appropriate) must be consistent in all of the Transvene● Lead manuals. The information regarding the Transvene● Leads in the PCD● Manual must also be included in the Transvene● Lead manuals.

c. There should be an identifying mark on the package label which distinguishes nonthoracotomy leads from thoracotomy leads.

d. The Warnings and Precautions in the labeling must be identified and reported separately according to FDA's Blue Book Memorandum of March 8, 1991, (a copy of this memorandum was previously sent to you).

4. Provide a copy of the Patient's Manual which includes a reference to use of the non-thoracotomy leads with the PCD● models.

The PMA must be amended to include your concurrence with, or suggested revision of, the enclosed "Conditions of Approval for Implantable Defibrillators and Programmers."

The condition that the sale, distribution and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act.

The device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the approved labeling specifies the requirements that apply to the training of physicians who may use the device.

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In addition to the above, an FDA inspection must find that the manufacturing facilities, methods and controls comply with applicable device Good Manufacturing Practice Regulations (21 CFR Part 820). If applicable, amend the PMA to include required manufacturing information not previously submitted.

This is to advise you that, following receipt of an approvable letter, an applicant is required by 21 CFR 814.20(e) to update its pending PMA with new safety and effectiveness information learned about the device from ongoing or completed studies that may reasonably affect an evaluation of the safety or effectiveness of the device or that may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling. This updated reporting is limited to studies sponsored by the applicant or to which the applicant has reasonable access. The update report shall be consistent with the data reporting provisions of the protocol. Any update report shall be submitted in three copies as an amendment to the PMA and shall include the FDA reference number assigned to the PMA.

CDRH will issue an approval order after the requested information has been reviewed and determined to be acceptable. You may not begin commercial distribution of the device until you have received an approval order.

As provided by 21 CFR 814.44(e)(2), you may amend your PMA as requested, or withdraw it, or you may treat this letter as a formal denial of approval. If you choose the latter, you may request administrative review,.either through a hearing or review by an independent advisory committee, under section 515(d)(3) and 515(g) of the act by filing a petition with the Food and Drug Administration, Dockets Management Branch (HFA-305), Room 1-23, 12420 Parklawn Drive, Rockville, Maryland 20857, within 30 days of the date you receive this letter. A petition for administrative review must be submitted in accordance with general administrative procedures for submission of documents to the Dockets Management Branch (21 CFR 10.20) and in the form of a petition for reconsideration (21 CFR 10.33). After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issues to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

The above requested information must be submitted in the form of an amendment (3 copies). Unless you amend this PMA to request an extension, and the extension is approved, FDA will consider the PMA to have been withdrawn voluntarily if you fail to respond in writing to this request for an amendment within 180 days of the date of this letter as provided under 21 CFR 814.44(g). Any request for an extension must be submitted within the 180-day period, justify the need for the extension, and provide a reasonable estimate as to when the requested information will be submitted.

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All amendments to the PMA must be submitted in triplicate to the address below and shall reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

In addition, under Section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under Section 522(a)(1)(A) the above noted device as requiring postmarket surveillance.

Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study to include the evaluation of the explanted leads for evidence of metal ion oxidation (MIO), and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

Postmarket Studies Document Center
Room 408 (HFZ-107)
12720 Twinbrook Parkway
Rockville, Maryland 20852

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will cause your product to be misbranded and could lead to the imposition of civil money penalties or other regulatory actions. Any distribution of a misbranded device is a violation of the act and may result in a number of FDA enforcement actions, including (but not limited to) withdrawal of your PMA.

If you have questions concerning postmarket surveillance study requirements, contact Postmarket Surveillance Studies Branch at (301) 594-0639.

Finally, on August 16, 1993, the Final Rule for Device Tracking was published in the FEDERAL REGISTER, pages 43442-43455 (enclosed). FDA is required to provide notice to PMA applicants in an approvable letter that their device is

subject to the regulation. Therefore, be advised that under Section 519(e) of the act, FDA has identified the above device as a device which requires tracking. You are required to adopt a method of tracking that follows the devices through the distribution chain and then identifies and follows the patients who receive them. The specific requirements of the regulation are found in 21 CFR 821 as described in the August 16, 1993, FEDERAL REGISTER beginning on page 43447.

If you have questions concerning this approvable letter please contact Doris Terry at (301) 594-2018 or Arnold Alpert, Ph.D., at (301) 594-2186.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Acting Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

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ATTACHMENT B

1. **The labeling should be modified to include the following directions for use:**

   a. **diagrams which demonstrate the proper insertion technique and final anatomic position of the intravascular leads and the Sub-Q patch;**

   RESPONSE:

   Diagrams in all of the lead manuals have been modified. They are located on the following pages:

   Model 6963 - page 8
   Model 6966 - page 10
   Model 6999 - page 5

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b. **defibrillation efficacy data on the different lead configurations, various polarity combinations and sequential versus simultaneous discharges;**

RESPONSE:

The following paragraphs have been added to page 43 of the PCD® technical manual.

> Clinical experience with the TRANSVENE® lead system has shown that most patients (65.6%) received an RV-SVC-SQ system, an additional 29.3% received an RV-CS-SQ system, and the remaining 5.1% received an RV-CS-SVC system. The majority of patients were programmed to Sequential Pulse (75.3%), 23.4% were programmed to the Simultaneous Pulse, and 1.3% were programmed to Single Pulse.
>
> The RV electrode was COMMON in the majority (75.3%) of the clinical implants, the SQ patch in 13.9%, the CS in 7.6%, and the SVC electrode in 2.4% of the clinical implants. The overall efficacy in terminating spontaneous episodes of VF was approximately 98% for all pathways, pulsing techniques and choice of cathode.

c. **information and/or recommendations regarding specific implantation techniques and methods of testing the different configurations. For example, when is it recommended to use a two-lead configuration versus a three-lead configuration, when to implant in the superior vena cava (SVC) versus the coronary sinus (CS), and how the most advantageous position of the Sub-Q patch is determined;**

RESPONSE:

Page 45 has been modified as follows:

The two lead systems available include:

- Right ventricle, coronary sinus
- Right ventricle, superior vena cava
- Right ventricle, subcutaneous patch

Figure 23 shows a flow chart for lead system evaluation that begins with the two lead system and adds an additional lead if the implant criteria is not met with the two lead system. The decision to evaluate a two lead system is based on the desire to achieve the simplest transvenous defibrillation system.

The three lead systems available include:

- Right ventricle, superior vena cava, subcutaneous patch
- Right ventricle, coronary sinus, subcutaneous patch
- Right ventricle, coronary sinus, superior vena cava

Clinical results do not indicate superiority of any pulsing technique, lead system, or choice of cathode for transvenous defibrillation. The choice of lead system for initial evaluation can therefore be based on other factors including simplicity (SVC vs CS lead placement) and physician preference.

Figure 23 has been modified to include evaluation of 2 lead systems.

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d. **information or recommendations, based on your experience, regarding implantation in patients who do not have at least a 10 Joule safety margin;**

RESPONSE:

Medtronic recommends that patients without a 10 Joule safety margin should not receive the Transvene® system. They should be allowed to recover from the lead evaluation procedure and receive an epicardial system at a later date. Therefore, page 40 of the PCD® technical manual has been changed to read:

> If patients do not meet the implant criteria (demonstration of a 10 Joule safety margin) for a transvenous lead system, physicians should consider implanting an epicardial cardioversion/defibrillation lead system. If an epicardial system is to be implanted after testing a transvenous system, consider performing the procedure at a later date. The Transvene® clinical study showed a 9.3% perioperative death rate for patients failing the implant criteria for a Transvene® system and receiving an epicardial system. This compares to 0.7% for those patients receiving a Transvene® system without the additional epicardial surgical procedure.

e. **information aimed at reducing the incidence of infection;**

RESPONSE:

Sterilization instructions are included in all of the manuals on the following pages:

Model 6963 - page 4
Model 6966 - page 5
Model 6999 - page 4

Additional information has been added to each of the Transvene® lead technical manuals. This information is presented below:

> Proper surgical procedures and sterile techniques are the responsibility of the medical professional. The implant procedures described in this manual are furnished for information only. Each physician must apply the information in these instructions according to professional medical training and experience.

The paragraph above is presented on the following pages:

Model 6963 - page 4
Model 6966 - page 5
Model 6999 - page 5

f. **instructions stressing the importance of pausing between inductions of ventricular fibrillation (VF) at the time of implantation for at least a specified period of time in order to decrease morbidity and mortality. the comments and the pause duration suggested should be based on the experience of the primary investigators in your study;**

RESPONSE:

Page 47 of the PCD® technical manual has been modified to address these concerns. The new information is reproduced below:

> In order to keep patient morbidity and mortality to a minimum, patients should be rescued promptly with an external device if the lead system and ETCD fails to terminate the VF episode and at least 5 minutes should elapse between VF inductions.

g. **information regarding the change in defibrillation thresholds that one may experience of your investigators in your study;**

RESPONSE:

Page 58 of the PCD® technical manual has been modified to address these concerns. The new information is reproduced below:

> Although the Transvene® clinical study provided evidence that defibrillation thresholds remain stable in the study population, individual patients may experience threshold changes relative to changes in their underlying disease state. Therefore, VF therapy number 1 should be programmed to at least twice the lowest energy of defibrillation or 34 Joules.

h. **guidance and techniques for separating permanent pacemaker leads from the Transvene® leads to minimize the interaction between the two devices, and diagnostic methods which can be employed at implant or predischarge to confirm the absence of adverse interaction;**

RESPONSE:

Page 82 of the PCD® technical manual has been modified to address these concerns. The new information is reproduced below:

Bradycardia Pacemakers

Previously implanted bradycardia pacemakers, tachyarrhythmia devices and leads should be explanted. The output pulses of an implanted device may adversely affect the tachyarrhythmia detection capabilities of the PCD device. If leads must be abandoned rather than removed they should be capped to ensure they will not become a pathway for currents to or from the heart. If a patient requires a separate atrial or dual chamber pacemaker for hemodynamic reasons, either permanent or temporary, consider the following to minimize potential interaction between the pacemaker and the PCD:

- Use only bipolar pacemakers that remain bipolar after exposure to high voltage shocks.
- Use pacemaker leads with close interelectrode spacing.
- Allow adequate space between the pacing lead electrodes and the defibrillation lead electrodes.
- Test the PCD device to determine if output pulses from the pacemaker are sensed by the PCD.
- Induce all the patients ventricular tachyarrhythmias and ventricular fibrillation with the pacemaker programmed to an asynchronous mode at maximum output to evaluate possible inhibition of detection by the PCD due to pacing artifacts.
- Program the pacemaker to the lowest amplitude allowable for capture chronically, the maximum sensitivity and the minimum rate acceptable to the patient.

The following information has been added to the Model 6966 and the Model 6963 TRANSVENE® lead technical manual. This information was not added to the Model 6999 TRANSVENE® lead technical manual since the subcutaneous patch is not located near bradycardia pace/sense leads.

Bradycardia Pacemakers

Previously implanted bradycardia pacemakers, tachyarrhythmia devices and leads should be explanted. The output pulses of an implanted device may adversely affect the tachyarrhythmia detection capabilities of the PCD device. If leads must be abandoned rather than removed they should be capped to ensure they will not become a pathway for current to or from the heart. If a patient requires a separate atrial or dual chamber pacemaker for hemodynamic reasons, either permanent or temporary, allow adequate space between the pacing lead electrodes and the defibrillation lead electrodes.

The above information is found on the following pages:

Model 6963 - page 8
Model 6966 - page 12

i. **a statement which emphasizes the need for x-rays and pace/sense threshold testing at follow-up to check for lead dislodgement (x-rays should be done at 3-month intervals for 1 year):**

RESPONSE:

The TRANSVENE® technical manuals and the PCD® technical manual have been modified to recommend that x-rays and pace/sense thresholds be performed at three month intervals for the first year post implant and every six months thereafter. These recommendations are contained on the following pages:

Model 6963 - page 15
Model 6966 - page 19
Model 6999 - page 11
PCD® 7217B - page 64

j. **information regarding techniques for placing the leads via the cephalic vein when possible; and**

RESPONSE:

Information regarding techniques for placing leads is provided in each of the TRANSVENE® lead technical manuals. This information is contained on the following pages under "Selecting an Insertion Site":

Model 6963 - page 5
Model 6966 - page 8

The significant information presented on lead placement is presented below:

> The lead may be inserted by venotomy through several different venous routes, including the right or left cephalic vein or the external or internal jugular vein.

k. **an explanation regarding the necessity for explant and return of the leads upon the patient's death.**

RESPONSE:

The following statement asking for return of leads in the case of patient death has been added to the following pages of the Transvene® leads technical manual under the heading of "Post Implant Evaluation":

Model 6963 - page 15
Model 6966 - page 19
Model 6999 - page 11

In the event of a patient death, all implanted leads and devices should be explanted and returned to Medtronic with a completed PCD® Product Information Report. Any questions on product handling procedures can be addressed by calling 1-800-PCD-INFO.

2. **The labeling should be modified to include the following warnings:**

   a. **a statement that the Sub-Q patch lead is not for use on the pericardium or epicardium, because it is too inflexible to be used as such;**

   RESPONSE:

   Page 1 of the Transvene® Model 6999 Subcutaneous Patch Lead technical manual has been modified to warn against pericardial and epicardial placement.

   > NOTE: The Model 6999 TRANSVENE® SQ patch lead is not intended for epicardial or pericardial placement.

   Medtronic recognizes the FDA request to add the reason "because it is too inflexible to be used as such" came from the FDA panel meeting on the Transvene® System, but believes this explicit statement on lead stiffness is not appropriate for inclusion in the lead's technical manual. Testing has not been performed to determine if stiffness is an issue in epicardial or pericardial lead placement. Therefore, it is inappropriate to include this unsubstantiated statement, we have simply warned against use on the epicardium or pericardium.

b. **stronger and more specific language regarding the use of dual anchoring sleeves on the right ventricle (RV), SVC, and CS leads. Based on the experience of your investigators, please describe the techniques used to fixate the lead at the insertion into the vein to minimize dislodgement; and**

RESPONSE:

The TRANSVENE® Model 6966 and the Model 6963 technical manuals contain specific language regarding the use of dual anchoring sleeve and techniques used to fixate the lead at the insertion into the vein to minimize dislodgement. A copy of this section is attached.

This information provided on the following pages of the Transvene® technical manual:

Model 6966 - pages 14 and 15
Model 6963 - pages 10 and 11

c. **information which states that after extensive VF inductions at implant testing with the nonthoracotomy lead system, serious consideration should be given to delaying the thoracotomy for at least 2 days. Please include a statement which states that the clinical data showed that when a thoracotomy was performed immediately after testing, the perioperative mortality rate was increased from 0.7 to 9.3 percent.**

RESPONSE:

If a thoracotomy is planned after evaluation of a TRANSVENE® lead system, patients should be allowed to recover from the lead evaluation procedure before proceeding with the additional surgery. The thoracotomy should be performed at a latter date. Therefore, page 40 of the PCD® technical manual has been changed to read:

> If patients do not meet the implant criteria (demonstration of a 10 Joule safety margin) for a transvenous lead system, physicians should consider implanting an epicardial cardioversion/defibrillation lead system. If an epicardial system is to be implanted after testing a transvenous system, consider performing the procedure at a later date. The Transvene® clinical study showed a 9.3% perioperative death rate for patients failing the implant criteria for a Transvene® system and receiving an epicardial system. This compares to 0.7% for those patients receiving a Transvene® system without the additional epicardial surgical procedure.

3. **In addition you should note the following:**

a. **The indications and contraindications for use of the Medtronic® Transvene® Lead System must be identical (except for certain modifications which pertain to the Transvene® Leads and those described below) to those for the PCD® Epicardial System. Please change your second indication to read: Poorly tolerated, sustained ventricular tachycardia and/or fibrillation which recurs spontaneously or can be induced despite the best antiarrhythmic drug therapy. Please also include the following statement in your indications section:**

NOTE: The clinical outcome of hemodynamically stable, sustained VT patients is not fully known. The safety and effectiveness of the PCD® Transvene System in this subgroup of VT patients has not been determined.

RESPONSE:

The indication section of the PCD® Model 7217B and the three Transvene® lead manuals have been modified to include the requested information. These modifications are presented on the following pages of the technical manuals:

PCD® Model 7217B - page 2	Model 6966 - page 2
Model 6963 - page 1	Model 6999 - page 1

The relevant section of the manuals read as follows:

> The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated. Current medical research indicates that such patients should:
>
> - have survived at least one episode of a cardiac arrest, presumably due to a ventricular tachyarrhythmia as evidenced be resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; OR
>
> - in the absence of a prior cardiac arrest, have poorly tolerated sustained VT and/or VF, which occurs spontaneously or can be induced despite the best antiarrhythmic drug therapy.
>
> The natural history of patients with hemodynamically stable sustained VT is not well defined. While this patient population was included in the TRANSVENE® clinical study, the study objectives did not include stratification of this specific patient group.

b. **The technical manuals for the Transvene® Leads must state that the leads are for use together as a system. The labeling (where appropriate) must be consistent in all of the Transvene® Lead manuals. The information regarding the Transvene® Leads in the PCD® manual must also be included in the Transvene® Lead manuals.**

RESPONSE:

The Transvene® technical manuals state that the leads are to be used together as a system and the appropriate information regarding the Transvene® leads presented in the PCD® technical manual is also presented in the Transvene® lead technical manuals.

Statements about use of Transvene® leads as a system is presented on the following pages of the Transvene technical manuals:

Model 6963 - page 1

> The Medtronic® TRANSVENE®-SVC Model 6963 is intended for single long-term use in the superior vena cava on coronary sinus and is designed to be used only with a compatible Medtronic implantable tachyarrhythmia control device along with at least one other Medtronic defibrillation lead.

Model 6966 - page 2

> The Medtronic® TRANSVENE®-RV Model 6966 is intended for single long-term use in the ventricle and is designed to be used only with a compatible Medtronic implantable tachyarrhythmia control device along with at least one other Medtronic defibrillation lead.

Model 6999 - page 1

> The Medtronic® TRANSVENE®-SQ Model 6999 is intended for single long-term use only with a compatible Medtronic implantable tachyarrhythmia control device along with at least one other Medtronic defibrillation lead.

c. **There should be an identifying mark on the package label which distinguishes nonthoracotomy leads from thoracotomy leads.**

RESPONSE:

The statement "Thoracotomy Not Required" been added to the outer package of all Transvene® leads. A copy of this label is included in attachment C.

d. **The Warnings and Precautions in the labeling must be identified and reported separately according to FDA's Blue Book memorandum was previously sent to you).**

RESPONSE:

Warnings and Precautions have been identified and are presented separately is the Transvene® lead manuals. They are presented on the following pages:

Model 6963 - pages 2 and 3
Model 6966 - pages 3 and 4
Model 6999 - pages 2 and 3

4. **Provide a copy of the Patient's Manual which includes a reference to use of the non-thoracotomy leads with the PCD® models.**

RESPONSE:

The patient manual entitled "Restoring the Rhythms of Life" contains a reference to the use of non-thoracotomy leads. A copy is enclosed in Attachment E.

Additional changes to the TRANSVENE® technical manuals:

Package Contents

Each lead will be packaged with an end cap included in the package. This has, therefore, been added to the "Package Contents" section of each lead manual. This addition is found on the following pages of the TRANSVENE® leads manuals:

Model 6963 - page 2
Model 6966 - page 2
Model 6999 - page 2

Contraindications

The following contraindication has been added to each of the TRANSVENE® technical manuals.

> The TRANSVENE® lead system is contraindicated for use in any system other than a Medtronic implantable tachyarrhythmia control device system for which it has been tested. Refer to the appropriate Medtronic technical manual for the contraindications to the ICD system.

This contraindication statement is found on the following pages of the TRANSVENE® leads manuals:

Model 6963 - page 2
Model 6966 - page 3
Model 6999 - page 2

C

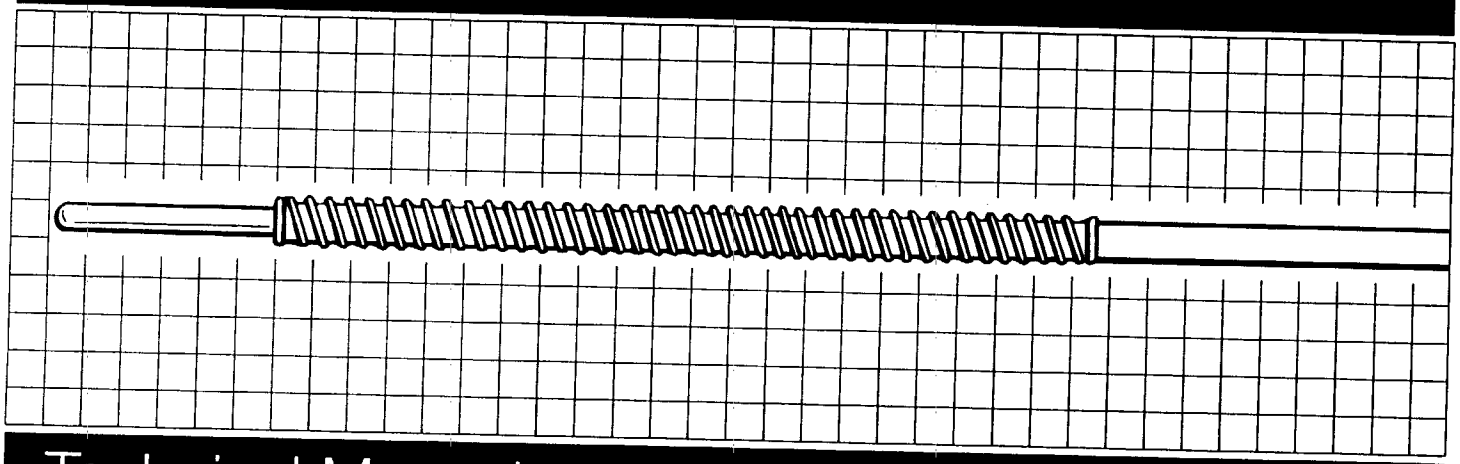
TRADSVERSE
TECHNICAL
MANUAL

Medtronic

TRANSVENE®-SVC

6963

Unipolar, Endocardial, Superior Vena Cava or Coronary Sinus Lead



Technical Manual

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TECHNICAL MANUAL

TRANSVENE®-SVC UNIPOLAR, ENDOCARDIAL, SUPERIOR VENA CAVA OR CORONARY SINUS LEAD FOR CARDIOVERSION AND DEFIBRILLATION

MODEL 6963

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PACKAGE LABELS

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THE PCD® TACHYARRHYTHMIA CONTROL DEVICE

MODEL 7217B TECHNICAL MANUAL

An Implantable Device for the Control of Ventricular Arrhythmias Through Pacing, Cardioversion, and Defibrillation

Medtronic

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SPECIFICATIONS[a,b]

Programmable Functions	Capability	Increments	Programmer Default[c]	Tolerance	Other Notes
Sensing/Pacing					
Mode	VVI				Only mode available
Pacing Rate[d]	30-64, 65, 66-82, 85, 86, 88, 90 ppm	2 ppm	65 ppm	± 1 ppm	
Pulse Width	0.03–1.59 ms	0.03 ms	0.49 ms	– 0.0, + .03 ms	
Sensitivity[e,f]	0.3–2.4 mV	0.3 mV	0.3 mV	± 0.15 mV ± 0.20 mV ± 0.25 mV ± 0.40 mV	For 0.3 mV For 0.6 mV For 0.9–1.5 mV For 1.8–2.4 mV
Pulse Amplitude	2.8 and 5.4 V		5.4 V	2.5 & 5.2 V min	
Refractory After Pace	320–480 ms	40 ms	320 ms	– 20, + 0 ms	
VT Detection					
Enable	ON/OFF		OFF		
VT Detection Interval[g]	280–600 ms	10 ms	400 ms	± 1 ms	TDI should be at least 40 ms longer than FDI
Number of Intervals to Detect	4-52	4	16		NID value applies to all VT Detections
Onset Criterion	ON/OFF		OFF		
R-R Percent[g]	56–62, 66–87, 91–97%	3%	81%	± 0.5%[h,i]	
Onset Counter	ON/OFF		OFF		
Interval Stability[g]	OFF, 30–130 ms	10 ms	OFF	± 1 ms[h]	

a. Due to Medtronic's continuing deveopment, it is not possible to list all currently available programming configurations. See the appropriate Medtronic programmer manual for specific details.
b. Parameter and tolerance values apply at 37° C and 510 ohm load at time of manufacture. Values may vary depending on the specific test procedures used.
c. Programmer default values are associated with the Model 9788 MemoryMod.
d. Escape interval equals pulse interval (–10, + 50 ms).
e. With a 40 ms sine^2 waveform.
f. When using the Cenelec waveform, the rated sensing threshold value will be 1.5 times the rated sine^2 sensing threshold value.
g. With a periodic (constant amplitude and wave shape) signal.
h. Does not include an additional (-0, +10 ms) rounding tolerance associated with each interval measurement.
i. Does not include an additional ± 5 ms rounding tolerance associated with an R-R average calculation.

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Programmable Functions	Capability	Increments	Programmer Default	Tolerance	Other Notes
VF Detection					
Enable	ON/OFF		OFF		
VF Detection Interval[a,b]	240-400 ms	10 ms	320 ms	± 1 ms	FDI should be at least 40 ms less than TDI
Number of Intervals to Detect	6-30	6	18		
VT Therapies	0-4				
Burst					
Enable	ON/OFF		OFF		
Number of S_1 Pulses	1–15	1	6		
S_1–S_1 Interval	50–62, 66–87, 91–97%	3%	84%	± 0.5%[c]	
Number of Sequences	1–15	1	5		
Decrement per Sequence	0–40 ms	10 ms	10 ms	± 1 ms	
Minimum Pulse Interval[d]	150–300 ms	10 ms	200 ms	± 1 ms	
Ramp					
Enable	ON/OFF		OFF		
Initial Number of S_1 Pulses	1-15	1	5		
First R–S Interval	50–62, 66–87, 91–97%	3%	97%	± 0.5 %[c]	
Decrement per Pulse	0–40 ms	10 ms	10 ms	± 1 ms	
Number of Sequences	1–15	1	8		
Minimum Pulse interval[d]	150–300 ms	10 ms	200 ms	± 1 ms	

a. With a periodic (constant amplitude and wave shape) signal.
b. When VF Detection is enabled, the programmed setting for this parameter serves as the minimum interval to identify a VT event.
c. Tolerance does not include rounding tolerances associated with the R–R interval measurement (–0,+10 ms), R–R average calculation (± 5 ms), and the stimulation interval calculation (± 5 ms).
d. The Minimum Pulse Interval selected applies to both Burst and Ramp therapies and is used for all programmed therapies and sequences.

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Programmable Functions	Capability	Increments	Programmer Default	Tolerance	Other Notes
Cardioversion					
Enable	ON/OFF		OFF		
Current Path	Single, Simultaneous, or Sequential		Sequential		
Pulse Width	0.5–2.0 ms	0.5 ms	6.3 ms	+0.2, –0.1 ms	
	2.4–5.9 ms	0.5 ms		+0.2, –0.1 ms	
	6.3–7.8 & 8.1 ms	0.5 ms		+0.2, –0.1 ms	
					Peak voltage with 75 ohm load:
Energy (Stored)	0.2–1.8 joules	0.2 J	0.6 J[a]	± 35%	± 16%
	2.0–15.0 joules	1.0 J		± 15%	± 5%
	16.0–34.0 joules	2.0 J		± 15%	± 5%
VF Therapy	0–4				
Enable	ON/OFF		OFF		
Current Path	Single, Simultaneous, or Sequential[b]		Sequential		
Pulse Width	2.0 & 2.4–5.9 ms	0.5 ms	6.3 ms	+0.2, –0.1 ms	
	6.3–7.8 & 8.1 ms	0.5 ms		+0.2, –0.1 ms	
					Peak voltage with 75 ohm load:
Energy (Stored)	0.2–1.8 joules[c]	0.2 J	34 J	± 35%	± 16%
	2.0–9.0 joules[c]	1.0 J		± 15%	± 5%
	10.0–15.0 joules	1.0 J		± 15%	± 5%
	16.0–34.0 joules	2.0 J		± 15%	± 5%
VT Manual Prescriptions					Programmer-initiated therapies (Manual Prescriptions) do not involve the automatic detection criteria. Only one pacing sequence or therapy per command.
Burst	See Above				
Ramp	See Above				
Cardioversion	See Above				
VF Manual Prescriptions					
Defibrillation	See Above				
Electrophysiological Studies[d]					Delivered: in VVI Mode
S_1–S_1	300–2000 ms	10 ms	600 ms	± 2 ms	Asynchronously
S_1–S_2	150–600 ms	10 ms	400 ms	± 1 ms	Asynchronously
S_2–S_3	150–600 ms	10 ms	OFF	± 1 ms	Asynchronously
S_3–S_4	150–600 ms	10 ms	OFF	± 1 ms	Asynchronously
Number of S_1	1–20	1	8		
	20–95	5			

a. Default setting is 34.0 J for therapy #3 and #4
b. The programmed current path applies to all four VF therapies.
c. Energy range available only for Therapies #1 and #2.
d. Specifications may vary with the specific Medtronic programming system used.

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Programmable Functions	Capability	Increments	Programmer Default	Tolerance	Other Notes
Electrophysiological Studies (continued)					
High Rate Pacing (Fib)					
Manual–Interval	100-400 ms	10 ms	400 ms	± 1 ms	
Automatic					
Interval Limit	100–200 ms	10 ms	200 ms	± 1 ms	
	210–250 ms	20 ms		± 1 ms	
	300–400 ms	50 ms		± 1 ms	
Telemetry					
Permanent	OFF, 1-63 hrs Continuous	1 hr	OFF		Based on 4,000 events per hour
Type	Marker Channel		Marker Channel		
	EGM–Near Field				PACE/SENSE to SENSE2
	EGM–Far Field				PULSE1 to COMMON
Manual Capacitor Charging					Peak voltage with 75 ohm load
	0.2–1.8 J	0.2 J		± 35%	± 16%
	2.0–15.0 J	1.0 J		± 15%	± 5%
	16.0–34.0 J	2.0 J		± 15%	± 5%

Nonprogrammable Functions	Capability	Tolerance	Other Notes
Blanking	120 ms[a,b]	–20, +0 ms[c]	After sensed event
	320 ms	–20, +0 ms[c]	After paced event
	300 ms	–20, +90 ms[c]	After Charging Period
	300 ms	–20, +0 ms[c]	After VT/VF therapy or failure to synchronize
Refractory	200 ms	–20, +0 ms[c]	After sense, during CV Synchronization Sequence
	400 ms	–20, +90 ms[c]	After Charging Period
	520 ms	–20, +0 ms[c]	After VT/VF therapy or failure to synchronize
VF Synch Period	500 ms	± 1 ms	If no sensed event, the defibrillation shock is delivered
Escape Interval	1000 ms	±2 ms	After VT/VF therapy
Maximum Allowable Charging Period	34.95 seconds	+20, –10 ms	For cardioversion and VF therapy

a. Using a periodic (constant amplitude and waveform) signal.
b. Measured from the time of the previous sensed event.
c. Based on a 40 ms sine^2 waveform at twice the programmed sensitivity threshold.

Nonprogrammable Functions	Capability	Tolerance	Other Notes
Time Between Sequential Pulses	244 µsec	± 225 µsec	
Disabling of VT Detection	64 events		After a VF detection
Rate Limit (Protective Feature)	120 ppm	± 20 ppm	Does not apply during therapies or programmed high rates
Input Impedance (min)	50 Kohms		

Data	Range	Tolerance	Other Notes
PCD Status			
Memory Retention	OK, Reset (by Power Inadequate, Memory Loss, Both)		
Charge Circuit	OK, Timeout, Inactive		
Last Charge Time	10 ms – 34.95 seconds	+ 20, – 10 ms	
Battery Voltage	Measured Voltage	± 200 mV	
VT Onset Counter	0–65,535		
VT Episode and Therapy Data			
Episode Count	0–255[a]		
VT Therapy Success Count	0–255[a]		Reports for each of 4 therapies
Number of VTs PCD Ineffective	0–255[a]		
PCD Efficacious on Last VT	YES/NO		
Last Therapy Used	0–4		
Number of Sequences in Last Therapy	1–15		Applies to Burst and Ramp therapies only
R-R Average for Last Pace Therapy	None, 150–600 ms		Applies to Burst and Ramp therapies only

a. An increment to a counter that causes the value to exceed the maximum will cause the counter to go to the minimum value.

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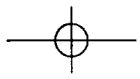
Nonprogrammable Functions	Capability	Tolerance	Other Notes
VF Episode and Therapy Data			
Episode Count	0–255[a]		
VF Therapy Success Count	0–255[a]		Reports for each of 4 therapies
Number of VFs PCD Ineffective	0–255[a]		
PCD Efficacious on Last VF	YES/NO		
Last Therapy Used	0-4		
Last Episode Sequence	20 intervals		Prior to last VT or VF episode detection
Cycle Length Intervals	100 – 2000 ms	+ 12, –2 ms	
Last Therapy Sequence	10 intervals		Following last VT or VF therapy delivered during last episode
Mechanical Dimensions			
Size: Height	101 mm		
Length	70 mm		
Width	20 mm		
Mass	197 grams		
Displacement Volume	113 cc		
External Shield	Titanium		
Battery	Lithium Silver Vanadium Oxide		(6.4 V nominal)
Factory Preset Parameters	As indicated on Package Labeling		

a. An increment to a counter that causes the value to exceed the maximum will cause the counter to go to the minimum value.



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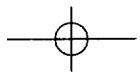

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Restoring The Rhythms Of Life

Medtronic PCD™ Device

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Introduction

Your doctor has asked you to read this booklet to help you understand why the Medtronic PCD™ tachyarrhythmia control device is being recommended to treat your rapid heart rhythm. This booklet will answer many of your questions about the PCD device and about which activities you can participate in and which to avoid. You will learn what the PCD device is designed to do and how it treats your rapid heart rhythm. The booklet discusses how the device might affect you and your family. A glossary at the end defines words you may hear your doctors or nurses use.

Receiving a PCD device need not be a frightening experience. Devices have been in use for several years and have helped people like you lead normal fulfilling lives. If you have questions after reading this booklet, write them down and ask your doctor.

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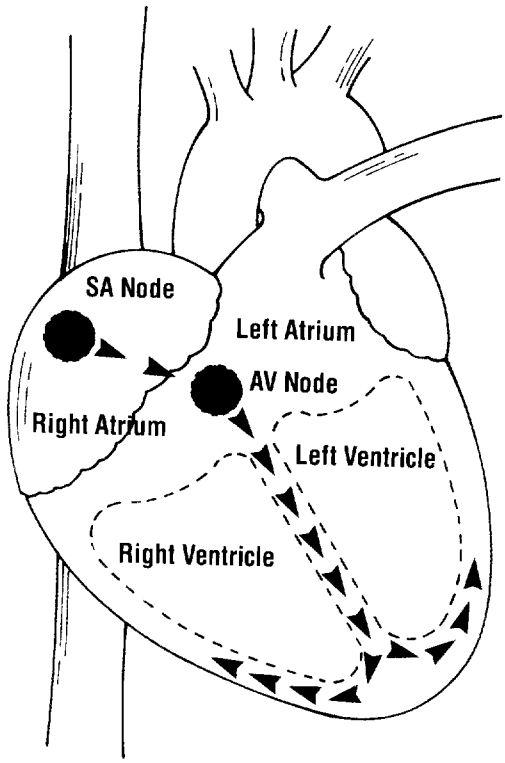
The Heart Has A Natural Rhythm

The normal heart is about the size of your clenched fist small for the amount of work it does. This special muscle pumps about five quarts (4.7 liters) of blood throughout your body each minute, or 75 gallons (284 liters) every hour. Its steady, rhythmic pumping sends oxygen-rich blood to all your body's cells.

Your heart has two upper chambers, the **atria**, and two lower chambers, the **ventricles**. The atria pump blood into the ventricles. The right ventricle then pumps blood to the lungs while the left ventricle pumps blood to all your body's organs. Normally, your heart's pumping is controlled by steady electrical signals produced by your heart's "natural pacemaker," the **sinoatrial (SA) node**. The signals travel through the atria to a junction in the middle of the heart, the **atrioventricular (AV) node**. The signals then continue throughout the ventricles. The heart then rests until the next pulse begins the cycle over again.

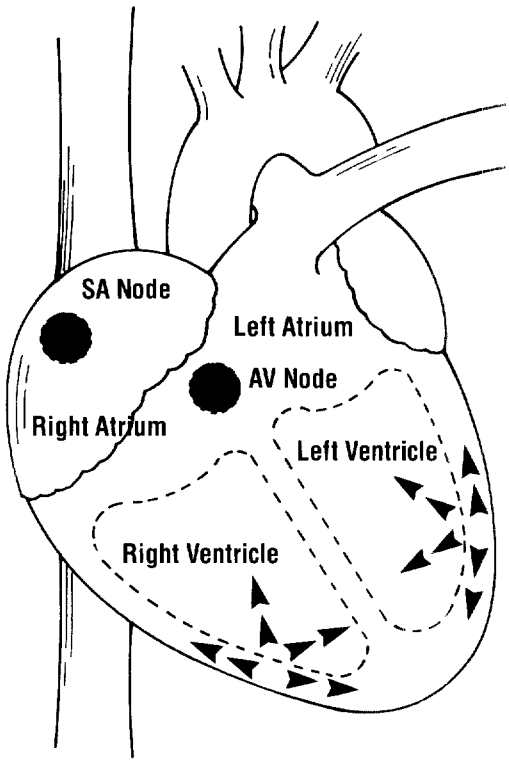
These signals keep your heart beating steadily and rhythmically at about 60 to 80 beats per minute.



The heart's natural pacemaker, the sinoatrial node, sends out electrical signals that make the heart beat. These signals move down the right atrium and split into two main "transmission" lines to the pumping chambers (the ventricles) to make them contract uniformly.

When The Heart Beats Too Fast

The heart's electrical system may develop a defect which prevents the electrical signals from reaching the pumping chambers regularly or which causes the signals to be generated erratically or too quickly. When the signals are generated too quickly, the heart beats too fast. This rhythm disorder is called a **tachyarrhythmia**. Tachyarrhythmias may result from heart disease such as coronary artery disease, heart attack, or heart muscle disease (cardiomyopathy).



If your heart's electrical signals come from places other than your heart's natural pacemaker, an abnormal rhythm called an arrhythmia may result. If the arrhythmia is a rapid one, it is called a tachyarrhythmia.

When your heart beats too quickly and the impulses start in the lower chambers, the tachyarrhythmia is called a **ventricular tachycardia** (VT).

When your heart goes into VT it may not pump blood as efficiently as it does during a normal rhythm. Rapid contractions prevent it from filling adequately with blood between beats. Less blood reaches your brain. During VT you may feel your heart pound or feel faint or dizzy. You may even pass out. VT can be dangerous, even life-threatening, if not properly treated.

When a ventricular tachyarrhythmia becomes unstable and irregular, it is called **ventricular fibrillation** (VF). During VF, your heart beats in a disorganized manner. It quivers. No blood is pumped and your body is quickly starved of oxygen. If your heart goes into VF, you usually pass out within a few seconds. Your heart's electrical activity may become so erratic that your heart no longer pumps blood at all, a situation commonly called a **cardiac arrest**.

Cardiac arrest usually occurs without warning. Emergency medical teams try to revive people from cardiac arrest by using the paddles of machines called external defibrillators to apply strong defibrillation shocks to the chest. These shocks pass through to the heart, stop the erratic electrical activity, and allow the heart to return to a more regular rhythm.

Unfortunately, emergency teams and their external defibrillators are rarely available in the first moments of cardiac arrest. The PCD device contains an **internal** defibrillator and pacemaker. The device acts as an automatic "watch dog" during those first crucial seconds. When your heart goes into a tachyarrhythmia the PCD device can pace or shock your heart out of VT or shock it out of VF.

Why The PCD System Has Been Recommended

Your cardiologist has studied your tachyarrhythmia and has determined that it could be dangerous and could occur again. The PCD system has been recommended because it automatically detects this tachyarrhythmia and stops it with a carefully selected electrical therapy.

Although the device is not a cure, it acts as a safety net against cardiac arrest due to VT or VF. You and your family should view the device as a symbol of security that can restore personal confidence.

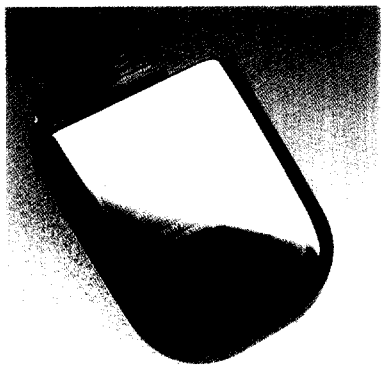
Your doctor will tell you why the PCD has been recommended for you. Patients who have similar devices have experienced one or more of the following conditions:

- At least one episode of VT or VF
- Previous cardiac arrest
- Life-threatening and recurrent tachycardia
- Drug therapy that does not control the tachyarrhythmia
- Severe side effects from drug therapy
- An arrhythmia that cannot be controlled with surgery

What Is The PCD System?

The PCD device is similar to a pacemaker. It is implanted inside your body and works automatically. The device is designed to monitor your heart rhythm and to stop dangerous tachyarrhythmias such as VT and VF. When the PCD detects VT or VF, it delivers electrical stimuli to return your heart to a more normal rhythm.

Your cardiologist will program the device to deliver the best therapy for you. The therapies may start with mild pacing impulses to interrupt your arrhythmia and progress to stronger impulses, as needed.



The PCD pulse generator is implanted surgically and continually monitors your heart rhythm.

Parts Of The PCD System

The PCD system has three main parts. The **pulse generator** and the **leads**, which connect the generator to your heart, are implanted inside your body. The third part, an **external programmer**, remains in your doctor's office for use during follow-up care.

Pulse Generator

The pulse generator continually monitors your heart rhythm, watching for your arrhythmia. When it detects one, it delivers an electrical therapy to stop the arrhythmia and return your heart to a more normal rhythm. The pulse generator contains a battery, microprocessor (small computer), and electronic circuitry.

The pulse generator's memory stores important information that your doctor retrieves during follow-up visits. The device recalls the number and types of treatments you receive, how successful each is in stopping your arrhythmia, what your heart was doing during your most recent episode, and the status of the device's batteries and programmed settings.

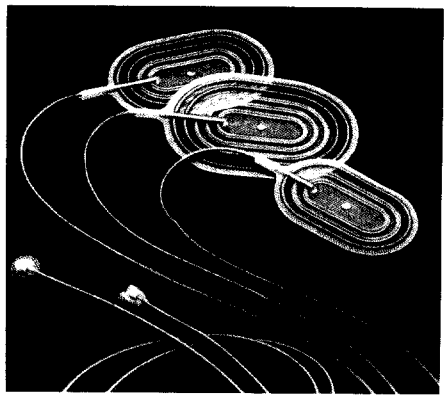
Leads

The wires that connect the pulse generator to your heart are called leads. They carry electrical impulses between the generator and your heart.

There are two different lead systems. Your cardiologist will determine which system is best for you.

The **epicardial** lead system involves placing wires on the outside surface of your heart. Two or three oval-shaped patch leads carry electrical impulses from the pulse generator to the heart

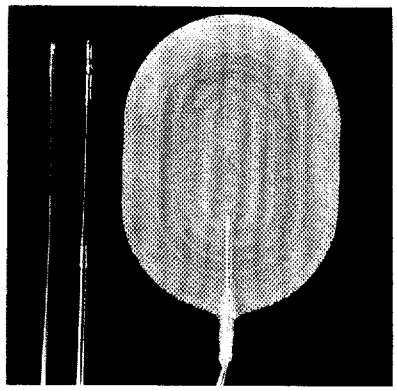
The **transvenous** lead system consists of two or three leads placed on the inside surface of your heart and a patch electrode. The leads are threaded through a vein and into your heart without the need for open-chest surgery.



Epicardial leads are placed on the outside surface of the heart.

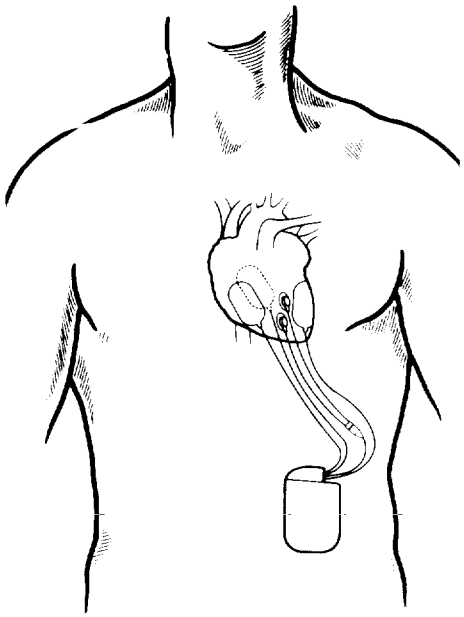
Programmer

Prior to hospital discharge, your nurse will use the external programmer to "talk" to your pulse generator - to fine-tune it to detect and treat your arrhythmia properly. The nurse will also use the programmer during follow-up visits to retrieve many useful facts stored in the pulse generator's memory. The programmer operates with the use of radio signals much like those in a television remote control. Follow-up sessions last about half an hour.



Transvenous leads are placed on the inside surface of the heart.

How Your PCD Device Is Implanted



The PCD is implanted near the stomach. The leads connect the generator to the heart.

Your doctor will decide what type of surgery is needed to implant the pulse generator and leads. He or she will base the decision on your size and shape, whether you have already had chest surgery, and what method is safest for you. Whichever method is used, the pulse generator will likely be implanted under the skin or muscles near your stomach.

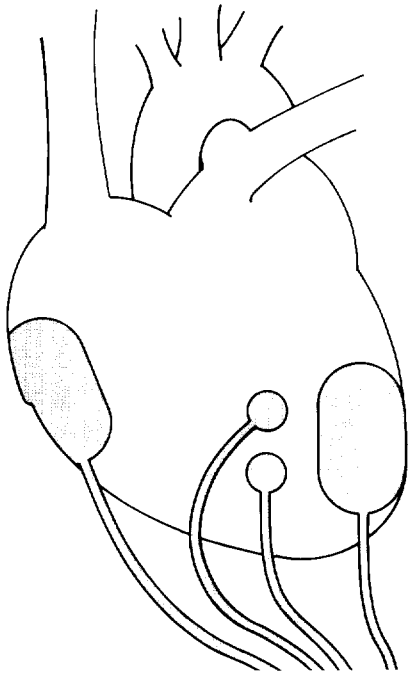
If the **epicardial** lead system is used, the leads will be attached to the outside (epicardial) surface of your heart. You will be under general anesthesia for this open-chest operation.

If you receive a **transvenous** lead system, open-chest surgery will not be required. Instead, a small incision will be made so that the doctor can pass the leads into your heart through a vein and attach them to the inside of your heart. A patch lead may also be implanted under the skin.

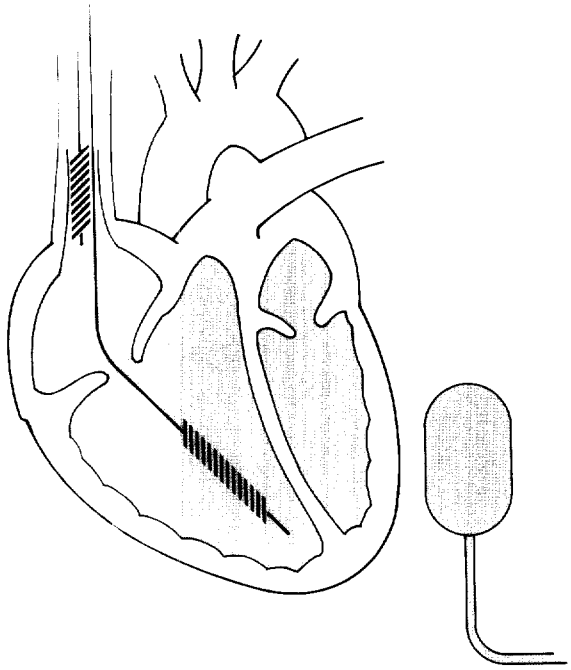
During surgery, your cardiologist will test the PCD system to ensure that it is working properly. During this test, the doctor will start your arrhythmia and allow the device to detect the arrhythmia and to correct it on its own. This test is done to ensure that the device will do its job if/when you experience your arrhythmia away from the hospital.

After the operation, your heart rhythm will be carefully monitored.

Before you leave the hospital, your doctor may test the device by starting the arrhythmia and again having the device correct the rhythm. This test may also let you know what the therapies might feel like (see **What The Treatments May Feel Like**).



In the epicardial lead system, the leads are placed on the outside of your heart.



In the tranvenous lead system, the leads are positioned on the inside of your heart.

How Your PCD System Works

When your PCD device detects your tachyarrhythmia, it tries to correct it with therapies programmed by your physician. The device can be programmed to deliver therapies that begin mildly and become progressively stronger, as needed. It can deliver three types of therapy: *pacing*, *cardioversion*, and *defibrillation*.

Pacing: If your VT is relatively slow, your doctor may program the device to deliver small, rapid **pacing** signals when it detects the VT. If the normal rhythm is restored, no further treatment is delivered.

Cardioversion: If pacing does not stop the arrhythmia, the device can be programmed to deliver stronger impulses. These **cardioversion** shocks may progress from low energy to high energy, as needed.

Defibrillation: If the device detects VF, it will send a high energy shock to your heart. This **defibrillation** shock breaks up the arrhythmia so a more normal rhythm can be restored.

Bradycardia Pacing: In some cases your heart may beat too slowly. If the PCD detects a very slow heart rate, it will pace your heart until it maintains a normal rate.

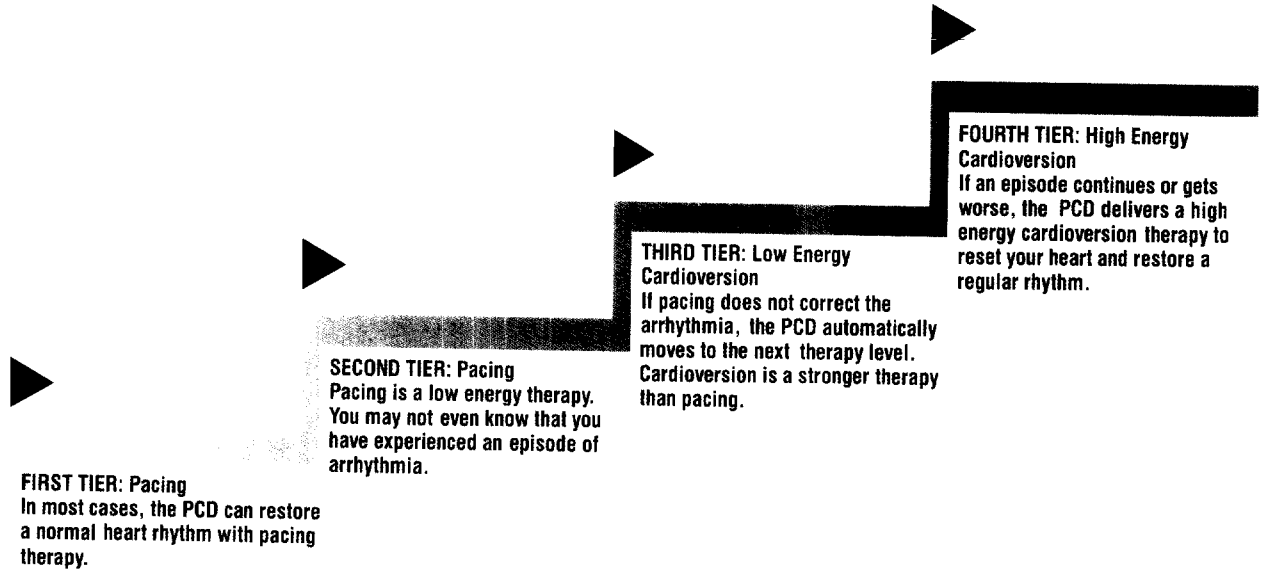
For Your Comfort And Safety: A Step Approach

Your physician can program the PCD device to deliver therapies in a stepped approach to increase your comfort without compromising safety. By first trying mild therapies, the device may correct your arrhythmia without your even knowing it, and the higher energy shocks may seldom be needed.

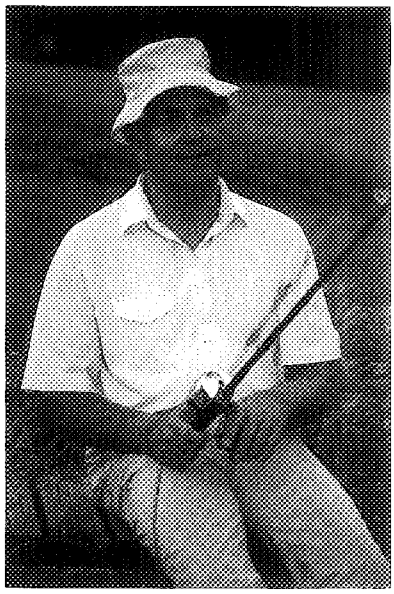
What The Treatments May Feel Like

Patients who have the PCD device have described the experience of receiving the therapies in the following way:

- Pacing: Most patients do not feel these impulses. A few do and describe the impulses as painless. Clinical data indicates that about 90% of VTs are stopped by pacing.
- Cardioversion: Patients often describe this shock as "a thump on the chest" and associate it with mild discomfort.
- Defibrillation: Most people lose consciousness when their hearts go into VF, so they are not aware of receiving this shock. Others who are awake during a defibrillation shock describe it as feeling like a "kick in the chest." They say it startles them, but passes very quickly and does not bother them after that. In fact, they find it reassuring. Some people find the shock temporary and fleeting but also distressing.



Example of how the PCD may be programmed to treat VT.



As you adapt to living with the PCD, you will be able to resume your normal activities and hobbies.

Living With Your PCD Device

As you recover, follow your doctor's suggestions about resuming normal activities. Expect a gradual recovery over a number of months. At first you may be very aware of the device, but soon you will begin to think of it as a friend and confidence builder.

Because the PCD device is a life-saving aid, you may be able to enjoy activities that take you far from emergency care.

The PCD device may prevent you from passing out if your heart begins its fast rhythm. The device may also enable you to take fewer arrhythmia medications or even to discontinue them. If it does, you may feel better as any drug side effects diminish. Your doctor will decide which medications you should take.

The First Few Weeks

As you recover from the surgery, follow your doctor's directions including:

- Reporting any redness, swelling, or drainage from your incisions
- Avoiding lifting heavy objects, unless your doctor says otherwise
- Exercising, bathing, and walking according to your doctor's directions
- Avoiding tight belts or other clothing that may irritate the skin over the pulse generator
- Limiting arm movements as directed by your doctor, if you have a transvenous lead system
- Avoiding contact sports that could result in blows to your abdomen
- Telling your doctors and dentist that you have the PCD device. They may need to give you antibiotics before and after dental work or surgery to prevent infection.

Activities And Exercise

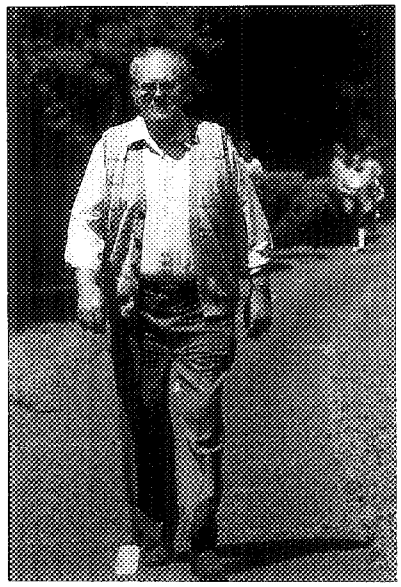
Depending on your condition, your doctor may ask you to avoid situations where a few seconds of unconsciousness due to your arrhythmia could be dangerous to you or others. Such activities may include driving, swimming or boating alone, or climbing a ladder.

You may be able to resume driving, depending on the laws in your area and on your individual condition. Your doctor will decide what is best for your safety and the safety of others.

Upon the advice of your physician, you will gradually return to your normal lifestyle without fear of harming yourself or your PCD device. Such activities might include:

- Returning to your job
- Traveling
- Bathing, showering
- Resuming sexual activity
- Pursuing hobbies or recreation such as gardening, walking, bowling, golfing, or fishing

The key to returning to your daily activities is that they should make you feel better, not worse.



A program of gradually increased activity and heart conditioning will help restore your confidence in yourself and in the device.

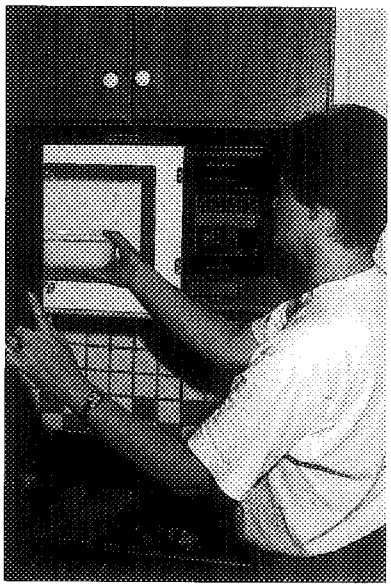
Precautions: Operating Household Appliances And Tools

The PCD device's built-in features protect it from most interference produced by electrical appliances. You can safely operate most household appliances and tools that are properly grounded and in good repair including:

- Microwave ovens
- Televisions, AM/FM radios, VCRs
- Tabletop appliances such as toasters, blenders, and electric can openers
- Hand-held items such as hair dryers and shavers
- Major appliances including washers, dryers, and electric stoves
- Electric blankets and heating pads
- Electric knives
- Spark-ignited internal combustion engines such as lawn mowers, leaf-blowers and automobiles

You can also safely operate the following office and light shop equipment that is properly grounded and in good repair:

- Electric typewriters and copying machines
- Machine shop tools such as drills and table saws
- Personal computers



You can safely operate kitchen appliances such as microwave ovens that are properly grounded and in good repair.

Things To Avoid

Avoid strong magnetic or electric fields which can interfere with the function of the PCD device. To minimize interference, stay an arm's length away from the following sources of strong electric or magnetic fields:

- Magnets
- Stereo speakers
- Airport security wands
- Industrial equipment

- Arc or resistance welders
- Induction furnaces
- Large generators and power plants
- Antennas typically used in the operation of ham or citizens band (CB) radios

Avoid the maintenance or repair of any electrical or gas-powered appliance or tool.

If you have questions about any situation or piece of equipment, contact your doctor.

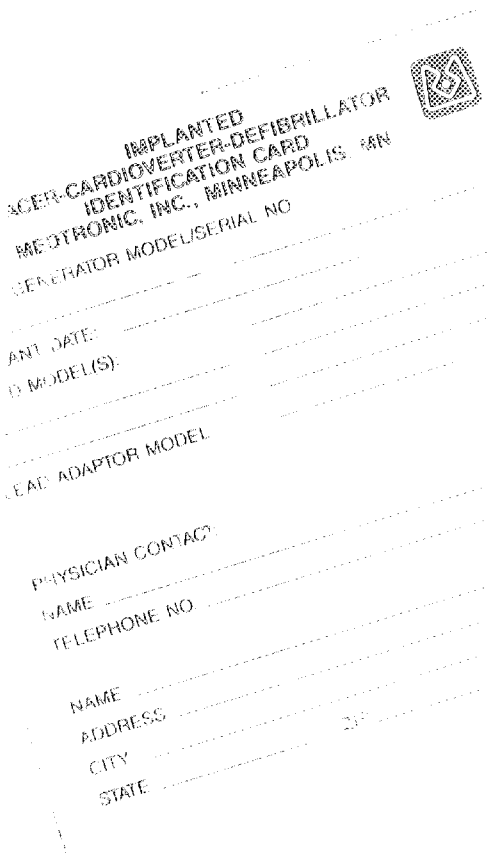
Airport Security And Medical Procedures

Your implanted pulse generator may set off airport security systems. The hand-held scanning tool used by airport security personnel could temporarily suspend the PCD's arrhythmia detection. So, when you travel, make sure to present your PCD identification card to airport security and ask them to clear you after only a hand search (see **PCD Identification Card**).

Hospitals sometimes have magnetic resonance imagers which contain strong magnets that can temporarily suspend the PCD device's arrhythmia detection. They are housed in rooms that are clearly marked with signs to notify you about the strong magnets inside. Do not go past these signs.

Some medical procedures, such as radiation therapy, magnetic resonance imaging, cautery, or diathermy may interfere with the PCD device. If you are to undergo a dental or surgical treatment, tell your dentist or doctor that you have the PCD device and have them contact your physician to discuss the best way to handle the treatment.

Present your PCD identification card to airport security and ask to be cleared for passage with a hand search only.



Carry your PCD identification card with you at all times and wear a Medic Alert chain.

PCD Identification Card

You will be given a PCD identification card before you leave the hospital. Carry this with you at all times. In case of an accident, the card will tell those attending you that you have the PCD device. It will give them important information about the device and an emergency phone number to call if there are questions or problems.

If you need a new identification card, send the information from your present card along with any changes to:

Device Registration Services
Medtronic, Inc.
7000 Central Avenue, N.E.
P.O. Box 1399
Minneapolis, MN 55432 USA

Medic Alert

Ask your doctor or nurse for information and an order form for the Medic Alert chain, bracelet, or necklace. If you become unconscious or very ill, this chain will tell those caring for you that you have the PCD device. Medic Alert is a world-wide program (not associated with Medtronic or this hospital) which gives emergency information about people who have medical conditions that are not easily seen.

Follow-up Visits

Follow-up visits are important to ensure that your device continues to work properly. During these visits your doctor checks the battery status, monitors any drugs you are taking, and checks for possible interactions with the PCD device. Also, as your condition changes, your doctor may reprogram the device to better treat your arrhythmia.

Your first follow-up visit will likely be one month after you receive the device, then two months later and every three months after that (i.e., at 1, 3, 6, 9, and 12 months).

Be sure to keep your regular appointments for follow-up visits. They are important to ensure that your device is working properly.

Replacement

Because the pulse generator runs on a battery that is sealed inside it, the device will have to be replaced in three to five years. This procedure is typically much easier and quicker than the first implant was. How long the PCD device lasts depends on the number and types of treatments it delivers.

At replacement time, the doctor will make a new incision over the old scar in your abdomen, remove the old pulse generator, and disconnect and check the implanted leads. If the leads are working properly, the doctor will then connect them to the new pulse generator. Usually, the leads will not have to be changed.

Your Responsibilities

Although the PCD device monitors your heart automatically, you should follow your doctor's directions and keep all your appointments. Make sure to:

- Ask your doctor about anything unusual or anything you do not understand about your therapy.
- Follow your doctor's schedule for any medicines prescribed.
- Carry your identification card with you at all times.
- Tell your family doctor, dentist, and local emergency medical team that you have the device.
- Ask your doctor about the activity level that is best for you.

Ask your doctor or nurse about anything you do not understand.

When To Call Your Doctor

Phone your cardiologist if you:

- Receive a shock from the device (see **What To Do If You Receive A Shock**)
- Have symptoms of your arrhythmia that last longer than three minutes or the length of time specified by your doctor
- Notice any swelling, warmth, or drainage at any incision
- Develop a fever that does not go away in two or three days
- Have any questions about the device or your medications
- Plan to travel or move
- Notice anything unusual, such as new unexplained symptoms or symptoms such as those you had before you received the device

What To Do If You Receive A Shock

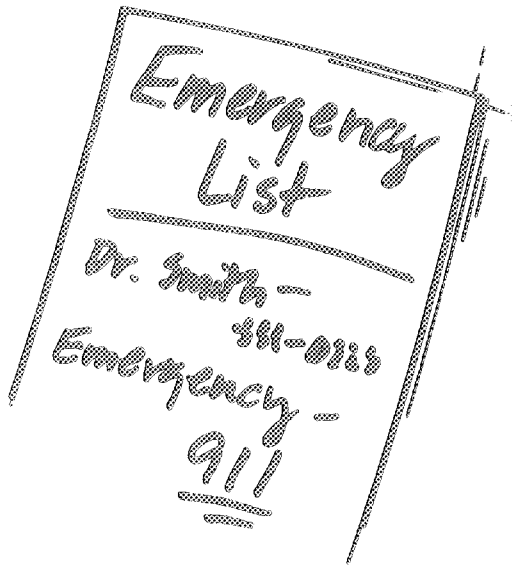
It is a good idea to have an emergency plan. There is space in the back of this booklet for local emergency medical phone numbers and information about your current medications. Keep this information near your phone.

If you feel the symptoms that tell you your arrhythmia has begun:

1. Stay calm and move to where you can lie down or sit comfortably.
2. Have someone stay with you throughout the event, if possible.
3. Have a friend or family member phone for an ambulance if you receive shocks and remain unconscious for more than a minute.
4. If you do not feel well after the shock, have someone call your doctor and help you prepare to be taken to the emergency room of the nearest hospital.
5. If you feel fine after the shock, you do not need to seek medical attention. Instead, call your doctor at your earliest convenience. For example, if the shock occurs at night, call the next morning. Someone there will ask you questions such as:

- What were you doing right before the shock?
- What symptoms did you notice before the shock?
- How did you feel right after the shock?

Anyone touching you while the PCD device shocks you might feel the muscles of your chest and upper arms contract and might see you jump as though startled. The discharge will not harm the person touching you. It is no cause for worry, and is a sign that the device is doing its job.



It is a good idea to have an emergency plan and to keep it near your phone.

What Your Family And Friends Should Know

Because the PCD device is designed as a life-saving aid, your family and friends may feel more relaxed about being alone with you and traveling with you away from emergency medical care.

Emotions: Adjusting To The Device

Give yourself and your family a few months to adjust to living with your PCD device. Most people develop a positive attitude toward the device and view it as a friend. At times, some feel depressed, anxious, vulnerable, angry, or afraid. These feelings are normal. They may come and go or may linger for a few months.

You may also want to speak to other patients who have the PCD device and ask them how their families have adjusted to the device. Ask if there is a support group of patients who have the device.

With time, any feelings of vulnerability should recede and your confidence will return as you resume work, activities, and a full family life.

Your family has likely been a big support for you during your hospitalization. Encourage them to learn about your PCD and about how they can continue to support you at home. If they have any questions or concerns, have them call your doctor.

Some friends and family members may want to receive training in cardiopulmonary resuscitation (CPR).

Travel

With your doctor's permission, you will be free to travel with the PCD device. When you plan a trip, remember to:

- Contact your doctor for instructions on whom to call in an emergency.
- Show your ID card to airport security to avoid being searched with a hand-held magnetic scanner.
- Arrange with your doctor to see another physician if you will be away for more than three months.
- Wear your Medic Alert bracelet at all times.

Give yourself and your family some time to adjust to the PCD device.

Common Questions

Q. Will I notice the device once it has been implanted?
A. During the first few months you may be aware of the device's presence and weight in your body, but you will soon grow used to it as it allows you to live a fuller lifestyle.

Q. Will I be able to do things I enjoy, like walking and fishing?
A. As you feel better, and with the advice of your doctor, you should be able to go back to work and resume the activities you enjoy.

Q. Will the PCD device cure my heart disease?
A. No, it will not. The PCD device is designed only to detect your tachyarrhythmia and to try to correct it when it occurs. It will not prevent the arrhythmia from happening. The underlying disease that causes your tachyarrhythmia can be treated separately. The device will not cure the disease or prevent its progression.

Q. Will the device show under my clothes?
A. Most people will not notice you have the device. You will be able to wear all your normal clothes. If you wear form-fitting clothes, such as a swimsuit, the device will appear as a bulge near your beltline.

Q. Will I be able to stop taking drugs once I have the device?
A. Your cardiologist will determine which, if any, drugs you will have to take. Some people are able to reduce the dosage of drugs or even to stop taking them altogether.

Q. What do the shocks feel like?
A. People describe the experience of receiving a shock in many different ways. A cardioversion shock may feel like a thump in your chest. You will not feel the defibrillation shock if, like most people, you pass out when your heart goes into VF. People who receive this shock when they are awake sometimes describe it as feeling like a kick in the chest. They say it startles them but the feeling passes very quickly

Q. If someone is touching me when the device shocks me, will they get a shock too? Will they feel anything?
A. A person touching your back or chest while you are being shocked might feel the muscles of your chest and upper arms contract, or might see you jump as though startled. These are harmless signs that the device is doing its job.

Q. Will I be able to travel after I get the device?
A. Yes, you will be free to travel. Before doing so you should:

- Contact your cardiologist for instructions on whom to contact in case of an emergency.
- If you plan to be away for more than three months, make arrangements through your physician to see another doctor in the area you are visiting.
- Wear your Medic Alert bracelet and carry your PCD identification card.
- Show your ID card to airport security for clearance involving only a hand search.

Q. How long will the PCD device last?
A. The PCD device may last three to five years, depending on how many and what types of therapies it delivers. Generally, the fewer therapies it delivers, the longer the device lasts.

Q. How will my doctor know when it is time to replace the device?
A. During your follow-up visits, your cardiologist will check your device to find out how much energy remains. The doctor will schedule a replacement before the battery has been depleted.

Q. If the device is automatic, why must I come in for check-ups?
A. Follow-up visits are important to ensure that your device continues to work properly. They permit your doctor to check the battery status, monitor any drugs you are taking, and check for possible drug interactions with the PCD device. Also, as your heart's condition changes, your doctor may reprogram the device to best treat your arrhythmia.

Questions To Ask My Doctor

Use this page to record questions you want to ask your physician.

Tachyarrhythmia Glossary

Arrhythmia - any abnormal rhythm of the heart. Fast arrhythmias are called tachyarrhythmias or tachycardias. Slow arrhythmias are termed bradyarrhythmias or bradycardias.

Atrium - the heart is divided into two upper chambers and two lower chambers. Each upper chamber is called an atrium. Each lower chamber is called a ventricle.

Bradycardia - a slow heart rate, usually less than 60 beats per minute.

Contraction - the shortening of the heart muscles which forces blood out of the heart and into body tissues.

EKG or ECG (electrocardiogram) - a recording of your heart's rhythm printed on a paper strip. The recording is made by an electrocardiograph. Cardiologists use the ECG to determine how electrical impulses flow through the heart.

Electrocautery - an electrical current used to stop bleeding or to make a cut through tissue.

Electrode - the exposed metal tip or coil at the end of a lead.

Electromagnetic field - a magnetic field produced by a device that relies on electric current as its power source. An electromagnetic field does not interfere with the operation of the PCD device unless it is strong enough to cause electromagnetic interference (EMI). Some sources of EMI include arc welders, radio transmission antennas, and power plants.

Electrophysiologic (EP) study - tests used to measure the electrical signals of the heart. The results of an EP study help the electrophysiologist diagnose tachyarrhythmias, decide which treatments will best prevent or control them, and assess whether the treatments are doing their job.

Endocardial - the inside surface of the heart chambers. Leads may be placed on the endocardial surface of the heart via a vein.

Epicardial - the outside surface of the heart. Leads are placed on the outside surface of the heart during open-chest surgery.

Heart attack - also called a myocardial infarction, is caused by the blockage of an artery in the heart. When a cardiac artery is blocked, little or no blood gets through to supply the heart muscle and part of the heart muscle dies. A heart attack differs from cardiac arrest in that a heart attack is caused by a blocked artery, not by an electrical problem. Patients who have had heart attacks are frequently at high risk for cardiac arrest due to arrhythmias.

Implanted - placed inside the body. The pulse generator is implanted under the skin in the abdomen and the leads are implanted on the outside or inside surface of the heart.

Incision - a cut made in the body during surgery.

Leads - insulated metal wires which carry electrical signals between the pulse generator and the heart.

Normal sinus rhythm - the heart's normal, regular rhythm that originates from the sinoatrial node.

PCD™ device - the brand name for the implantable tachyarrhythmia control device manufactured by Medtronic, Inc. The PCD system has three parts: a pulse generator, leads, and an external programmer.

Pulse generator - the part of the PCD system that is implanted in the body under the skin. It produces the electrical signals that detect and stop an arrhythmia and return it to a more normal rhythm.

Sinoatrial (SA) node - the heart's natural pacemaker, located in the right upper (atrial) chamber. The heart's electrical signals normally start here and travel through the heart, causing it to beat regularly.

Sudden cardiac death (SCD) - cardiovascular collapse due to an electrical problem in the heart such as ventricular fibrillation. The PCD system is designed to reduce the risk of sudden cardiac death by detecting and stopping arrhythmias before they become life-threatening.

Syncope - loss of consciousness due to a lack of blood reaching the brain.

Tachycardia - a rapid heart rhythm, usually more than 120 beats per minute. Tachycardia symptoms may include dizziness, faintness, palpitations, chest pain and shortness of breath.

Transvenous - passed through a vein. To implant a lead transvenously, the surgeon makes a small incision near the collar bone and threads the lead inside the vein and into the heart (see endocardial).

Ventricle - the heart is divided into two upper chambers and two lower chambers. Each lower chamber is called a ventricle.

Ventricular fibrillation (VF) - a very fast, irregular heart rhythm caused by abnormal electrical signals coming from several areas of the ventricle. The heart does not beat rhythmically. Instead, it quivers rapidly so that not enough blood reaches the brain or other organs. This rapidly causes unconsciousness. An episode of VF is the most common explanation for cardiac arrest. A person who experiences VF needs immediate medical attention to survive.

Ventricular tachycardia (VT) - a very fast but regular heart rhythm caused by abnormal electrical signals. The heart beats so quickly that it cannot pump enough blood to the brain and other organs. VT may cause symptoms of dizziness, faintness, palpitations, or shortness of breath in some patients.

Notes

If you receive a treatment from the PCD device, please note:

- The date and time of the treatment
- What you were doing just before and after the treatment
- What physical sensations you had just before and after the treatment

PCD System And Personal Information

Ask your cardiologist or nurse to complete the important information on this page.

PCD device model number .....

PCD device serial number .....

Date implanted .....

Programmed lower rate .....

Programmed values:

Rates above ..... bpm are treated as VT

Rates above ..... bpm are treated as VF

If you receive a treatment from the device, or notice anything unusual, call your doctor or EP nurse:

Electrophysiologist ..... Phone # .....

Electrophysiology Nurse ..... Phone # .....

Cardiologist ..... Phone # .....

Emergency Medical Service: Phone 911

Medications .....

.....

.....

Hospital ..... Phone # .....

Address .....

Disclosure

Intended Uses

The Model 7217B PCD device is intended for use in patients who are at risk of sudden death due to ventricular tachyarrhythmia. See the technical manual for detailed information regarding the intended use of the device.

Contraindications

The Model 7217B PCD device is contraindicated:

- for patients with transient ventricular tachyarrhythmias due to reversible causes.
- for patients with transient ventricular tachyarrhythmias due to other factors, e.g., myocardial infarction and electrocution.
- for treatment of atrial arrhythmias.

Warnings/Precautions

The physician should be aware of the following considerations:

- Underlying cardiovascular disease may alter the heart's electrophysiological characteristics and the efficacy of the programmed parameters of the Model 7217B PCD device.
- Concomitant pacemakers should be explanted.
- Electromagnetic interference (EMI) may prevent VT/VF detection or cause inappropriate detection and delivery of therapy. The delivery of therapy may result in induction of VT/VF. Therefore, keep patients away from sources of EMI.
- Depending on programmed parameters, supraventricular arrhythmias may be detected as VT/VF and result in the delivery of therapy.
- Do not use diathermy on PCD patients.
- The Model 7217B PCD device may be damaged by direct or transthoracic defibrillatory discharges. Do not directly contact the exposed metal surface of any electrode with the paddles. When performing transthoracic defibrillation, do not place a paddle directly over the PCD device.
- Electrosurgical units should not be used in the vicinity of a Model 7217B PCD device and its associated lead system. See the technical manual for specific warnings and precautions.

Potential Complications

Potential complications related to the use of the Model 7217B PCD device include, but are not limited to, the following:

- Failure to detect and/or terminate ventricular tachycardia or ventricular fibrillation,
- Acceleration of a ventricular tachycardia, and
- Lead system related complications.

Consequently, no representation or warranty is made that failure or cessation of function of the Model 7217B PCD device or leads will not occur, that the body will not react adversely to the leads, that medical complications will not follow, that the Model 7217B PCD device and leads will effectively restore adequate cardiac function, or that use of the Model 7217B PCD device will prevent sudden death.

See the technical manual for complete labeling information.

Certain antitachycardia pacing modes of this device, invented by Dr. Fred Zacouto of Paris, France, fall under one or more patent claims of U.S. Patents 3,857,399 and 4,052,991 and corresponding patents in other countries, which are licensed exclusively to Medtronic, Inc.

The primary reference for background information is Zacouto FI, Guize LJ. Fundamentals of orthorhythmic pacing. In: Luderitz B., ed. *Cardiac Pacing Diagnostic and Therapeutic Tools*. New York: Springer-Verlag;1976:212-218.

See these additional references for more background information:

1. Theisen K, Zacouto F, et al. Refraktarzeitmessung bei absoluter Arrhythmie mit orthorhythmischer Serienstimulation. *Klin. Wschr.* 1974;52:1082-1084.

2. Guize L. Zacouto F, et al. Stimulation endocardiaques orthorhythmiques. *La Nouvelle Presse medicale*. 1974;3(33):2083-2086.

3. Effert S. Automatische Uberwachungsgerate und Indikation zur Implantation von elektrischen Schrittmachern. *Thoraxchirurgie und Vaskulare Chirurgie*. 1963;11:158-165. This describes the automatic defibrillation equipment of Dr. F. Zacouto.

United States of America
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432 U.S.A.
Telephone: (612) 574-4000
FAX: (612) 574-4879
Toll-free: 1-800-328-2518
(24-hour consultation service)

Canada, Latin America
Medtronic of Canada Ltd.
6733 Kitimat Road
Mississauga, Ontario L5N 1W3
Canada
Telephone: (416) 826-6020
FAX: (416) 826-6620
Toll-free: 1-800-268-5346
(24-hour consultation service)

Europe
Medtronic Europe
Immeuble Myron
6, avenue E. van Nieuwenhuyse
B-1160, Brussels
Belgium
Telephone: (32) 2-676 08 11
FAX: (32) 2-676 08 15

Asia-Pacific
Medtronic Asia-Pacific
Shuwa Kioi-cho Park Building, 5F
3-6 Kioi-cho, Chiyoda-ku
Tokyo 102, Japan
Telephone: (81) 3-3230-2919
Telex: J23920 HYMEDTRO
FAX: (81) 3-3230-0446

Medtronic

Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432
U.S.A.

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Medtronic

Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576
Telephone: (612) 574-4000
Cable: Medtronic Telex: 29-0598

January 7, 1994

Office of Device Evaluation
PMA Documentation Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

ACIVI

Re: Ammendment to P920015: Medtronic® TRANSVENE® Lead System
Final Labeling

Enclosed, in compliance with the Conditions of Approval for the above referenced PMA, are three copies of the approved labeling in final printed form. The system components relative to the market release of the PCD® TRANSVENE® lead system include the following:

Model 7217B PCD Device	195828-003 - Technical Manual 192976-002 - Package Labels
Model 6963 CS/SVC Lead	196060-002 - Technical Manual 193711-001 - Package Labels
Model 6966 RV Lead	196061-002 - Technical Manual 193710-001 - Package Labels
Model 6999 SQ Lead	196062-002 - Technical Manual 193712-001 - Package Labels

Sincerely,

MEDTRONIC, INC.

Dennis H. Connolly, M.D.
Product Regulation Manager
Cardiac Pacing Business Unit
Tel: (612 574-4696
Fax: (612) 574-6424

Attachment

Model
6963
LEAD

MODEL 6963 LEAD
TECHNICAL MANUAL

Medtronic

TRANSVENE®-SVC 6963

Technical Manual

4

TECHNICAL MANUAL

TRANSVENE®-SVC UNIPOLAR, ENDOCARDIAL, SUPERIOR VENA CAVA OR CORONARY SINUS LEAD FOR CARDIOVERSION AND DEFIBRILLATION

MODEL 6963

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DESCRIPTION

The Medtronic® TRANSVENE®-SVC Model 6963 Unipolar, Endocardial, Superior Vena Cava or Coronary Sinus Lead is designed for the delivery of cardioversion and defibrillation therapies.

Silicone insulation surrounds the low resistance conductor coil and the coil electrode is a platinum alloy. The lead also has a 6.5 mm connector.

INDICATIONS FOR USE

The Medtronic® TRANSVENE®-SVC Model 6963 is intended for single long-term use in the superior vena cava or coronary sinus and is designed to be used only with a compatible Medtronic implantable tachyarrhythmia control device along with at least one other Medtronic defibrillation lead.

The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated. Current medical research indicates that such patients should:

- have survived at least one episode of a cardiac arrest, presumably due to a ventricular tachyarrhythmia as evidenced by resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; OR
- in the absence of a prior cardiac arrest, have poorly tolerated sustained VT and/or VF, which occurs spontaneously or can be induced despite the best antiarrhythmic drug therapy.

The natural history of patients with hemodynamically stable sustained VT is not well defined. While this patient population was included in the TRANSVENE® Lead clinical study, no conclusions were drawn from the data obtained on this specific patient group.

Prior to TRANSVENE® implant, it is strongly recommended that patients undergo a complete cardiac evaluation, which should include extensive electrophysiologic testing. Also, extensive electrophysiologic evaluation and testing of the safety and efficacy of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the TRANSVENE® system.

CONTENTS OF PACKAGE

The leads are supplied sterile. Each package contains:

- 1 TRANSVENE®-SVC lead with two non-radiopaque anchoring sleeves, stylet, and stylet guide
- 1 vein lifter
- Extra stylets
- End Cap
- Product literature

CONTRAINDICATIONS

The TRANSVENE® system is contraindicated for patients:

- with transient ventricular tachyarrhythmias due to reversible causes, e.g., drug intoxication, electrolyte imbalance, sepsis, or hypoxia.
- with transient ventricular tachyarrhythmias due to other factors, e.g., myocardial infarction and electrocution.

The TRANSVENE® system is contraindicated for the sole use of detection and treatment of atrial arrhythmias.

WARNINGS

Do not attempt to use the TRANSVENE® lead system with any device other than a Medtronic implantable tachyarrhythmia control device for which it has been tested. While there has been no testing of the TRANSVENE® leads with a non-Medtronic device, the potential adverse consequences of using such a combination may include, but are not limited to, undersensing cardiac activity and failure to deliver necessary therapy.

Use only battery-powered equipment during lead implantation and testing to protect against fibrillation that may be caused by alternating currents. Line-powered equipment used in the vicinity of the patient must be properly grounded. Lead connector pins must be insulated from any leakage currents that may arise from line-powered equipment.

Two anchoring sleeves are provided with the lead. Both anchoring sleeves should be used as described in the section of this manual "Anchoring the Lead" to assure adequate fixation.

If patients do not meet the implant criteria (demonstration of a 10 Joule safety margin) for a transvenous lead system, physicians should consider implanting an epicardial

cardioversion/defibrillation lead system. If an epicardial system is to be implanted after testing a transvenous system, consider performing the procedure at a later date. The TRANSVENE® clinical study showed a 9.3% perioperative death rate for patients failing the implant criteria for a TRANSVENE® system and receiving an epicardial system. This compares to 0.7% for those patients receiving a TRANSVENE® system without the additional epicardial surgical procedure.

See also the section titled "General Warning."

PRECAUTIONS

Necessary Hospital Equipment

Defibrillation equipment should be kept nearby for immediate use during the acute lead system testing, implantation procedure, and whenever arrhythmias are possible or intentionally induced during post-implant testing.

Inspecting the Package

Carefully inspect the lead package prior to opening; if the seal or package is damaged, contact your local Medtronic representative.

Resterilization

For resterilization use ethylene oxide only. Do not resterilize more than one time.

Handling the Lead

Leads should be handled with great care at all times. **Any severe bending, kinking, stretching, or handling with surgical instruments may cause permanent damage to the lead.**

Lead insulators attract small particles such as lint and dust. Therefore, protect the lead from materials shedding these substances. Handle the lead with sterile gloves that have been wiped with a sterile moist sponge or equivalent.

Do not immerse leads in mineral oil, silicone oil, or any other liquid.

Using an Anchoring Sleeve

Always use an anchoring sleeve with all leads to secure the lead from moving and to protect the lead insulation and conductor coil from damage. A second anchoring sleeve is provided for additional fixation. Do not use the anchoring sleeve tabs for suturing.

Chronic Repositioning

Chronic repositioning of the lead may be difficult because of the fibrotic tissue. **However, if a lead must be removed or repositioned, proceed with extreme caution.** If a lead is abandoned, it should be capped to avoid transmitting electrical signals. Return all removed or unused leads or portions thereof to Medtronic.

Implant Technique

Avoid placing the lead under extreme tension or angulation to prevent dislodgement and possible lead fracture. Do not grip the lead with surgical instruments.

Do not use surgical instruments to grasp the lead or connector pin when tunneling.

Stylet Usage

To avoid damage to the lead or body tissue, do not use excessive force or surgical instruments to insert a stylet into the lead. When handling a stylet, avoid overbending, kinking, or blood contact.

Repeated insertions of a stylet increases the chance that blood or other fluids may accumulate on it, which may cause difficulty in passing the stylet through the lead and may cause damage to the lead.

To avoid damage to the stylet, do not use a sharp object to impart a curve to the distal end.

Always remove the stylet before connecting the lead to the pulse generator. Failure to remove the stylet may result in lead failure.

Insertion Site

Given the body diameter of transvenous defibrillation leads, insertion via a subclavian approach should be done as far lateral as possible to avoid clamping the lead body between the clavicle and the first rib. Clamping the lead can eventually cause the conductor to fracture, can cause damage to the insulation, or can cause other damage to the lead. This can result in complications such as loss of pacing therapies, and/or loss of cardioversion/defibrillation therapy. Certain anatomical abnormalities, such as thoracic outlet syndrome, can also precipitate pinching and subsequent fracture of the lead. If the subclavian approach is required, avoid techniques that can damage the lead. Specifically, do not force the lead if significant resistance is encountered. Do not use techniques such as adjusting the patient's posture (i.e., raising the arm or putting a towel behind the person's back) to facilitate the passage of the lead. If resistance is encountered, it is recommended that an alternate venous entry site be used, e.g., the cephalic vein.

POTENTIAL ADVERSE EFFECTS

The potential adverse effects related to the use of endocardial leads include, but are not limited to, the following patient-related conditions: fibrillation or other arrhythmias, air embolism, cardiac perforation, heart wall rupture, cardiac tamponade, infection, endocarditis, constrictive pericarditis, pneumothorax, hemothorax, and tissue necrosis.

Other potential adverse effects related to the lead system, but are not limited to the following: lead dislodgement, lead conductor or electrode fracture, insulation failure, and poor connection which may lead to loss of pacing therapies, and/or cardioversion/defibrillation therapy.

ENSURING PRODUCT INTEGRITY

Carefully inspect the sterile package before opening. It is not recommended that you use the product after its expiration date.

If the integrity of the sterile package has been compromised prior to the product expiration date, place the contents in a gas-permeable bag and resterilize them with ethylene oxide as described below.

CAUTION: Use ethylene oxide only. Do not resterilize more than one time.

The process should not exceed temperatures of 55°C (130°F). Allow proper aeration of ethylene oxide residues prior to implantation. Use an acceptable method to determine sterilizer effectiveness, such as a biological indicator.

Due to the variability between sterilizers, precise sterilization instructions cannot be provided. Contact your sterilizer manufacturer for more information regarding sterilization procedures.

SUGGESTED IMPLANTATION PROCEDURE

General Instructions

The implantation procedure generally includes using a stylet guide, stylets, and a vein lifter; selecting an insertion site; positioning the lead; taking electrical and defibrillation efficacy measurements; anchoring the lead; tunneling the lead; connecting the lead to the pulse generator; and closing the pocket.

Proper surgical procedures and sterile techniques are the responsibility of the medical professional. The implant procedures described in this manual are furnished for information only. Each physician must apply the information in these instructions according to professional medical training and experience.

Opening the Package

Open the package according to the instructions and inspect the lead. Carefully remove the disc from the distal end of the lead by opening the slot in the protector prior to lead removal. Verify that two anchoring sleeves are present.

Using the Stylet Guide and Stylets

The lead is packaged with a stylet guide attached and a stylet already inserted. Use of the stylet guide is optional. An attached stylet guide may be removed by gently pulling it off. To attach a stylet guide, gently push it as far as possible onto the connector pin that accepts the stylet (Figure 1).

A stylet provides additional stiffness and controlled flexibility for maneuvering the lead into position. Stylets vary in stiffness for different lead and stylet flexibility. Each stylet knob is etched with the stylet diameter and length.

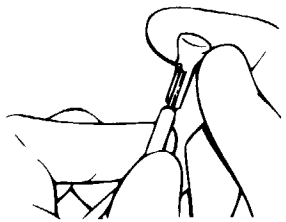


Figure 1. Stylet guide attachment.

If a slight curve is needed for the stylet, refer to instructions in the section titled "Positioning a Lead."

CAUTION: To avoid damage to the lead or body tissue, do not use excessive force or surgical instruments to insert a stylet into the lead. When handling a stylet, avoid overbending, kinking, or blood contact.

CAUTION: Repeated insertions of a stylet increases the chance that blood or other fluids may accumulate on it, which may cause difficulty in passing the stylet through the lead and may cause damage to the lead.

Selecting an Insertion Site

The lead may be inserted by venotomy through several different venous routes, including the right or left cephalic vein or the external or internal jugular vein. In general, a left venous entry site will aid in maneuvering the lead into the coronary sinus orifice.

CAUTION: Given the body diameter of transvenous defibrillation leads, insertion via a subclavian approach should be done as far lateral as possible to avoid clamping the lead body between the clavicle and the first rib (Figure 2). Clamping the lead can eventually cause the conductor to fracture, can cause damage to the insulation, or can cause other damage to the lead. This can result in complications such as loss of pacing therapies, and/or loss of

cardioversion/defibrillation therapy. Certain anatomical abnormalities, such as thoracic outlet syndrome, can also precipitate pinching and subsequent fracture of the lead. If the subclavian approach is required, avoid techniques that can damage the lead. Specifically, do not force the lead if significant resistance is encountered. Do not use techniques such as adjusting the patient's posture (i.e., raising the arm or putting a towel behind the person's back) to facilitate the passage of the lead. If resistance is encountered, it is recommended that an alternate venous entry site be used, e.g., the cephalic vein.

Use fluoroscopy to facilitate accurate lead placement.

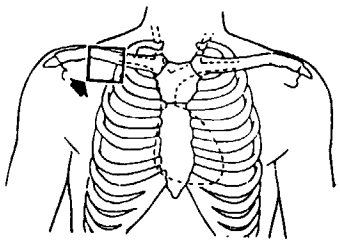


Figure 2. Insertion site.

Using a Vein Lifter

A vein lifter facilitates lead introduction. Insert its tapered end into the incised vein and gently push the lead tip underneath and into the vein (Figure 3). During insertion of the lead into the vein, make sure the anchoring sleeves do not slide off the distal end of the lead.

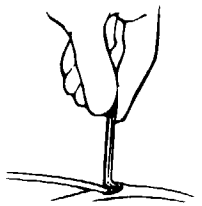


Figure 3. Using the vein lifter.

CAUTION: Avoid placing the lead under extreme tension or angulation to prevent lead dislodgement and possible lead fracture. **Do not grip the lead with surgical instruments.**

Positioning a Lead

For added control in maneuvering the lead tip, the distal end of the lead may be slightly curved by inserting a gently curved stylet as shown in Figure 4. A possible angle of curvature is illustrated in Figures 5 and 6.

CAUTION: To avoid damage to the stylet, do not use a sharp object to impart a curve to the distal end (Figure 4).

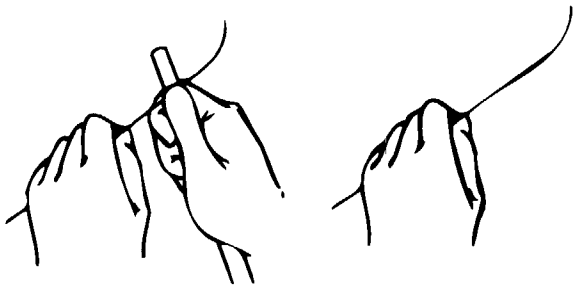


Figure 4. Imparting a curve to the stylet.

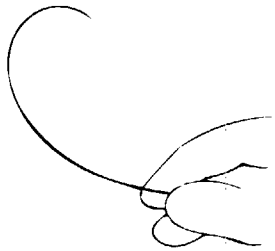


Figure 5. Bend the stylet into a gentle spiral. This gives the lead a gentle curve upward, to the left, and posterior.

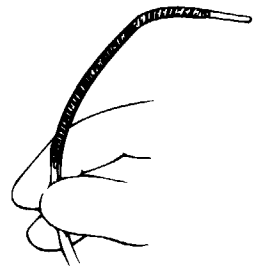


Figure 6. The curve in the stylet is designed to facilitate passage of the lead across the superior surface of the tricuspid valve. The second bend helps to position the lead to the left and posterior toward the coronary sinus ostium.

The electrode may be placed in either the superior vena cava or the coronary sinus.

If placing the electrode in the superior vena cava, advance the tip so that the distal portion of the electrode is approximately 3 to 5 cm proximal to the superior vena cava—right atrial junction.

If the electrode is to be placed in the coronary sinus, advance the lead into the right atrium and rotate the curved stylet to manipulate the tip over the tricuspid valve. Move the tip medially and posteriorly to the coronary sinus ostium and advance the lead into the coronary sinus. Continue advancing the lead through the coronary sinus to the desired position.

If the lead goes through the tricuspid valve opening, retract the lead with a gentle posterior rotation and then advance it toward the coronary sinus ostium.

The electrode for the TRANSVENE®-SVC must be as far as possible from other defibrillation electrodes. Also, the cardiac mass between the electrodes should be as large as possible. Insufficient separation between the electrodes may result in reduced defibrillation efficacy.

Proper positioning of the electrode is essential for defibrillation efficacy (Figure 7). Use fluoroscopy (P-A and lateral position) to ensure that the distal end of the electrode is properly positioned in the superior vena cava or is lodged in the coronary sinus with the proximal end of the electrode advanced beyond the coronary sinus ostium.

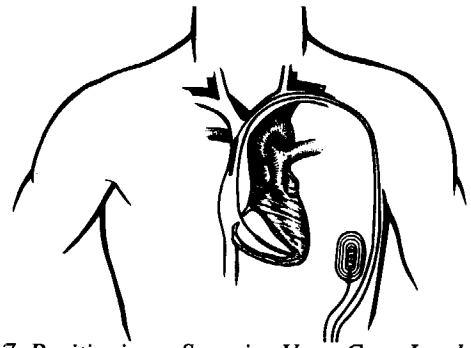


Figure 7. Positioning a Superior Vena Cava Lead

Bradycardia Pacemakers

Previously implanted bradycardia pacemakers, tachyarrhythmia devices and leads should be explanted. The output pulses of an implanted device may adversely affect the tachyarrhythmia detection capabilities of the PCD device. If leads must be abandoned rather than removed they should be capped to ensure they will not become a pathway for currents to or from the heart. If a patient requires a separate atrial or dual chamber pacemaker for hemodynamic reasons, either permanent or temporary, allow adequate space between the pacing lead electrodes and the defibrillation lead electrodes.

Taking Electrical Measurements and Defibrillation Efficacy Measurements

Initial electrical measurements may deviate from the recommendations because of acute cellular trauma. If this occurs, wait five to fifteen minutes and repeat the testing procedure. Values may vary depending upon lead type, pulse generator settings, cardiac tissue condition, and drug interactions. If electrical measurements do not stabilize to acceptable levels, it may be necessary to reposition the lead and repeat the testing procedure.

To demonstrate reliable defibrillation efficacy with acute or chronic leads, it is recommended that VF be initiated and terminated either two consecutive times at a stored energy of 24 joules or less, or 3 out of 4 times at a stored energy of 24 joules or less. If more than one of the four VF inductions are not terminated by the ETCD and lead system, the decision to implant the PCD device should be re-evaluated.

In order to keep patient morbidity and mortality to a minimum, patients should be rescued promptly with an external device if the lead system and ETCD fails to terminate the VF episode and at least 5 minutes should elapse between VF inductions.

For more information on obtaining electrical measurements, consult the technical manual supplied with the testing device.

Recommended Pacing/Sensing Measurements at Implant
(when using a pacing system analyzer)

Measurements Required	Acute Lead System	Chronic Lead System
Capture threshold (at 0.5 ms pulse width)	≤ 1.0 V	≤ 3.0 V
Impedance	200 - 800 ohms	200 - 800 ohms
Filtered R-wave amplitude	≥ 5 mV (during sinus rhythm)	≥ 3 mV (during sinus rhythm)
Slew rate	≥ 0.75 V/s	≥ 0.45 V/s

Anchoring the Lead

Do not secure the ligatures so tightly that they damage the vein, lead, or anchoring sleeve. Do not tie a ligature directly to the lead body (Figure 8). During anchoring, take care to avoid dislodging the lead tip.

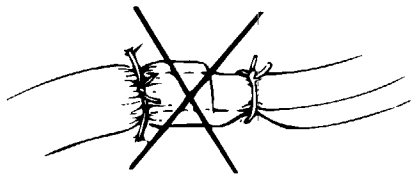


Figure 8. Do NOT secure the sutures too tightly and do NOT tie a suture to the lead body.

Use an anchoring sleeve to secure the lead from moving and to protect the lead insulation and conductor coil from damage caused by tight ligatures. A second anchoring sleeve should be placed in the tunnel entry site or in the pocket area for additional fixation.

Anchor the lead with nonabsorbable sutures.

The TRANSVENE®-SVC uses the triple groove anchoring sleeve illustrated in Figure 9. The triple groove anchoring sleeves are already situated at the connector end of the lead.

With a triple groove anchoring sleeve, all three grooves should be used with the following procedure (Figure 10).

- Partially insert the distal anchoring sleeve into the vein.
- **Use all three grooves to secure the anchoring sleeve (s) to the lead body.**
- Use the most distal suture groove to secure the anchoring sleeve to the vein.
- Use the middle groove to secure the anchoring sleeve to the fascia, vein, and lead body. First, create a base by looping a suture through the fascia underneath the middle groove and tying a knot. Continue by firmly wrapping the suture around the middle groove and tying a second knot.

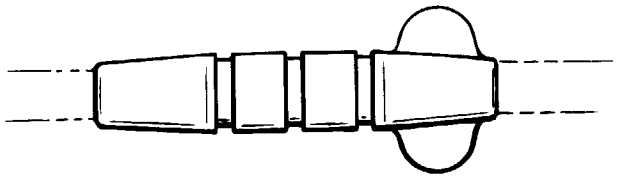


Figure 9. The triple groove anchoring sleeve.

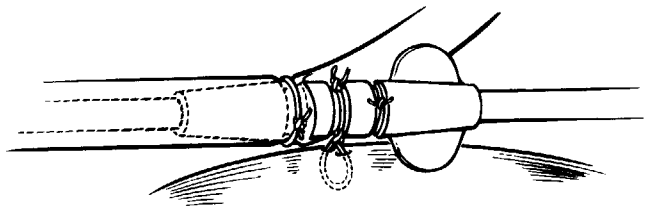


Figure 10. Triple groove anchoring sleeve secured to the lead and fascia using three grooves.

CAUTION: Do not use the anchoring sleeve tabs for suturing.

Tunneling the Lead

Before tunneling the lead connector, record each lead's serial number along with the function of the lead. Use of a chest tube is suggested in tunneling the lead connector to the pulse generator to prevent damage to the lead. Tunnel the lead subcutaneously to the pulse generator pocket.

CAUTION: Do not use surgical instruments to grasp the lead or connector pin when tunneling.

Connecting the Lead to a Tachyarrhythmia Device

Refer to Figures 11a and 11b for instructions and illustrations showing lead connections to the Medtronic® PCD® Tachyarrhythmia Control Device Model 7217B.

Insert the lead connector into the connector block. Refer to the PCD® Tachyarrhythmia Control Device technical manual for the use of setscrews and setscrew tools.

Before closing the pocket, verify sensing, pacing, and defibrillation efficacy.

CAUTION: Always remove the stylet before connecting the lead to the pulse generator. Failure to remove the stylet may result in lead failure.

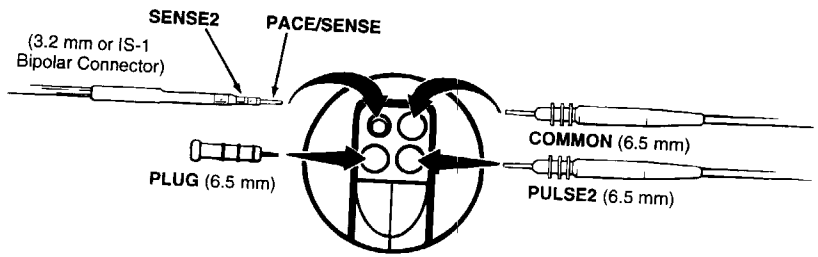
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillation Electrodes	Two-Electrode System Connection Diagram
Medtronic® Model 7217B PCD® Device	2	**PACE/SENSE, SENSE2** Insert the Pace/Sense lead connector of the TRANSVENE®-RV into the PACE/SENSE, SENSE2 port. **COMMON** Insert the unipolar lead connector of the TRANSVENE®-RV, -SVC, or -SQ into the COMMON port.  **PULSE1** Insert the connector plug packaged with the pulse generator into the PULSE1 port. **PULSE2** Insert the lead connector of the TRANSVENE®-RV, -SVC, or -SQ lead into the PULSE2 port.

Figure 11a. Connections for two-electrode system leads (single pulse) into the Medtronic® PCD® Tachyarrhythmia Control Device Model 7217B.

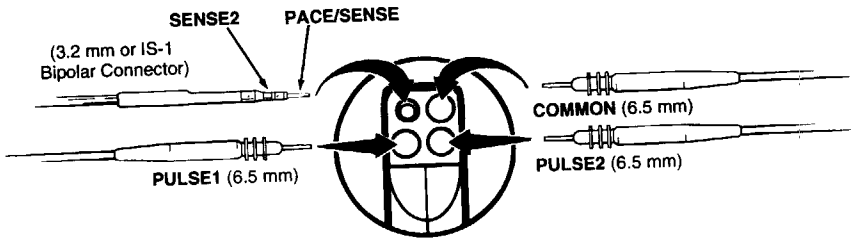
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillation Electrodes	Three-Electrode System Connection Diagram
Medtronic® Model 7217B PCD® Device	3	**PACE/SENSE, SENSE2** Insert the Pace/Sense lead connector of the TRANSVENE®-RV into the PACE/SENSE, SENSE2 port. **COMMON** Insert the unipolar lead connector of the TRANSVENE®-RV, -SVC, or -SQ into the COMMON port.  **PULSE1** Insert the lead connector of the TRANSVENE®-RV, -SVC, or -SQ lead into the PULSE1 port. **PULSE2** Insert the lead connector of the TRANSVENE®-RV, -SVC, or -SQ lead into the PULSE2 port.

Figure 11b. Connections for three-electrode system leads (simultaneous or sequential pulse) into the Medtronic® PCD® Tachyarrhythmia Control Device Model 7217B.

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Closing the Pocket

To prevent undesirable twisting of the lead body, wrap the excess lead length loosely under the pulse generator and place both into the subcutaneous pocket (Figure 12). Ensure that the leads do not leave the pulse generator at an acute angle. Sharp angles place undue stress on the lead conductor and insulation.

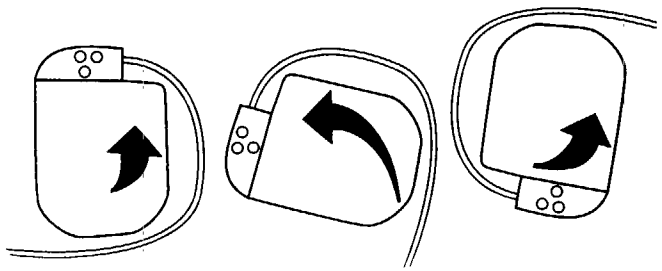

Figure 12. While rotating the pulse generator, loosely wrap the excess lead length and place it under the pulse generator.

To reduce the potential for abrasion on the lead body, it is recommended that the PCD be placed in a Parsonnet pouch.

When placing the pulse generator and leads into the subcutaneous pocket:

- Do NOT coil the lead. Coiling the lead can twist the lead body and may result in lead dislodgement (Figure 13).
- Do NOT grip the lead or pulse generator with surgical instruments.

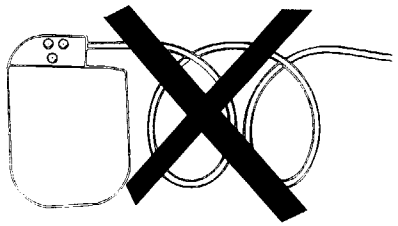

Figure 13. Do not coil or twist the lead body.

Post-Implant Evaluation

After implantation, monitor the patient's electrocardiogram continuously. If a lead dislodges, it usually occurs during the immediate postoperative period.

The patient should have X-rays and pacing/sensing thresholds taken every three months for the first year after implant and every six months thereafter to verify proper lead position and to check for conductor fractures.

In the event of a patient death, all implanted leads and devices should be explanted and returned to Medtronic with a completed PCD® Product Information Report. Any questions on product handling procedures can be addressed by calling 1-800-PCD-INFO.

SPECIFICATIONS (Nominal)

PARAMETER		MODEL 6963
Type		Unipolar
Position		Superior Vena Cava/ Coronary Sinus
Fixation		None. Tip lodges in the Superior Vena Cava or is placed in the Coronary Sinus
Length		110 cm
Connector		6.5 mm
Materials	Conductor:	Multifilar MP35N Composite
	Insulator:	Silicone
	Electrode:	Platinum Alloy

PARAMETER		MODEL 6963
Electrode Surface Area	Coil:	90 mm^2 (5 cm)
Diameters	Body:	1.7 mm
	Electrode:	2.3 mm
Unipolar Resistance		3.3 ohms
Lead Introducer (recommended size)		7.0 French

GENERAL WARNING

Medtronic® implantable leads are implanted in the extremely hostile environment of the human body. Leads are necessarily very small in diameter and must still be very flexible, which unavoidably reduces their potential performance or longevity. Leads may fail to function for a variety of causes, including, but not limited to: medical complications, body rejection phenomena, allergic reaction, fibrotic tissue, or failure of leads by breakage or by breach of their insulation covering. In addition, despite the exercise of all due care in design, component selection, manufacture, and testing prior to sale, leads may be easily damaged before, during, or after insertion by improper handling or other intervening acts. Consequently, no representation or warranty is made that failure or cessation of function of leads will not occur or that the body will not react adversely to the implantation of leads or that medical complications (including perforation of the heart) will not follow the implantation of leads or that the lead will, in all cases, restore adequate cardiac function.

For complete warranty information, see the accompanying card enclosed in the package.

SERVICE

Medtronic employs highly trained representatives and engineers located throughout the world to serve you and, upon request, to provide training to qualified hospital personnel in the use of Medtronic products. In addition, Medtronic maintains a professional staff of consultants to provide technical and medical consultation to product users. For supplemental information, contact your local Medtronic representative, or call or write Medtronic at the appropriate address or telephone number listed on the back cover.

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Medtronic Europe S.A./N.V.
Woluwe Office Garden
Woluwedal 26
1932 St. Stevens Woluwe
Belgium
Telephone: (32-2) 716 88 11
FAX: (32-2) 716 88 15

Asia-Pacific

Japan
Medtronic Asia-Pacific
Shuwa Kioi-cho Park Building, 5F
3-6 Kioi-cho, Chiyoda-ku
Tokyo 102, Japan
Telephone: (81-3) 3230-2701
FAX: (81-3) 3230-0446

Australia
Medtronic Australasia Pty. Ltd.
22 Clarke Street
Crows Nest, Sydney, N.S.W., 2065
Australia
Telephone: (61) 2 437-6066
FAX: (61) 2 437-6869

Asia
Medtronic International Ltd.
2002 CC Wu Building
308 Hennessey Road, Wanchai
Hong Kong, B.C.C.
Telephone: (852-5) 891-4068
FAX: (852) 891-6830

Latin America

Medtronic, Inc.
450 Fairway Drive
Suite 103
Deerfield Beach, FL 33441
USA
Telephone: (305) 428-8556
FAX: (305) 428-8984

North America

Canada
Medtronic of Canada Ltd.
6733 Kitimat Road
Mississauga, Ontario L5N 1W3
Canada
Telephone: (905) 826-6020
FAX: (905) 826-6620
Toll-free: 1-800-268-5346
(24-hour consultation service)

United States
Medtronic, Inc.
7000 Central Avenue, NE
Minneapolis, MN 55432-3576
USA
Telephone: (612) 574-4000
FAX: (612) 574-4879
Toll-free: 1-800-328-2518
(24-hour consultation service)

Medtronic

December 1993
UC9303161aEN 196060-002

STERILE
PAK
LABEL

Medtronic

TRANSVENE®-SVC

Unipolar Connector (6.5 mm)/Connecteur Unipolaire (6,5 mm)/Unipolarer Konnektor (6,5 mm)/Conector Monopolar (6,5 mm)/Connettore Monopolare (6,5 mm)

Serial Number
Numéro de Série
Seriennummer
Número de Serie
Numero di Serie

Use Before
Utiliser Avant
Zu Implantieren vor dem
Fecha de Caducidad
Data di Scadenza

Lead Length
Longueur de la Sonde
Länge der Elektrode
Longitud del Cable
Lunghezza dell'Elettrocatetere

Sterilization Date
Date de Stérilisation
Sterilisationsdatum
Fecha de Esterilización
Data di Sterilizzazione

Non Reusable
Non Réutilisable
Nicht wiederverwendbar
Interior Desechable
Materiale Sterile Involucro Non Riutilizzabile

Contents: One lead with silicone insulation and accessories
Contenu: Une sonde avec isolant en silicone et accesoires
Inhalt: Eine Elektrode mit Silikonisolation und Zubehör
Contenido: Un electrodo con aislante de silicona y accesorios
Contenuto: Un elettrocatetere con isolante in silicone e accessori

Sterilization :Ethylene oxide gas
Stérilisation :Gaz d'oxyde d'éthylène
Sterilisation :Äthylenoxydgas
Esterilización :Gas óxido de etileno
Sterilizzazione :Gas ossido di etilene

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician.
ATTENTION: La réglementation américaine (FDA) n'autorise la vente de ce produit que sur prescription médicale.
ACHTUNG: Ein US-Bundesgesetz schränkt den Verkauf dieses Produkts auf Ärzte oder auf Anordnung durch einen Arzt ein.
PRECAUCION: Las Leyes Federales (EE.UU.) restringen la venta de este dispositivo únicamente a médicos o per prescripciónmédica.
ATTENZIONE: La Legge Federale (U.S.A.) limita la vendita di questo prodotto esclusivamente ai medici o su richiesta del medico.

The contents of this package are **STERILE**
Le contenu de cet emballage est **STERILE**
Der Inhalt dieser Packung ist **STERIL**
El contenido de este envoltorio está **ESTERIL**
Il contenuto de questo imballaggio è **STERILE**

Recommended lead introducer size
Dimension recommandée de l'introducteur
Empfohlene Größe des Elektroden-Einführungsbestecks **7** French
Tamaño recomendado del introductor de cable
Dimensioni raccomandati dell'introduttore

If the package is damaged or opened see the Technical Manual for information
Si l´emballage est endommagé ou ouvert voir le Manuel Technique pour information
Im Falle einer beschädigten oder geöffneten Packung siehe Gebrauchsanweisung
Si el paquete ha sido dañado o abierto, ver el Manual Técnico para información
Se la confezione è danneggiata o aperta vedere il Manuale Tecnico per informazione

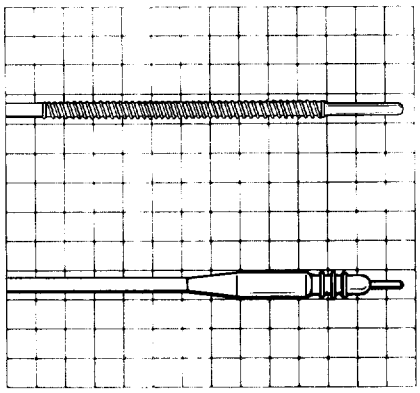
CE 0123

SHELF
BOX
LABEL

Medtronic

TRANSVENE®-SVC

Unipolar Connector (6.5 mm)/Connecteur Unipolaire (6,5 mm)/Unipolarer Konnektor (6,5 mm)/Conector Monopolar (6.5 mm)/Connettore Monopolare (6.5 mm)



Serial Number
Numéro de Série
Seriennummer
Número de Serie
Numero di Serie

Use Before
Utiliser Avant
Zu Implantieren vor dem
Fecha de Caducidad
Data di Scadenza

Lead Length
Longueur de la Sonde
Länge der Elektrode
Longitud del Cable
Lunghezza dell'Elettrocatetere

Sterilization Date
Date de Stérilisation
Sterilisationsdatum
Fecha de Esterilización
Data di Sterilizzazione

Contents: One lead with silicone insulation, accessories and product literature
Contenu: Une sonde avec isolant en silicone, accesoires et documentation relative au produit
Inhalt: Eine Elektrode mit Silikonisolation, Zubehör und Produktbeschreibung
Contenido: Un electrodo con aislante de silicona, accesorios y literatura del producto
Contenuto: Un elettrocatetere con isolante in silicone, accessori e letteratura del prodotto

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician.
ATTENTION: La réglementation américaine (FDA) n'autorise la vente de ce produit que sur prescription médicale.
ACHTUNG: Ein US-Bundesgesetz schränkt den Verkauf dieses Produkts auf Ärzte oder auf Anordnung durch einen Arzt ein.
PRECAUCION: Las Leyes Federales (EE.UU.) restringen la venta de este dispositivo únicamente a médicos o per prescripción médica.
ATTENZIONE: La Legge Federale (U.S.A.) limita la vendita di questo prodotto esclusivamente ai medici o su richiesta del medico.

The contents (**STERILE**) of the inner package have been sterilized by ethylene-oxide gas
Le contenu (**STERILE**) du paquet interne a été stérilisé au gaz d´oxyde d´éthylène
Der Inhalt (**STERIL**) der inneren Verpackung ist in Äthylenoxydgas sterilisiert
El contenido (**ESTERIL**) del paquete interior ha sido esterilizado con gas óxido de etileno
Il contenuto (**STERILE**) della confezione interna è stato sottoposto a sterilizzazione con gas ossido di etilene

STORAGE: Store below 40° C/104° F
STOCKAGE: Au-dessous de 40° C/104° F
LAGERUNG: Unter 40° C/104° F
ALMACENAMIENTO: Por debajo de 40° C/104° F
IMMAGAZZINAGGIO: Al di sottodi 40° C/104° F

Recommended lead introducer size
Dimension recommandée de l'introducteur
Empfohlene Größe des Elektroden-Einführungsbestecks **7** French
Tamaño recomendado del introductor de cable
Dimensioni raccomandati dell'introduttore

A thoracotomy is not required
Une thoracotomie n'est pas nécessaire
Eine Thorakotomie ist nicht erförderlich
No es necesaria una toracotomía
Una toracotomia no è richiesta

DER GRÜNE PUNKT

CE 0123

END
LABEL

TRANSVENE®-SVC 6963

Unipolar, Endocardial, Coronary Sinus/SVC Lead for Cardioversion and Defibrillation

Unipolar Connector (6.5mm)

USE BEFORE

SERIAL NO.

INDIVIDUAL
DATA SHEET

INDIVIDUAL DATA SHEET
FICHE TECHNIQUE INDIVIDUELLE
INDIVIDUELLES TECHNISCHES DATENBLATT
HOJA DE DATOS
FOGLIO D'INFORMAZIONI SPECIFICO

MODEL/MODELE/MODELL/MODELO/MODELLO

6963

Serial Number Numéro de Série Seriennummer Número de Serie Numero di Serie	Use Before Utiliser Avant Zu Implantieren vor dem Fecha de Caducidad Data di Scadenza

Sterilization	:Ethylene oxide gas	Sterilization Date
Stérilisation	:Gaz d'oxyde d'éthylène	Date de Stérilisation
Sterilisation	:Äthylenoxydgas	Sterilisationsdatum
Esterilización	:Gas óxido de etileno	Fecha de Esterilización
Sterilizzazione	:Gas ossido di etilene	Data di Sterilizzazione

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LEAD

LEAD

MODEL 6966 LEAD
TECHNICAL MANUAL

Medtronic

TRANSVENE®-RV 6966

Technical Manual

TECHNICAL MANUAL

TRANSVENE®-RV TRIPOLAR, ENDOCARDIAL, SCREW-IN LEAD FOR VENTRICULAR PACING, SENSING, CARDIOVERSION AND DEFIBRILLATION

MODEL 6966

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DESCRIPTION

The Medtronic® TRANSVENE®-RV Model 6966 Tripolar, Endocardial, Screw-In Ventricular Lead is designed for pacing, sensing, and delivering cardioversion and defibrillation therapies.

The Medtronic® TRANSVENE®-RV lead has a helical electrode made of platinum alloy that can be actively fixed in the endocardium. The helix can be extended or retracted by rotating the lead connector pin with a special fixation tool. Active fixation leads are particularly beneficial for patients who have smooth or hypertrophic hearts where lead dislodgement may be a potential problem.

The three electrodes of this lead are: coil, ring, and helix (Figure 1).

The defibrillating coil electrode is most proximal to the pulse generator and connects electrically to the connector PIN of the UNIPOLAR leg of the bifurcation. This UNIPOLAR leg will not accept a stylet. The coil electrode is intended to be used for delivery of cardioversion and defibrillation pulses.

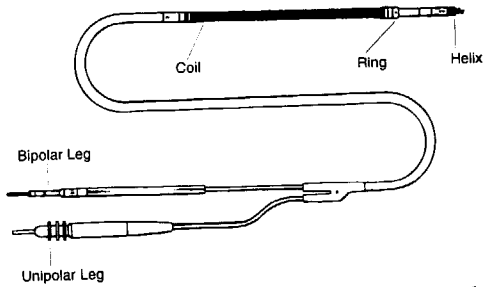

Figure 1. The three electrodes and two connector legs.

The ring electrode is proximal to the helix and connects electrically to the connector RING of the BIPOLAR leg of the bifurcation.

The helix tip electrode is most distal to the pulse generator and provides active fixation in the endocardium. It can be extended or retracted by rotating the lead connector PIN with a special fixation tool. The helix electrode connects electrically to the connector PIN of the BIPOLAR leg of the bifurcation. This BIPOLAR leg is the only one that will accept a stylet.

The helix tip electrode and the ring electrode may be used for bipolar pacing and sensing; however, when used with the standard bipolar PCD® pulse generators, pacing occurs between the tip electrode and the coil electrode.

The lead's conductors are in a multifilar configuration and are insulated with polyurethane.

INDICATIONS FOR USE

The Medtronic® TRANSVENE®-RV Model 6966 is intended for single long-term use in the ventricle and is designed to be used only with a compatible Medtronic implantable tachyarrhythmia control device along with at least one other Medtronic defibrillation lead.

The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated. Current medical research indicates that such patients should:

- have survived at least one episode of a cardiac arrest, presumably due to a ventricular tachyarrhythmia as evidenced by resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; OR
- in the absence of a prior cardiac arrest, have poorly tolerated sustained VT and/or VF, which occurs spontaneously or can be induced despite the best antiarrhythmic drug therapy.

The natural history of patients with hemodynamically stable sustained VT is not well defined. While this patient population was included in the TRANSVENE® Lead clinical study, no conclusions were drawn from the data obtained on this specific patient group.

Prior to TRANSVENE® implant, it is strongly recommended that patients undergo a complete cardiac evaluation, which should include extensive electrophysiologic testing. Also, extensive electrophysiologic evaluation and testing of the safety and efficacy of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the TRANSVENE® system.

CONTENTS OF PACKAGE

The leads are supplied sterile. Each package contains:

- 1 TRANSVENE®-RV lead with two non-radiopaque anchoring sleeves, stylet, and stylet guide
- 2 fixation tools
- 1 vein lifter
- Extra stylets
- End Caps
- Product literature

CONTRAINDICATIONS

When tricuspid valvular disease or a mechanical heart valve is present, use of a ventricular endocardial lead is contraindicated.

The TRANSVENE® system is contraindicated for patients:

- with transient ventricular tachyarrhythmias due to reversible causes, e.g., drug intoxication, electrolyte imbalance, sepsis, or hypoxia.
- with transient ventricular tachyarrhythmias due to other factors, e.g., myocardial infarction and electrocution.

The TRANSVENE® system is contraindicated for the sole use of detection and treatment of atrial arrhythmias.

WARNINGS

Do not attempt to use the TRANSVENE® lead system with any device other than a Medtronic implantable tachyarrhythmia control device for which it has been tested. While there has been no testing of the TRANSVENE® leads with a non-Medtronic device, the potential adverse consequences of using such a combination may include, but are not limited to, undersensing cardiac activity and failure to deliver necessary therapy.

Use only battery-powered equipment during lead implantation and testing to protect against fibrillation that may be caused by alternating currents. Line-powered equipment used in the vicinity of the patient must be properly grounded. Lead connector pins must be insulated from any leakage currents that may arise from line-powered equipment.

Two anchoring sleeves are provided with the lead. Both anchoring sleeves should be used as described in the section of this manual "Anchoring the Lead" to assure adequate fixation.

If patients do not meet the implant criteria (demonstration of a 10 Joule safety margin) for a transvenous lead system, physicians should consider implanting an epicardial

cardioversion/defibrillation lead system. If an epicardial system is to be implanted after testing a transvenous system, consider performing the procedure at a later date. The TRANSVENE® clinical study showed a 9.3% perioperative death rate for patients failing the implant criteria for a TRANSVENE® system and receiving an epicardial system. This compares to 0.7% for those patients receiving a TRANSVENE® system without the additional epicardial surgical procedure.

See also the section titled "General Warning."

PRECAUTIONS

Necessary Hospital Equipment

Defibrillation equipment should be kept nearby for immediate use during the acute lead system testing, implantation procedure, and whenever arrhythmias are possible or intentionally induced during post-implant testing.

Inspecting the Package

Carefully inspect the lead package prior to opening; if the seal or package is damaged, contact your local Medtronic representative.

Resterilization

For resterilization use ethylene oxide only. Do not resterilize more than one time.

Handling the Lead

Leads should be handled with great care at all times. **Any severe bending, kinking, stretching, or handling with surgical instruments may cause permanent damage to the lead.**

Lead insulators attract small particles such as lint and dust. Therefore, protect the lead from materials shedding these

substances. Handle the lead with sterile gloves that have been wiped with a sterile moist sponge or equivalent.

Do not immerse leads in mineral oil, silicone oil, or any other liquid.

Rotating the Helix

The maximum number of revolutions of the electrode fixation tool needed to extend or retract the helix is 20. **Exceeding the maximum revolutions may damage the lead.**

Using an Anchoring Sleeve

Always use an anchoring sleeve with all leads to secure the lead from moving and to protect the lead insulation and conductor coil from damage. A second anchoring sleeve is provided for additional fixation. Do not use the anchoring sleeve tabs for suturing.

Chronic Repositioning

Chronic repositioning or removal of screw-in leads may not be possible because of blood or fibrotic tissue development into the helix mechanism. Removal of the lead could result in avulsion of the endocardium, valve, or vein. In addition, the lead junctions may separate, leaving the lead tip and bare wire in the heart or vein. In most clinical situations, it is preferable to abandon unused leads in place.

However, if a lead must be removed or repositioned, proceed with extreme caution. If a helix does not disengage from the endocardium by rotating the connector pin, rotating the lead body counterclockwise may withdraw the helix and decrease the possibility of damage to the cardiovascular structures during removal.

If a lead is abandoned, it should be capped to avoid transmitting electrical signals. Return all removed or unused leads or portions thereof to Medtronic.

Implant Technique

Avoid placing the lead under extreme tension or angulation to prevent dislodgement and possible lead fracture. Do not grip the lead with surgical instruments.
Do not use surgical instruments to grasp the lead or connector pin when tunneling.

Stylet Usage

To avoid damage to the lead or body tissue, do not use excessive force or surgical instruments to insert a stylet into the lead. When handling a stylet, avoid overbending, kinking, or blood contact.

Repeated insertions of a stylet increases the chance that blood or other fluids may accumulate on it, which may cause difficulty in passing the stylet through the lead and may cause damage to the lead.

To avoid damage to the stylet, do not use a sharp object to impart a curve to the distal end.

Always remove the stylet before connecting the lead to the pulse generator. Failure to remove the stylet may result in lead failure.

Insertion Site

Given the body diameter of transvenous defibrillation leads, insertion via a subclavian approach should be done as far lateral as possible to avoid clamping the lead body between the clavicle and the first rib. Clamping the lead can eventually cause the conductor to fracture, can cause damage to the insulation, or can cause other damage to the lead. This can result in complications such as loss of pacing therapies, and/or loss of cardioversion/defibrillation therapy. Certain anatomical abnormalities, such as thoracic outlet syndrome, can also precipitate pinching and subsequent fracture of the lead. If the subclavian approach is required, avoid techniques that can damage the lead. Specifically, do not force the lead if significant resistance is encountered. Do not use techniques such as adjusting the patient's posture (i.e., raising the arm or putting a towel behind the person's back) to facilitate the passage of the lead. If resistance is encountered, it is recommended that an alternate venous entry site be used, e.g., the cephalic vein.

POTENTIAL ADVERSE EFFECTS

The potential adverse effects related to the use of endocardial leads include, but are not limited to, the following patient-related conditions: fibrillation or other arrhythmias, air embolism, cardiac perforation, heart wall rupture, cardiac tamponade, infection, endocarditis, constrictive pericarditis, pneumothorax, hemothorax, and tissue necrosis.

Other potential adverse effects related to the lead system, but are not limited to the following: lead dislodgement, lead conductor or electrode fracture, insulation failure, and poor connection which may lead to loss of pacing therapies, and/or loss of cardioversion/defibrillation therapy.

ENSURING PRODUCT INTEGRITY

Carefully inspect the sterile package before opening. It is not recommended that you use the product after its expiration date.

If the integrity of the sterile package has been compromised prior to the product expiration date, place the contents in a gas-permeable package and resterilize them with ethylene oxide as described below.

CAUTION: Use ethylene oxide only. Do not resterilize more than one time.

The process should not exceed temperatures of 55°C (130°F). Allow proper aeration of ethylene oxide residues prior to implantation. Use an acceptable method to determine sterilizer effectiveness, such as a biological indicator.

Due to the variability between sterilizers, precise sterilization instructions cannot be provided. Contact your sterilizer manufacturer for more information regarding sterilization procedures.

SUGGESTED IMPLANTATION PROCEDURE

General Instructions

The implantation procedure generally includes checking the mechanical functioning of the lead electrode before it is inserted; using a stylet guide, stylets, and vein lifter; selecting an insertion site; positioning the lead; securing the lead; taking electrical and defibrillation efficacy measurements; anchoring the lead; tunneling the lead; connecting the lead to the pulse generator; and closing the pocket.

Proper surgical procedures and sterile techniques are the responsibility of the medical professional. The implant procedures described in this manual are furnished for information only. Each physician must apply the information in these instructions according to professional medical training and experience.

Opening the Package

Open the package according to the instructions and inspect the lead.Carefully remove the disc from the distal end of the lead by opening the slot in the protector prior to lead removal. Verify that two anchoring sleeves are present.

Verifying the Mechanical Functioning of the Helix Electrode

Before implantation, verify the mechanical functioning of the electrode, as described below.

1. Within the sterile field, remove the lead and the accompanying stylets from the sterile packaging. The lead is packaged with a stylet guide attached and a stylet already inserted. The connector pin that accepts the stylet controls the helix mechanism.
2. To attach the fixation tool, first remove the stylet guide. Press both legs of the fixation tool together and place the most distal hole of the fixation tool on the connector pin that accepts the stylet (Figure 2).

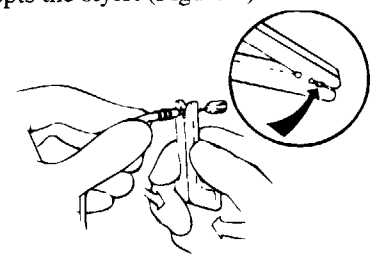

Figure 2. Attachment of the fixation tool to the connector pin.

3. Rotate the tool clockwise until the coiled electrode is completely exposed (Figure 3). Maximum electrode exposure reveals 2 coils.

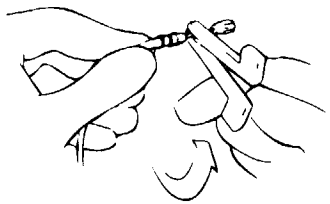

Figure 3. Rotating the fixation tool.

The maximum number of revolutions of the fixation tool needed to extend or retract the helix is 20.

CAUTION: Exceeding the maximum number of revolutions may damage the lead.

4. Disconnect the fixation tool from the connector pin and release the proximal end of the lead body. Allow several seconds for the lead and its conductor coil to unwind.
5. After allowing the lead and its conductor coil to unwind, reattach the fixation tool and turn it counterclockwise until the helix tip is retracted in the sheath.

Using the Stylet Guide and Stylets

The lead is packaged with a stylet guide attached and a stylet already inserted. The connector pin with the stylet in it controls the helix mechanism. Use of the stylet guide is optional. An attached stylet guide may be removed by gently pulling it off. To attach a stylet guide, gently push it as far as possible onto the connector pin that accepts the stylet (Figure 4).

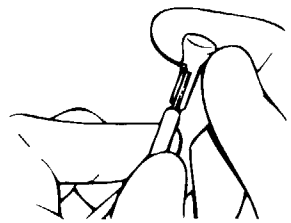

Figure 4. Stylet guide attachment.

A stylet provides additional stiffness and controlled flexibility for maneuvering the lead into position. Stylets vary in stiffness for different lead and stylet flexibility. Each stylet knob is etched with the stylet diameter and length.

If a slight curve is needed for the stylet, refer to instructions in the section titled "Positioning a Lead."

CAUTION: To avoid damage to the lead or body tissue, do not use excessive force or surgical instruments to insert a stylet into the lead. When handling a stylet, avoid overbending, kinking, or blood contact.

CAUTION: Repeated insertions of a stylet increases the chance that blood or other fluids may accumulate on it, which may cause difficulty in passing the stylet through the lead and may cause damage to the lead.

Selecting an Insertion Site

The lead may be inserted by venotomy through several different venous routes, including the right or left cephalic vein or the external or internal jugular vein.

CAUTION: Given the body diameter of transvenous defibrillation leads, insertion via a subclavian approach should be done as far lateral as possible to avoid clamping the lead body between the clavicle and the first rib (Figure 5). Clamping the lead can eventually cause the conductor to fracture, can cause damage to the insulation, or can cause other damage to the lead. This can result in complications such as loss of pacing therapies, and/or loss of cardioversion/defibrillation therapy. Certain anatomical abnormalities, such as thoracic outlet syndrome, can also precipitate pinching and subsequent fracture of the lead. If the subclavian approach is required, avoid techniques that can damage the lead. Specifically, do not force the lead if significant resistance is encountered. Do not use techniques such as adjusting the patient's posture (i.e., raising the arm or putting a towel behind the person's back) to facilitate the passage of the lead. If resistance is encountered, it is recommended that an alternate venous entry site be used, e.g., the cephalic vein.

Use fluoroscopy to facilitate accurate lead placement.

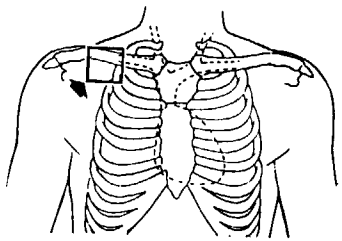

Figure 5. Insertion site.

Using the Vein Lifter

A vein lifter facilitates lead introduction. Insert its tapered end into the incised vein and gently push the lead tip underneath and into the vein (Figure 6).

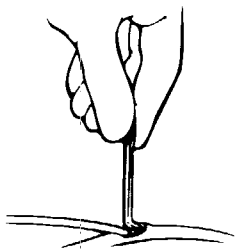

Figure 6. Using the vein lifter.

CAUTION: Avoid placing the lead under extreme tension or angulation to prevent lead dislodgement and possible lead fracture. **Do not grip the lead with surgical instruments.**

Positioning a Lead

Advance the lead into the right atrium. For added control in maneuvering the lead tip through the tricuspid valve, the distal end of the lead may be slightly curved by inserting a gently curved stylet (Figure 7). After the lead tip is passed into the ventricle, the curved stylet may be replaced with a straight stylet. The lead tip may then be advanced to the right ventricular apex while care is taken to avoid perforation of the ventricular wall.

CAUTION: To avoid damage to the stylet, do not use a sharp object to impart a curve to the distal end (Figure 7).

Figure 7. Imparting a curve to the stylet.

Accurate positioning of the electrode is essential for stable endocardial pacing. A satisfactory position is usually achieved when the lead tip points straight toward the apex, or when the distal end dips or bends slightly (Figure 8).

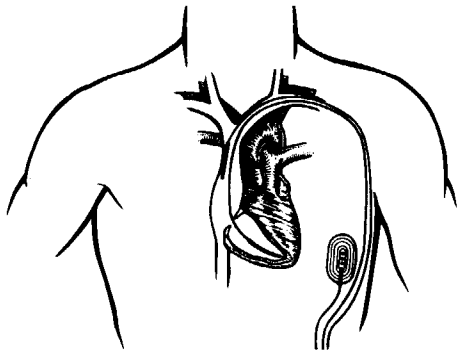

Figure 8. Positioning the Lead

Use fluoroscopy (lateral position) to ensure that the tip is not in a retrograde position or is not lodged in the coronary sinus.

After the stylet is inserted, gently remove the stylet guide so that it rests alongside the stylet knob.

Securing the Electrode into the Endocardium

The following procedure is recommended for electrode fixation:

1. Press both legs of the fixation tool together and place the most distal hole of the fixation tool on the connector pin that accepts the stylet (Figure 2).
2. Gently press the lead tip against the endocardium by pushing the stylet and the lead at the vein entry site. Then, rotate the tool clockwise until the coiled electrode is completely exposed (Figure 3). Maximum electrode exposure reveals 2 coils.

The maximum number of revolutions of the fixation tool needed to extend or retract the helix is 20.

CAUTION: Exceeding the maximum number of revolutions to extend or retract the helix may damage the lead.

3. Use fluoroscopy to verify helix electrode exposure. Closing of the space between the conductor (A) and the indicator ring (B) implies complete exposure of the helix electrode (Figure 9).

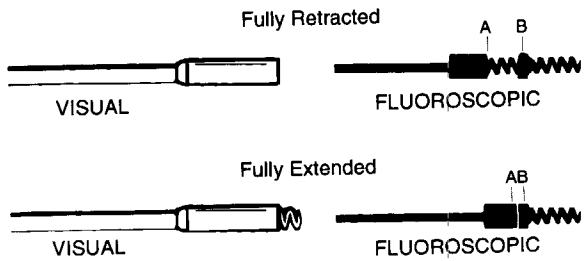

Figure 9. Possible views of the electrode.

4. Disconnect the fixation tool from the connector pin and release the proximal end of the lead body. Allow several seconds for the residual torque in the lead to be relieved.
5. After allowing the residual torque in the lead to be relieved, rotate the whole lead body clockwise approximately one revolution to ensure that the helical electrode is secured to the endocardium.
6. Carefully withdraw the stylet partially.
7. Obtain electrical measurements to verify satisfactory placement and electrode fixation. Refer to the following section, Taking Electrical and Defibrillation Efficacy Measurements, for recommended procedures and values.
8. Verify that the helix is affixed by gently pulling back on the lead and checking for resistance. A properly affixed helix will remain in position. If the helix is not properly affixed, the lead tip may become loose in the right ventricle.
9. If repositioning is required, reattach and rotate the fixation tool counterclockwise until the electrode is withdrawn. Use fluoroscopy to verify withdrawal. Repeat the procedure above.

CAUTION: When retracting the helix, do not rotate the fixation tool more than 20 revolutions. When the electrode is fully retracted, 2 coils of the helix will be visible between the indicator ring and the conductor.

10. Remove the stylet guide and stylet completely. When removing the stylet guide, grip the lead firmly just below the connector pin; this will help prevent possible lead dislodgement.

Bradycardia Pacemakers

Previously implanted bradycardia pacemakers, tachyarrhythmia devices and leads should be explanted. The output pulses of an implanted device may adversely affect the tachyarrhythmia detection capabilities of the PCD device. If leads must be abandoned rather than removed they should be capped to ensure they will not become a pathway for currents to or from the heart. If a patient requires a separate atrial or dual chamber pacemaker for hemodynamic reasons, either permanent or temporary, allow adequate space between the pacing lead electrodes and the defibrillation lead electrodes.

Taking Electrical Measurements and Defibrillation Efficacy Measurements

Initial electrical measurements may deviate from the recommendations because of acute cellular trauma. If this occurs, wait five to fifteen minutes and repeat the testing procedure. Values may vary depending upon lead type, pulse generator settings, cardiac tissue condition, and drug interactions. If electrical measurements do not stabilize to acceptable levels, it may be necessary to reposition the lead and repeat the testing procedure.

To demonstrate reliable defibrillation efficacy with acute or chronic leads, it is recommended that VF be initiated and terminated either two consecutive times at a stored energy of 24 joules or less, or 3 out of 4 times at a stored energy of 24 joules or less. If more than one of the four VF inductions are not terminated by the ETCD and lead system, the decision to implant the PCD® device should be re-evaluated.

In order to keep patient morbidity and mortality to a minimum, patients should be rescued promptly with an external device if the lead system and ETCD falls to terminate the VF episode and at least 5 minutes should elapse between VF inductions.

For more information on obtaining electrical measurements, consult the technical manual supplied with the testing device.

Recommended Pacing/Sensing Measurements at Implant
(when using a pacing system analyzer)

Measurements Required	Acute Lead System	Chronic Lead System
Capture threshold (at 0.5 ms pulse width)	≤ 1.0 V	≤ 3.0 V
Impedance	200 - 800 ohms	200 - 800 ohms
Filtered R-wave amplitude	≥ 5 mV (during sinus rhythm)	≥ 3 mV (during sinus rhythm)
Slew rate	≥ 0.75 V/s	≥ 0.45 V/s

Anchoring the Lead

Do not secure the ligatures so tightly that they damage the vein, lead, or anchoring sleeve. Do not tie a ligature directly to the lead body (Figure 10). During anchoring, take care to avoid dislodging the lead tip.

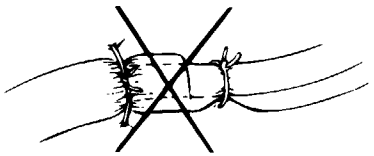

Figure 10. Do NOT secure the sutures too tightly and do NOT tie a suture to the lead body.

Use an anchoring sleeve to secure the lead from moving and to protect the lead insulation and conductor coil from damage caused by tight ligatures. A second anchoring sleeve should be placed in the tunnel entry site or in the pocket area for additional fixation.

Anchor the lead with nonabsorbable sutures.

TRANSVENE®-RV uses a triple groove anchoring sleeve illustrated in Figure 11. The triple groove anchoring sleeves are situated at the connector end of the lead.

Figure 11. The triple groove anchoring sleeve.

With a triple groove anchoring sleeve, all three grooves should be used with the following procedure (Figure 12):

- Partially insert the distal anchoring sleeve into the vein.
- **Use all three grooves to secure the anchoring sleeve (s) to the lead body.**
- Use the most distal suture groove to secure the anchoring sleeve to the vein.
- Use the middle groove to secure the anchoring sleeve to the fascia, vein, and lead body. First, create a base by looping a suture through the fascia underneath the

Taking Electrical Measurements and Defibrillation Efficacy Measurements

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In order to keep patient morbidity and mortality to a minimum, patients should be rescued promptly with an external device if the lead system and ETCD falls to terminate the VF episode and at least 5 minutes should elapse between VF inductions.

For more information on obtaining electrical measurements, consult the technical manual supplied with the testing device.

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(when using a pacing system analyzer)

Measurements Required	Acute Lead System	Chronic Lead System
Capture threshold (at 0.5 ms pulse width)	≤ 1.0 V	≤ 3.0 V
Impedance	200 - 800 ohms	200 - 800 ohms
Filtered R-wave amplitude	≥ 5 mV (during sinus rhythm)	≥ 3 mV (during sinus rhythm)
Slew rate	≥ 0.75 V/s	≥ 0.45 V/s

Anchoring the Lead

Do not secure the ligatures so tightly that they damage the vein, lead, or anchoring sleeve. Do not tie a ligature directly to the lead body (Figure 10). During anchoring, take care to avoid dislodging the lead tip.

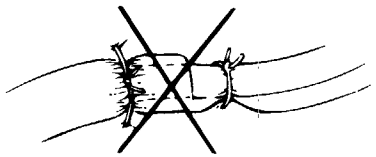


Figure 10. Do NOT secure the sutures too tightly and do NOT tie a suture to the lead body.

Use an anchoring sleeve to secure the lead from moving and to protect the lead insulation and conductor coil from damage caused by tight ligatures. A second anchoring sleeve should be placed in the tunnel entry site or in the pocket area for additional fixation.

Anchor the lead with nonabsorbable sutures.

TRANSVENE®-RV uses a triple groove anchoring sleeve illustrated in Figure 11. The triple groove anchoring sleeves are situated at the connector end of the lead.

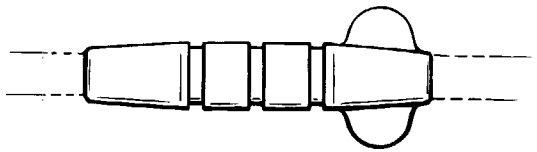


Figure 11. The triple groove anchoring sleeve.

With a triple groove anchoring sleeve, all three grooves should be used with the following procedure (Figure 12):

- Partially insert the distal anchoring sleeve into the vein.
- **Use all three grooves to secure the anchoring sleeve (s) to the lead body.**
- Use the most distal suture groove to secure the anchoring sleeve to the vein.
- Use the middle groove to secure the anchoring sleeve to the fascia, vein, and lead body. First, create a base by looping a suture through the fascia underneath the

middle groove and tying a knot. Continue by firmly wrapping the suture around the middle groove and tying a second knot.

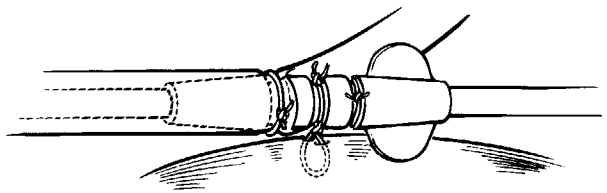


Figure 12. Triple groove anchoring sleeve secured to the lead and fascia using three grooves.

CAUTION: Do not use the anchoring sleeve tabs for suturing.

Tunneling the Lead

Before tunneling the lead connector, record each lead's serial number along with the function of the lead. Use of a chest tube is suggested in tunneling the lead connector to the pulse generator to prevent damage to the lead. Tunnel the lead subcutaneously to the pulse generator pocket.

CAUTION: Do not use surgical instruments to grasp the lead or connector pin when tunneling.

Connecting the Lead to a Tachyarrhythmia Device

Refer to Figures 13a and 13b for instructions and illustrations showing lead connections to the Medtronic® PCD® Tachyarrhythmia Control Device Model 7217B.

Insert the lead connector into the connector block. Refer to the PCD® Tachyarrhythmia Control Device technical manual for the use of setscrews and setscrew tools.

Before closing the pocket, verify sensing, pacing, and defibrillation efficacy.

CAUTION: Always remove the stylet before connecting the lead to the pulse generator. Failure to remove the stylet may result in lead failure.

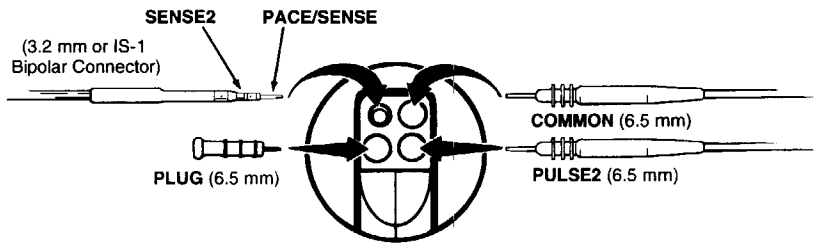
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillation Electrodes	Two-Electrode System Connection Diagram
Medtronic® Model 7217B PCD® Device	2	**PACE/SENSE, SENSE2** Insert the Pace/Sense lead connector of the TRANSVENE®-RV into the PACE/SENSE, SENSE2 port. **COMMON** Insert the unipolar lead connector of the TRANSVENE®-RV, -SVC, or -SQ into the COMMON port.  **PULSE1** Insert the connector plug packaged with the pulse generator into the PULSE1 port. **PULSE2** Insert the lead connector of the TRANSVENE®-RV, -SVC, or -SQ lead into the PULSE2 port.

Figure 13a. Connections for two-electrode system leads (single pulse) into the Medtronic® PCD® Tachyarrhythmia Control Device 7217B.

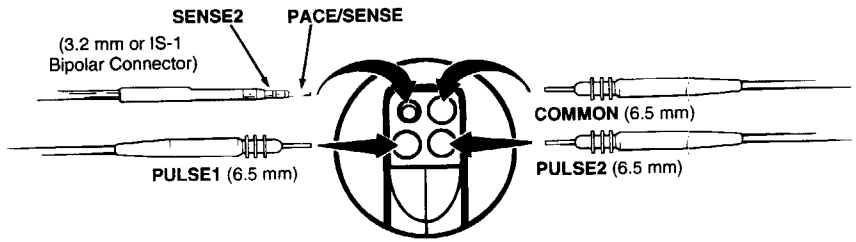
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillation Electrodes	Three-Electrode System Connection Diagram
Medtronic® Model 7217B PCD® Device	3	**PACE/SENSE, SENSE2** Insert the Pace/Sense lead connector of the TRANSVENE®-RV into the PACE/SENSE, SENSE2 port. **COMMON** Insert the unipolar lead connector of the TRANSVENE®-RV, -SVC, or -SQ into the COMMON port.  **PULSE1** Insert the lead connector of the TRANSVENE®-RV, -SVC, or -SQ lead into the PULSE1 port. **PULSE2** Insert the lead connector of the TRANSVENE®-RV, -SVC, or -SQ lead into the PULSE2 port.

Figure 13b. Connections for three-electrode system leads (simultaneous or sequential pulse) into the Medtronic® PCD® Tachyarrhythmia Control Device 7217B.

Closing the Pocket

To prevent undesirable twisting of the lead body, wrap the excess lead length loosely under the pulse generator and place both into the subcutaneous pocket (Figure 14). Ensure that the leads do not leave the pulse generator at an acute angle. Sharp angles place undue stress on the lead conductor and insulation.

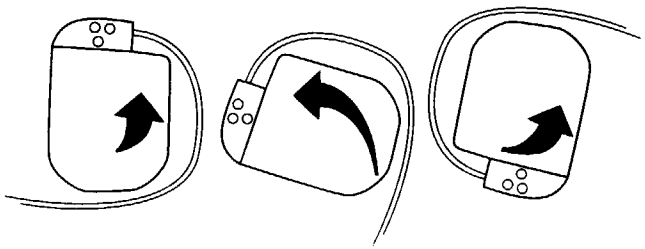


Figure 14. While rotating the pulse generator, loosely wrap the excess lead length and place it under the pulse generator.

To reduce the potential for abrasion on the lead body, it is recommended that the PCD be placed in a Parsonnet pouch.

When placing the pulse generator and leads into the subcutaneous pocket:

- Do NOT coil the lead. Coiling the lead can twist the lead body and may result in lead dislodgement (Figure 15).
- Do NOT grip the lead or pulse generator with surgical instruments.

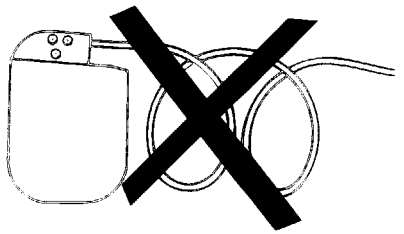


Figure 15. Do not coil or twist the lead body.

Post-Implant Evaluation

After implantation, monitor the patient's electrocardiogram continuously. If a lead dislodges, it usually occurs during the immediate postoperative period.

The patient should have X-rays and pacing/sensing thresholds taken every three months for the first year after implant and every six months thereafter to verify proper lead position and to check for conductor fractures.

In the event of a patient death, all implanted leads and devices should be explanted and returned to Medtronic with a completed PCD® Product Information Report. Any questions on product handling procedures can be addressed by calling 1-800-PCD-INFO.

SPECIFICATIONS (Nominal)

PARAMETER		MODEL 6966
Type		Tripolar
Position		Ventricle
Fixation		Screw-In
Length		110 cm
Connectors	Unipolar:	6.5 mm
	Bipolar:	3.2 mm
Materials	Conductors:	Multifilar MP35N Composite
	Insulator:	Polyurethane
	Electrode:	Platinum Alloy
Electrode Surface Area	Helix:	10 mm^2
	Ring:	37 mm^2
	Coil:	426 mm^2 (5 cm length)

PARAMETER		MODEL 6966
Diameters	Body:	3.3 mm
	Helix:	1.6 mm
	Maximum Head:	3.5 mm
Helix Length (fully extended)		2 mm
Conductor Resistances	Pacing:	45 ohms (unipolar) 190 ohms (bipolar)
	Defibrillation:	3.5 ohms
Lead Introducer (recommended size)		11 French
Maximum Revolutions that can be used to extend or retract the helix when using a straight stylet		20

GENERAL WARNING

Medtronic® implantable leads are implanted in the extremely hostile environment of the human body. Leads are necessarily very small in diameter and must still be very flexible, which unavoidably reduces their potential performance or longevity. Leads may fail to function for a variety of causes, including, but not limited to: medical complications, body rejection phenomena, allergic reaction, fibrotic tissue, or failure of leads by breakage or by breach of their insulation covering. In addition, despite the exercise of all due care in design, component selection, manufacture, and testing prior to sale, leads may be easily damaged before, during, or after insertion by improper handling or other intervening acts. Consequently, no representation or warranty is made that failure or cessation of function of leads will not occur or that the body will not react adversely to the implantation of leads or that medical complications (including perforation of the heart) will not follow the implantation of leads or that the lead will, in all cases, restore adequate cardiac function.

For complete warranty information, see the accompanying card enclosed in the package.

SERVICE

Medtronic employs highly trained representatives and engineers located throughout the world to serve you and, upon request, to provide training to qualified hospital personnel in the use of Medtronic products. In addition, Medtronic maintains a professional staff of consultants to provide technical and medical consultation to product users. For supplemental information, contact your local Medtronic representative, or call or write Medtronic at the appropriate address or telephone number listed on the back cover.

Europe

Medtronic Europe S.A./N.V.
Woluwe Office Garden
Woluwedal 26
1932 St. Stevens Woluwe
Belgium
Telephone: (32-2) 716 88 11
FAX: (32-2) 716 88 15

Asia-Pacific

Japan
Medtronic Asia-Pacific
Shuwa Kioi-cho Park Building, 5F
3-6 Kioi-cho, Chiyoda-ku
Tokyo 102, Japan
Telephone: (81-3) 3230-2701
FAX: (81-3) 3230-0446

Australia
Medtronic Australasia Pty. Ltd.
22 Clarke Street
Crows Nest, Sydney, N.S.W., 2065
Australia
Telephone: (61) 2 437-6066
FAX: (61) 2 437-6869

Asia
Medtronic International Ltd.
2002 CC Wu Building
308 Hennessey Road, Wanchai
Hong Kong, B.C.C.
Telephone: (852-5) 891-4068
FAX: (852) 891-6830

Latin America

Medtronic, Inc.
450 Fairway Drive
Suite 103
Deerfield Beach, FL 33441
USA
Telephone: (305) 428-8556
FAX: (305) 428-8984

North America

Canada
Medtronic of Canada Ltd.
6733 Kitimat Road
Mississauga, Ontario L5N 1W3
Canada
Telephone: (905) 826-6020
FAX: (905) 826-6620
Toll-free: 1-800-268-5346
(24-hour consultation service)

United States
Medtronic, Inc.
7000 Central Avenue, NE
Minneapolis, MN 55432-3576
USA
Telephone: (612) 574-4000
FAX: (612) 574-4879
Toll-free: 1-800-328-2518
(24-hour consultation service)

Medtronic

December 1993
UC9303162aEN 196061-002

60

STERILE
PAK
LABEL

Medtronic

TRANSVENE®-RV

High Voltage Unipolar Connector (6.5 mm)
Connecteur Unipolaire Haute Tension (6,5 mm)
Unipolarer Konnektor Für Hochspannung (6,5 mm)
Conector Monopolar Para Voltaje Aalto (6,5 mm)
Conettore Monopolare Per Alta Tensione (6,5 mm)

Pace/Sense Bipolar Connector (3.2 mm)
Connecteur Bipolaire Pace/Sense (3,2 mm)
Bipolarer Konnektor Für Stimulation/Wahrnehmung (3,2 mm)
Conector Bipolar Pace/Sense (3,2 mm)
Connettore Bipolare Per Stimolazione/Rivelamento (3,2 mm)

Serial Number
Numéro de Série
Seriennummer
Número de Serie
Numero di Serie

Use Before
Utiliser Avant
Zu Implantieren vor dem
Fecha de Caducidad
Data di Scadenza

Lead Length
Longueur de la Sonde
Länge der Elektrode
Longitud del Cable
Lunghezza dell'Elettrocatetere

Sterilization Date
Date de Stérilisation
Sterilisationsdatum
Fecha de Esterilización
Data di Sterilizzazione

Non Reusable
Non Réutilisable
Nicht wiederverwendbar
Interior Desechable
Materiale Sterile Involucro Non Riutilizzabile

Sterilization :Ethylene oxide gas
Stérilisation :Gaz d'oxyde d'éthylène
Sterilisation :Äthylenoxydgas
Esterilización :Gas óxido de etileno
Sterilizzazione :Gas ossido di etilene

Contents: One lead with polyurethane insulation and accessories
Contenu: Une sonde avec isolant en polyuréthane et accessoires
Inhalt: Eine Elektrode mit Polyurethan und Zubehör
Contenido: Un cable con material aislante de poliuretano y accesorios
Contenuto: Un catetere con materiale isolante in poliuretano ed accessori

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician.
ATTENTION: La réglementation américaine (FDA) n'autorise la vente de ce produit que sur prescription médicale.
ACHTUNG: Ein US-Bundesgesetz schränkt den Verkauf dieses Produkts auf Ärzte oder auf Anordnung durch einen Arzt ein.
PRECAUCION: Las Leyes Federales (EE.UU.) restringen la venta de este dispositivo únicamente a médicos o per prescripción médica.
ATTENZIONE: La Legge Federale (U.S.A.) limita la vendita di questo prodotto esclusivamente ai medici o su richiesta del medico.

The contents of this package are **STERILE**
Le contenu de cet emballage est **STERILE**
Der Inhalt dieser Packung ist **STERIL**
El contenido de este envoltorio está **ESTERIL**
Il contenuto de questo imballaggio è **STERILE**

Recommended lead introducer size
Dimension recommandée de l'introducteur
Empfohlene Größe des Elektroden-Einführungsbestecks 11 French
Tamaño recomendado del introductor de cable
Dimensioni raccomandati dell'introduttore

If the package is damaged or opened see the Technical Manual for information
Si l'emballage est endommagé ou ouvert voir le Manuel Technique pour information
Im Falle einer beschädigten oder geöffneten Packung siehe Gebrauchsanweisung
Si el paquete ha sido dañado o abierto, ver el Manual Técnico para información
Se la confezione è danneggiata o aperta vedere il Manuale Tecnico per informazione

CE 0123

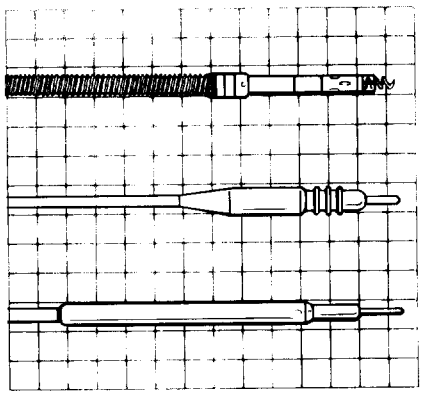
SHELF
BOX
LABEL

Medtronic

TRANSVENE®-RV

High Voltage Unipolar Connector (6.5 mm)
Connecteur Unipolaire Haute Tension (6,5 mm)
Unipolarer Konnektor Für Hochspannung (6,5 mm)
Conector Monopolar Para Voltaje Aalto (6,5 mm)
Connettore Monopolare Per Alta Tensione (6,5 mm)

Pace/Sense Bipolar Connector (3.2 mm)
Connecteur Bipolaire Pace/Sense (3,2 mm)
Bipolarer Konnektor Für Stimulation/Wahrnehmung (3,2 mm)
Conector Bipolar Pace/Sense (3,2 mm)
Connettore Bipolare Per Stimolazione/Rivelamento (3,2 mm)



Serial Number
Numéro de Série
Seriennummer
Número de Serie
Numero di Serie

Use Before
Utiliser Avant
Zu Implantieren vor dem
Fecha de Caducidad
Data di Scadenza

Lead Length
Longueur de la Sonde
Länge der Elektrode
Longitud del Cable
Lunghezza dell'Elettrocatetere

Sterilization Date
Date de Stérilisation
Sterilisationsdatum
Fecha de Esterilización
Data di Sterilizzazione

Contents: One lead with polyurethane insulation, accessories and product literature
Contenu: Une sonde avec isolant en polyuréthane, accesoires et documentation
Inhalt: Eine Elektrode mit Polyurethan Isolation, Zubehör und Dokumentation
Contenido: Un cable con material aislante de poliuretano, accesorios y documentacion
Contenuto: Un catetere con materiale isolante in poliuretano, accessori e documentazione

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician.
ATTENTION: La réglementation américaine (FDA) n'autorise la vente de ce produit que sur prescription médicale.
ACHTUNG: Ein US-Bundesgesetz schränkt den Verkauf dieses Produkts auf Ärzte oder auf Anordnung durch einen Arzt ein.
PRECAUCION: Las Leyes Federales (EE.UU.) restringen la venta de este dispositivo únicamente a médicos o per prescripción médica.
ATTENZIONE: La Legge Federale (U.S.A.) limita la vendita di questo prodotto esclusivamente ai medici o su richiesta del medico.

The contents (**STERILE**) of the inner package have been sterilized by ethylene-oxide gas
Le contenu (**STERILE**) du paquet interne a été stérilisé au gaz d'oxyde d'éthylène
Der Inhalt (**STERIL**) der inneren Verpackung ist in Äthylenoxydgas sterilisiert
El contenido (**ESTERIL**) del paquete interior ha sido esterilizado con gas óxido de etileno
Il contenuto (**STERILE**) della confezione interna è stato sottoposto a sterilizzazione con gas ossido di etilene

STORAGE: Store below 40° C/104° F
STOCKAGE: Au-dessous de 40° C/104° F
LAGERUNG: Unter 40° C/104° F
ALMACENAMIENTO: Por debajo de 40° C/104° F
IMMAGAZZINAGGIO: Al di sottodi 40° C/104° F

Recommended lead introducer size
Dimension recommandée de l'introducteur
Empfohlene Größe des Elektroden-Einführungsbestecks **11 French**
Tamaño recomendado del introductor de cable
Dimensioni raccomandati dell'introduttore

A thoracotomy is not required
Une thoracotomie n'est pas nécessaire
Eine Thorakotomie ist nicht erförderlich
No es necesaria una toracotomía
Una toracotomia no è richiesta

DER GRÜNE PUNKT

CE 0123

END
LABEL

TRANSVENE®-RV 6966

Tripolar, Endocardial, Screw-In Lead
For Ventricular Pacing, Sensing,
Cardioversion and Defibrillation

High Voltage Unipolar Connector (6.5mm)
Pace/Sense Bipolar Connector (3.2mm)

USE BEFORE

SERIAL NO.

INDIVIDUAL
DATA SHEET

INDIVIDUAL DATA SHEET
FICHE TECHNIQUE INDIVIDUELLE
INDIVIDUELLES TECHNISCHES DATENBLATT
HOJA DE DATOS
FOGLIO D'INFORMAZIONI SPECIFICO

MODEL/MODELE/MODELL/MODELO/MODELLO

6966

Serial Number
Numéro de Série
Seriennummer
Número de Serie
Numero di Serie

Use Before
Utiliser Avant
Zu Implantieren vor dem
Fecha de Caducidad
Data di Scadenza

Sterilization :Ethylene oxide gas
Stérilisation :Gaz d'oxyde d'éthylène
Sterilisation :Äthylenoxydgas
Esterilización :Gas óxido de etileno
Sterilizzazione :Gas ossido di etilene

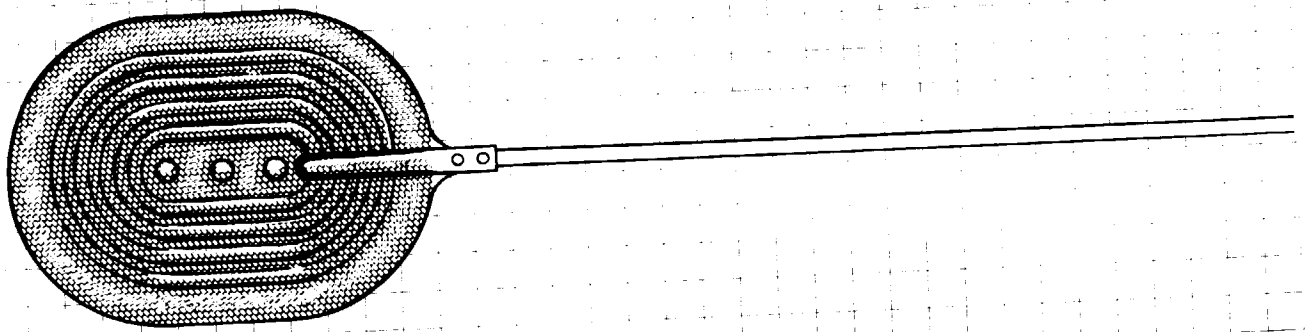
Sterilization Date
Date de Stérilisation
Sterilisationsdatum
Fecha de Esterilización
Data di Sterilizzazione

- model
6966
LEAD

MODEL 6999 LEAD
TECHNICAL MANUAL

Medtronic

TRANSVENE®-SQ 6999



Technical Manual

TECHNICAL MANUAL

TRANSVENE®-SQ UNIPOLAR, SUBCUTANEOUS, OVAL PATCH LEAD FOR CARDIOVERSION AND DEFIBRILLATION

MODEL 6999

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Printed in USA

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DESCRIPTION

The Medtronic® TRANSVENE®-SQ Model 6999 Unipolar, Subcutaneous, Oval Patch Lead is designed for the delivery of cardioversion and defibrillation therapies.

The lead features a low resistance conductor coil and platinum alloy electrode coils for cardioversion and defibrillation therapies. The outer edge of the lead is used for suturing. The lead also has a 6.5 mm unipolar connector.

There are 3 nodes on one side of the patch, and 2 nodes at the junction of the lead body and patch electrode. These nodes are intended to mark the insulated side of the patch electrode.

INDICATIONS FOR USE

The Medtronic® TRANSVENE®-SQ Model 6999 is intended for single long-term use only with a compatible Medtronic implantable tachyarrhythmia control device along with at least one other Medtronic defibrillation lead.

The lead has application for patients in which implantable tachyarrhythmia cardioversion or defibrillation systems are indicated. Current medical research indicates that such patients should:

- have survived at least one episode of a cardiac arrest, presumably due to a ventricular tachyarrhythmia as evidenced by resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; OR
- in the absence of a prior cardiac arrest, have poorly tolerated sustained VT and/or VF, which occurs spontaneously or can be induced despite the best antiarrhythmic drug therapy.

The natural history of patients with hemodynamically stable sustained VT is not well defined. While this patient population was included in the TRANSVENE® Lead clinical

study, no conclusions were drawn from the data obtained on this specific patient group.

Prior to TRANSVENE® implant, it is strongly recommended that patients undergo a complete cardiac evaluation, which should include extensive electrophysiologic testing. Also, extensive electrophysiologic evaluation and testing of the safety and efficacy of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the TRANSVENE® system.

CONTENTS OF PACKAGE

The leads are supplied sterile. Each package contains:

- 1 TRANSVENE®-SQ lead
- End Cap
- Product literature

CONTRAINDICATIONS

The TRANSVENE® system is contraindicated for patients:

- with transient ventricular tachyarrhythmias due to reversible causes, e.g., drug intoxication, electrolyte imbalance, sepsis, or hypoxia.
- with transient ventricular tachyarrhythmias due to other factors, e.g., myocardial infarction and electrocution.

The TRANSVENE® system is contraindicated for the sole use of detection and treatment of atrial arrhythmias.

WARNINGS

Do not attempt to use the TRANSVENE® lead system with any device other than a Medtronic implantable tachyarrhythmia control device for which it has been tested. While there has been no testing of the TRANSVENE® leads with a non-Medtronic device, the potential adverse consequences of using such a combination may include, but are not limited to, undersensing cardiac activity and failure to deliver necessary therapy.

Use only battery-powered equipment during lead implantation and testing to protect against fibrillation that may be caused by alternating currents. Line-powered equipment used in the vicinity of the patient must be properly grounded. Lead connector pins must be insulated from any leakage currents that may arise from line-powered equipment.

The Model 6999 TRANSVENE®-SQ patch lead is not intended for epicardial or pericardial placement since testing has not been performed to determine if epicardial or pericardial use is safe or effective.

Placement of a patch electrode over nerve tissue may result in nerve damage.

The Model 6999 TRANSVENE® leads have palpable nodes on the insulation side of the patch which must face the skin surface to assure the electrode surface is facing the heart. If the insulation side of the patch is facing the heart cardioversion/defibrillation energy may be inadequate to reliably convert arrhythmias.

If patients do not meet the implant criteria (demonstration of a 10 Joule safety margin) for a transvenous lead system, physicians should consider implanting an epicardial cardioversion/defibrillation lead system. If an epicardial system is to be implanted after testing a transvenous system, consider performing the procedure at a later date. The TRANSVENE® clinical study showed a 9.3% perioperative death rate for patients failing the implant criteria for a TRANSVENE® system and receiving an epicardial system. This compares to 0.7% for those patients receiving a TRANSVENE® system without the additional epicardial surgical procedure.

See also the section titled "General Warning."

PRECAUTIONS

Necessary Hospital Equipment

Defibrillation equipment should be kept nearby for immediate use during the acute lead system testing, implantation procedure, or whenever arrhythmias are possible or intentionally induced during post-implant testing.

Inspecting the Package

Carefully inspect the lead package prior to opening; if the seal or package is damaged, contact your local Medtronic representative.

Resterilization

For resterilization use ethylene oxide only. Do not resterilize more than one time.

Handling the Lead

Leads should be handled with great care at all times. **Any severe bending, kinking, stretching, or handling with surgical instruments may cause permanent damage to the lead.**

Lead insulators attract small particles such as lint and dust. Therefore, protect the lead from materials shedding these substances. Handle the lead with sterile gloves that have been wiped with a sterile moist sponge or equivalent.

Do not immerse leads in mineral oil, silicone oil, or any other liquid.

Chronic Repositioning

Chronic repositioning or removal of the lead may be difficult because of the fibrotic tissue. **However, if a lead must be removed or repositioned, proceed with extreme caution.** If a lead is abandoned, it should be capped to avoid transmitting electrical signals. Return all removed or unused leads or portions thereof to Medtronic.

Implant Technique

Do not use surgical instruments to grasp the lead or connector pin when tunneling.

POTENTIAL ADVERSE EFFECTS

The potential adverse effects related to the use of subcutaneous patch leads include, but are not limited to, the following patient-related conditions: serous fluid accumulation around the patch; infection; and bleeding after placement, after repositioning, or if sutures tear out.

Other potential adverse effects related to the lead system, but are not limited to the following: lead displacement, lead conductor or electrode fracture, insulation failure, and poor connection which may lead to loss of pacing therapies, and/or loss of cardioversion/defibrillation therapy.

ENSURING PRODUCT INTEGRITY

Carefully inspect the sterile package before opening. It is not recommended that you use the product after its expiration date.

If the integrity of the sterile package has been compromised prior to the product expiration date, place the contents in a gas-permeable bag and resterilize them with ethylene oxide as described below.

CAUTION: Use ethylene oxide only. Do not resterilize more than one time.

The process should not exceed temperatures of 55°C (130°F). Allow proper aeration of ethylene oxide residues prior to implantation. Use an acceptable method to determine sterilizer effectiveness, such as a biological indicator.

Due to the variability between sterilizers, precise sterilization instructions cannot be provided. Contact your sterilizer manufacturer for more information regarding sterilization procedures.

SUGGESTED IMPLANTATION PROCEDURE

General Instructions

The implantation procedure generally includes selecting an insertion site; positioning the lead; taking electrical and defibrillation efficacy measurements; tunneling the lead; connecting the lead to the pulse generator; and closing the pocket.

Proper surgical procedures and sterile techniques are the responsibility of the medical professional. The implant procedures described in this manual are furnished for information only. Each physician must apply the information in these instructions according to professional medical training and experience.

Opening the Package

Open the package according to the instructions and inspect the lead.

Positioning a Lead

The recommended starting position for the TRANSVENE®-SQ subcutaneous patch lead is along the left chest near the heart. The patch may be repositioned, if necessary, to meet the implant defibrillation efficacy criteria.

The subcutaneous patch should be placed subcutaneously, submuscularly, or directly on the periosteum of the ribs.

Place sutures through the outer edge of the patch electrode. It is recommended that two or more sutures be used for fixation.

CAUTION: The patch must be placed such that the nodes are facing away from the heart (Figure 1).

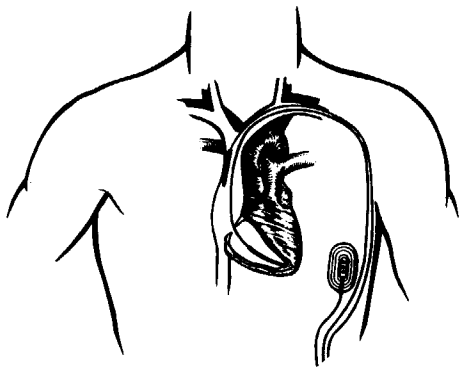


Figure 1. Positioning a Patch Lead

Taking Electrical Measurements and Defibrillation Efficacy Measurements

Initial electrical measurements may deviate from the recommendations because of acute cellular trauma. If this occurs, wait five to fifteen minutes and repeat the testing procedure. Values may vary depending upon lead type, pulse generator settings, cardiac tissue condition, and drug interactions. If electrical measurements do not stabilize to acceptable levels, it may be necessary to reposition the lead and repeat the testing procedure.

To demonstrate reliable defibrillation efficacy with acute or chronic leads, it is recommended that VF be initiated and terminated either two consecutive times at a stored energy of 24 joules or less, or 3 out of 4 times at a stored energy of 24 joules or less. If more than one of the four VF inductions are not terminated by the ETCD and lead system, the decision to implant the PCD device should be re-evaluated.

In order to keep patient morbidity and mortality to a minimum, patients should be rescued promptly with an external device if the lead system and ETCD fails to terminate the VF episode and at least 5 minutes should elapse between VF inductions.

For more information on obtaining electrical measurements, consult the technical manual supplied with the testing device.

Recommended Pacing/Sensing Measurements at Implant
(when using a pacing system analyzer)

Measurements Required	Acute Lead System	Chronic Lead System
Capture threshold (at 0.5 ms pulse width)	≤ 1.0 V	≤ 3.0 V
Impedance	200 - 800 ohms	200 - 800 ohms
Filtered R-wave amplitude	≥ 5 mV (during sinus rhythm)	≥ 3 mV (during sinus rhythm)
Slew rate	≥ 0.75 V/s	≥ 0.45 V/s

Tunneling the Lead

Before tunneling the lead connector, record each lead's serial number along with the function of the lead. Use of a chest tube is suggested in tunneling the lead connector to the pulse generator to prevent damage to the lead. Tunnel the lead subcutaneously to the pulse generator pocket.

CAUTION: Do not use surgical instruments to grasp the lead or connector pin when tunneling.

Connecting the Lead to a Tachyarrhythmia Device

Refer to Figures 2a and 2b for instructions and illustrations showing lead connections to the Medtronic® PCD® Tachyarrhythmia Control Device Model 7217B.

Insert the lead connector into the connector block. Refer to the PCD® Tachyarrhythmia Control Device technical manual for the use of setscrews and setscrew tools.

Before closing the pocket, verify sensing, pacing, and defibrillation efficacy.

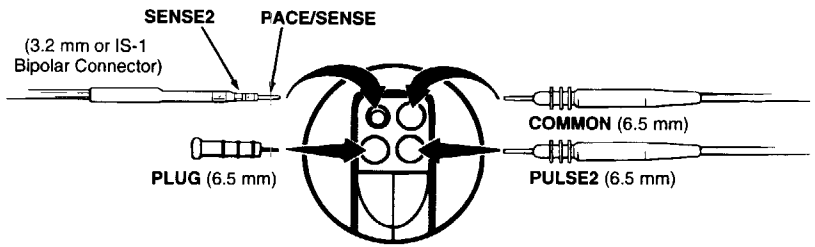
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillation Electrodes	Two-Electrode System Connection Diagram
Medtronic® Model 7217B PCD® Device	2	**PACE/SENSE, SENSE2** Insert the Pace/Sense lead connector of the TRANSVENE®-RV into the PACE/SENSE, SENSE2 port. **COMMON** Insert the unipolar lead connector of the TRANSVENE®-RV, -SVC, or -SQ into the COMMON port.  **PULSE1** Insert the connector plug packaged with the pulse generator into the PULSE1 port. **PULSE2** Insert the lead connector of the TRANSVENE®-RV, -SVC, or -SQ lead into the PULSE2 port.

Figure 2a. Connections for two-electrode system leads (single pulse) into the Medtronic® PCD® Tachyarrhythmia Control Device Model 7217B.

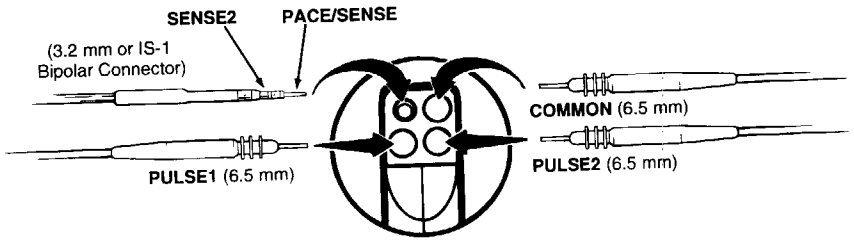
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillation Electrodes	Three-Electrode System Connection Diagram
Medtronic® Model 7217B PCD® Device	3	**PACE/SENSE, SENSE2** Insert the Pace/Sense lead connector of the TRANSVENE®-RV into the PACE/SENSE, SENSE2 port. **COMMON** Insert the unipolar lead connector of the TRANSVENE®-RV, -SVC, or -SQ into the COMMON port.  **PULSE1** Insert the lead connector of the TRANSVENE®-RV, -SVC, or -SQ lead into the PULSE1 port. **PULSE2** Insert the lead connector of the TRANSVENE®-RV, -SVC, or -SQ lead into the PULSE2 port.

Figure 2b. Connections for three-electrode system leads (simultaneous or sequential pulse) into the Medtronic® PCD® Tachyarrhythmia Control Device Model 7217B.

Closing the Pocket

To prevent undesirable twisting of the lead body, wrap the excess lead length loosely under the pulse generator and place both into the subcutaneous pocket (Figure 3). Ensure that the leads do not leave the pulse generator at an acute angle. Sharp angles place undue stress on the lead conductor and insulation.

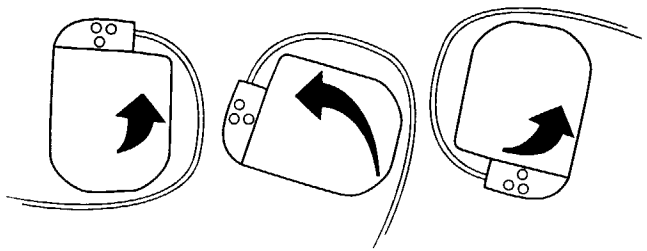


Figure 3. While rotating the pulse generator, loosely wrap the excess lead length and place it under the pulse generator.

To reduce the potential for abrasion on the lead body, it is recommended that the PCD be placed in a Parsonnet pouch.

When placing the pulse generator and leads into the subcutaneous pocket:

- Do NOT coil the lead. Coiling the lead can twist the lead body and may result in lead dislodgement (Figure 4).
- Do NOT grip the lead or pulse generator with surgical instruments.

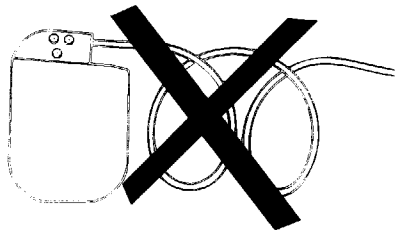


Figure 4. Do not coil or twist the lead body.

Post-Implant Evaluation

After implantation, monitor the patient's electrocardiogram continuously. If a lead dislodges, it usually occurs during the immediate postoperative period.

The patient should have X-rays and pacing/sensing thresholds taken every three months for the first year after implant and every six months thereafter to verify proper lead position and to check for conductor fractures.

In the event of a patient death, all implanted leads and devices should be explanted and returned to Medtronic with a completed PCD® Product Information Report. Any questions on product handling procedures can be addressed by calling 1-800-PCD-INFO.

SPECIFICATIONS (Nominal)

PARAMETER	MODEL 6999
Type	Unipolar
Position	Subcutaneous chest wall
Fixation	Sutures (may be placed through the outer edge of the patch body)
Length	50 cm
Connector	6.5 mm
Materials	Conductor: Multifilar MP35N Composite Insulator: Silicone Electrode: Platinum Alloy

PARAMETER	MODEL 6999
Number of Electrode Coils	4
Electrode Surface Area	660 mm^2
Body Diameter	2.5 mm
Patch Dimensions	8.0 cm x 11.0 cm
Silicone Patch Area	50 cm^2
Unipolar Resistance	1.2 ohms

GENERAL WARNING

Medtronic® implantable leads are implanted in the extremely hostile environment of the human body. Leads are necessarily very small in diameter and must still be very flexible, which unavoidably reduces their potential performance or longevity. Leads may fail to function for a variety of causes, including, but not limited to: medical complications, body rejection phenomena, allergic reaction, fibrotic tissue, or failure of leads by breakage or by breach of their insulation covering. In addition, despite the exercise of all due care in design, component selection, manufacture, and testing prior to sale, leads may be easily damaged before, during, or after insertion by improper handling or other intervening acts. Consequently, no representation or warranty is made that failure or cessation of function of leads will not occur or that the body will not react adversely to the implantation of leads or that medical complications will not follow the implantation of leads or that the lead will, in all cases, restore adequate cardiac function.

For complete warranty information, see the accompanying card enclosed in the package.

SERVICE

Medtronic employs highly trained representatives and engineers located throughout the world to serve you and, upon request, to provide training to qualified hospital personnel in the use of Medtronic products. In addition, Medtronic maintains a professional staff of consultants to provide technical and medical consultation to product users. For supplemental information, contact your local Medtronic representative, or call or write Medtronic at the appropriate address or telephone number listed on the back cover.

STERILE
PAK
LABEL

Medtronic

TRANSVENE®-SQ

Unipolar Connector (6.5mm)/Connecteur Unipolaire (6.5mm)/Unipolarer Konnektor (6.5mm)/Conector Monopolar (6.5mm)/Connettore Monopolare (6.5mm)

Serial Number
Numéro de Série
Seriennummer
Número de Serie
Numero di Serie

Use Before
Utiliser Avant
Zu Implantieren vor dem
Fecha de Caducidad
Data di Scadenza

Lead Length
Longueur de la Sonde
Länge der Elektrode
Longitud del Cable
Lunghezza dell'Elettrocatetere

Sterilization Date
Date de Stérilisation
Sterilisationsdatum
Fecha de Esterilización
Data di Sterilizzazione

Non Reusable
Non Réutilisable
Nicht wiederverwendbar
Interior Desechable
Materiale Sterile Involucro Non Riutilizzabile

Sterilization :Ethylene oxide gas
Stérilisation :Gaz d'oxyde d'éthylène
Sterilisation :Äthylenoxydgas
Esterilización :Gas óxido de etileno
Sterilizzazione :Gas ossido di etilene

Contents: One lead with silicone insulation and accessory.
Contenu: Une sonde avec isolation de silicone et accessoire.
Inhalt: Eine Elektrode mit Silikon-Isolation und Zubehör.
Contenido: Un cable con material aislante de silicona y accesorio.
Contenuto: Un elettrocatetere con materiale isolante in silicone e accessorio.

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician.
ATTENTION: La réglementation américaine (FDA) n'autorise la vente de ce produit que sur prescription médicale.
ACHTUNG: Ein US-Bundesgesetz schränkt den Verkauf dieses Produkts auf Ärzte oder auf Anordnung durch einen Arzt ein.
PRECAUCION: Las Leyes Federales (EE.UU.) restringen la venta de este dispositivo únicamente a médicos o per prescripción médica.
ATTENZIONE: La Legge Federale (U.S.A.) limita la vendita di questo prodotto esclusivamente ai medici o su richiesta del medico.

The contents of this package are **STERILE**
Le contenu de cet emballage est **STERILE**
Der Inhalt dieser Packung ist **STERIL**
El contenido de este envoltorio está **ESTERIL**
Il contenuto de questo imballaggio è **STERILE**

If the package is damaged or opened see the Technical Manual for information
Si l'emballage est endommagé ou ouvert voir le Manuel Technique pour information
Im Falle einer beschädigten oder geöffneten Packung siehe Gebrauchsanweisung
Si el paquete ha sido dañado o abierto, ver el Manual Técnico para información
Se la confezione è danneggiata o aperta vedere il Manuale Tecnico per informazione

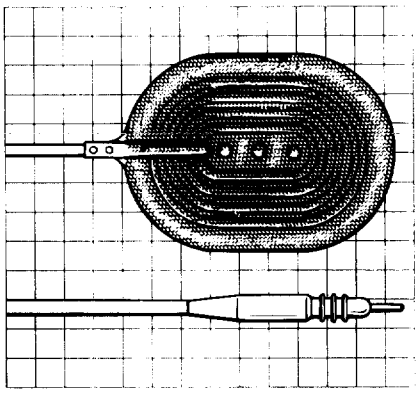
CE 0123

SHELF
BOX
LABEL

Medtronic

TRANSVENE®-SQ

Unipolar Connector (6.5mm)/Connecteur Unipolaire (6.5mm)/Unipolarer Konnektor (6.5mm)/Conector Monopolar (6.5mm)/Connettore Monopolare (6.5mm)



Serial Number
Numéro de Série
Seriennummer
Número de Serie
Numero di Serie

Use Before
Utiliser Avant
Zu Implantieren vor dem
Fecha de Caducidad
Data di Scadenza

Lead Length
Longueur de la Sonde
Länge der Elektrode
Longitud del Cable
Lunghezza dell'Elettrocatetere

Sterilization Date
Date de Stérilisation
Sterilisationsdatum
Fecha de Esterilización
Data di Sterilizzazione

Contents: One lead with silicone insulation accessory and product literature
Contenu: Une sonde avec isolation de silicone, accessoire et documentation
Inhalt: Eine Elektrode mit Silikon-Isolation, Zubehör und Dokumentation
Contenido: Un cable con material aislante de silicona, accesorio y documentación
Contenuto: Un elettrocatetere con materiale isolante in silicone, accessorio e documentazione

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician.
ATTENTION: La réglementation américaine (FDA) n'autorise la vente de ce produit que sur prescription médicale.
ACHTUNG: Ein US-Bundesgesetz schränkt den Verkauf dieses Produkts auf Ärzte oder auf Anordnung durch einen Arzt ein.
PRECAUCION: Las Leyes Federales (EE.UU.) restringen la venta de este dispositivo únicamente a médicos o per prescripción médica.
ATTENZIONE: La Legge Federale (U.S.A.) limita la vendita di questo prodotto esclusivamente ai medici o su richiesta del medico.

The contents (**STERILE**) of the inner package have been sterilized by ethylene-oxide gas
Le contenu (**STERILE**) du paquet interne a été stérilisé au gaz d'oxyde d'éthylène
Der Inhalt (**STERIL**) der inneren Verpackung ist in Äthylenoxydgas sterilisiert
El contenido (**ESTERIL**) del paquete interior ha sido esterilizado con gas óxido de etileno
Il contenuto (**STERILE**) della confezione interna è stato sottoposto a sterilizzazione con gas ossido di etilene

STORAGE: Store below 40° C/104° F
STOCKAGE: Au-dessous de 40° C/104° F
LAGERUNG: Unter 40° C/104° F
ALMACENAMIENTO: Por debajo de 40° C/104° F
IMMAGAZZINAGGIO: Al di sottodi 40° C/104° F

A thoracotomy is not required
Une thoracotomie n'est pas nécessaire
Eine Thorakotomie ist nicht erförderlich
No es necesaria una toracotomía
Una toracotomia no è richiesta

DER GRÜNE PUNKT

CE 0123

END
LABEL

TRANSVENE®-SQ 6999

Unipolar, Subcutaneous, Oval Patch
Lead for Cardioversion and Defibrillation
Unipolar Connector (6.5mm)

USE BEFORE

SERIAL NO.

INDIVIDUAL
DATA SHEET

INDIVIDUAL DATA SHEET
FICHE TECHNIQUE INDIVIDUELLE
INDIVIDUELLES TECHNISCHES DATENBLATT
HOJA DE DATOS
FOGLIO D'INFORMAZIONI SPECIFICO

MODEL/MODELE/MODELL/MODELO/MODELLO

6999

Serial Number Numéro de Série Seriennummer Número de Serie Numero di Serie	Use Before Utiliser Avant Zu Implantieren vor dem Fecha de Caducidad Data di Scadenza

Sterilization	:Ethylene oxide gas	Sterilization Date
Stérilisation	:Gaz d'oxyde d'éthylène	Date de Stérilisation
Sterilisation	:Äthylenoxydgas	Sterilisationsdatum
Esterilización	:Gas óxido de etileno	Fecha de Esterilización
Sterilizzazione	:Gas ossido di etilene	Data di Sterilizzazione

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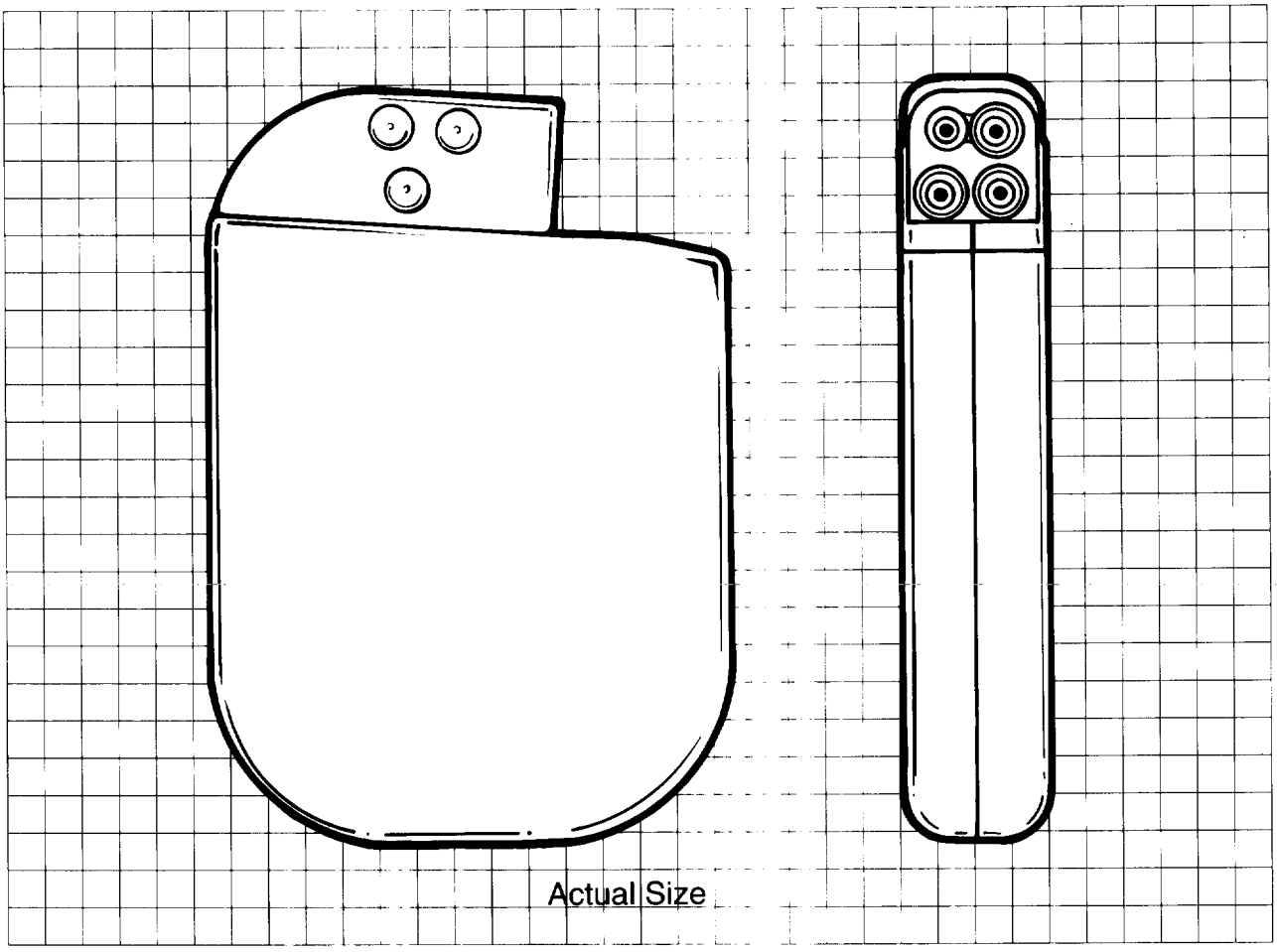
Model
7217B
PCD
Device

MODEL 7217B
TECHNICAL MANUAL

Medtronic

PCD®

7217B



Technical Manual

THE PCD® TACHYARRHYTHMIA CONTROL DEVICE

MODEL 7217B TECHNICAL MANUAL

An Implantable Device for the Control of Ventricular Arrhythmias Through Pacing, Cardioversion, and Defibrillation

Medtronic

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Printed in USA

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Before implanting a Model 7217B PCD device, it is strongly recommended that the physician do the following:

- Thoroughly read this manual, the systems applications manual for the programmer MemoryMod® cartridge, the External Tachyarrhythmia Control Device (ETCD™) technical manual, and the technical manuals for the leads used with the device.
- Provide a copy of the patient manual to the patient and discuss it with him or her and any other interested parties.
- Medtronic requires physicians to attend an education seminar on the complete PCD system. This includes the following topics:
  - Indications for use
  - Overview of the PCD system functions
  - Implant procedure
  - Patient management

Automatic defibrillation was invented and patented in 1953 by Dr. F. Zacouto, who designed an external device that delivered a defibrillation impulse to the heart upon detection of very rapid ECG activity in combination with the absence of arterial pulsations.

Certain antitachycardia pacing modes of this device, invented by Dr. Fred Zacouto of Paris, France, fall under one or more patent claims of U.S. Patents 3,857,399 and 4,052,991 and corresponding patents in other countries, which are licensed exclusively to Medtronic, Inc.

The primary reference for background information is Zacouto FI, Guize LJ. Fundamentals of Orthorhythmic Pacing. In: Luderitz B, ed. *Cardiac Pacing Diagnostic and Therapeutic Tools*. New York: Springer-Verlag; 1976: 212-218.

See these additional references for more background information:

1. Theisen K, Zacouto F, et al. Refraktarzeitmessung bei absoluter Arrhythmie mit orthorhythmischer Serienstimulation. *Klin. Wschr.* 1974; 52: 1082-1084.

2. Guize L, Zacouto F, et al. Stimulation endocardiaques orthorhythmiques. *La Nouvelle Presse medicale.* 1974; 3(33): 2083-2086.

3. Effert S. Automatische Uberwachungsgerate und Indikation zur Implantation von elektrischen Schrittmachern. *Thoraxchirurgie und Vaskulare Chirurgie.* 1963; 11: 158-165. This describes the automatic defibrillation equipment of Dr. F. Zacouto.

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GENERAL DESCRIPTION

The Medtronic Model 7217B PCD® (Pacer-Cardioverter-Defibrillator) Device is an implantable, multiprogrammable, automatic tachyarrhythmia control device. The PCD device is designed to automatically detect episodes of ventricular tachycardia (VT) or ventricular fibrillation (VF) and, upon detection, deliver the appropriate programmed pacing, cardioversion, or defibrillation therapies. The device has two independently programmable detection and therapy procedures, one for VT and a second for VF.

The VT Detection circuitry can use up to four separately programmable detection modes as it monitors the cardiac cycle length to identify the presence of a tachycardia. Upon detection, the PCD device delivers its first programmed VT therapy. If the VT episode persists and is again detected, up to three additional independently programmable VT therapies may be delivered to restore the patient's normal cardiac rhythm. This progression of four VT therapies can be tailored to each patient's needs. The therapies may be selected from two methods of overdrive pacing (Burst and Ramp) and synchronized Cardioversion.

The VF Detection circuitry uses three programmable parameters as it monitors the cardiac cycle length to identify a VF episode. Upon detection, VF therapy provides a programmable high-energy defibrillation shock. Up to a maximum of four VF therapies may be delivered for ongoing detected VF episodes. Each defibrillation therapy consists of a single shock or two simultaneous or sequential high-voltage pulses designed to restore the normal cardiac rhythm.

The PCD device provides bradycardia therapy via ventricular inhibited (VVI) pacing.

The PCD device requires an appropriate lead system, consisting of up to five electrodes. Cardioversion and defibrillation occur between the **PULSE1** and/or **PULSE2** and **COMMON** electrodes[1]. The optional **PULSE1** electrode and the **PULSE2** electrode serve as anodes for the cardioversion and defibrillation therapies. Pacing stimuli occur between the **PACE/SENSE** (pacing cathode) and **COMMON**. Sensing of cardiac activity occurs between the **PACE/SENSE** and **SENSE2** electrodes.

The PCD device is to be programmed with an appropriate Medtronic programmer (e.g., the Model 9710 or other equivalent unit). Instructions for programming the PCD device may be found in the Model 9788 MemoryMod® Software Cartridge Technical Manual (or equivalent). Programmers from other manufacturers are **NOT** compatible.

The physician may use the PCD device to conduct noninvasive electrophysiologic studies (EPS) via the Programmer and appropriate MemoryMod cartridge. The physician can also manually deliver various therapies via the Programmer to manage an induced or spontaneous tachyarrhythmia.

The PCD device will provide the physician with information, via the Programmer, about its present programmed parameters, status, and data on its operation accumulated between office visits. This information may be printed and retained in the patient's file.

1. See the Lead Technical Manuals for details on the lead system.

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PRESCRIBING THE MODEL 7217B PCD DEVICE

Intended Uses

The Model 7217B PCD device is intended for use in patients who are at high risk of sudden death due to ventricular tachyarrhythmia. Current medical research indicates that such patients should:

- have survived at least one episode of a cardiac arrest, presumably due to a ventricular tachyarrhythmia as evidenced by resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; OR
- in the absence of a prior cardiac arrest, have poorly tolerated sustained VT and/or VF, which occurs spontaneously or can be induced despite the best antiarrhythmic drug therapy.

The natural history of patients with hemodynamically stable sustained VT is not well defined. While this patient population was included in PCD clinical studies the study objectives did not include stratification of this specific patient group.

The PCD device may be used as a replacement for a previously implanted, commercially-available Automatic Implantable Cardioverter Defibrillator. The PCD device is intended for use only with the defibrillation lead systems with which it has been tested, which are Medtronic epicardial patch leads and Cardiac Pacemakers, Inc., patch leads.

Prior to implant, it is strongly recommended that patients undergo a complete cardiac evaluation, which should include extensive electrophysiologic testing. Also, extensive electrophysiologic evaluation and testing of the safety and efficacy of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the Model 7217B PCD device.

Before permanently programming the PCD device to the automatic detection and delivery of the VT and/or VF therapies, the patient should have demonstrated a satisfactory response to the proposed therapy. For more information, see "Programming Considerations" and "Pre-Hospital Discharge" in "Post-Implant Information."

Contraindications

The Model 7217B PCD device is contraindicated for patients:

- with transient ventricular tachyarrhythmias due to reversible causes, e.g., drug intoxication, electrolyte imbalance, sepsis, or hypoxia.
- with transient ventricular tachyarrhythmias due to other factors, e.g., myocardial infarction and electrocution.

The Model 7217B PCD device is contraindicated for the sole use of detection and treatment of atrial arrhythmias.

Because of the potential for damage to the PCD device and/or induction of life-threatening arrhythmias, the use of the following techniques and/or therapies is contraindicated in patients who have an implanted Model 7217B PCD device:

- Magnetic Resonance Imaging (MRI) and
- Hydraulic Shock-wave Lithotripsy

LONGEVITY EXPECTATIONS

The longevity of the Model 7217B PCD device depends upon several factors including programmed bradycardia pacing parameters, the percentage of paced to sensed events, the pacing load, and the frequency of high-voltage capacitor charging. The longevity projections found in Table 1 apply under the following conditions:

- 65 ppm pacing rate,
- 5.4 V pacing pulse amplitude,
- 0.49 ms pacing pulse width, and
- 500 ohm pacing load.

Table 1. Projected Longevity[1]

Pacing/Sensing	34-Joule Charging Frequency	Average Longevity
100% sensing	Quarterly	5.0 years
15% pacing	Monthly	4.2 years
100% pacing	Monthly	3.4 years

The longevity of the device decreases with the following:

- an increase in pacing rate,
- an increase in pacing amplitude,
- a decrease in pacing impedance,
- an increase in pacing pulse width,
- an increase in the percentage of bradycardia paced to sensed events, or
- an increase in the charging frequency.

Each 34-joule charging cycle will typically decrease the longevity of the device by approximately six days.

For information on when to replace the PCD device, see "Elective Replacement and Potential Loss of Function Indicators" in "Post-Implant Information."

1. These preliminary longevity projections are based upon accelerated battery discharge data and device modeling. They include an estimate of five months between time of manufacture of a PCD device and its implant. If a device was stored for the full twelve-month shelf life, the average longevity would be reduced an estimated 4.3 to 5.9 months, depending on device use. With the stated conditions, 100% pacing and monthly 34-joule charging cycles, the minimum longevity of the device will be 2.5 years. Average refers to the projected mean longevity of the modeled run of PCD devices at the stated conditions. Minimum longevity means that virtually all (i.e. 99.9%) of all modeled production runs of PCD devices will attain the value given.

100

PRINCIPLES OF OPERATION

Overview

The Model 7217B PCD device is designed to detect two types of sustained ventricular tachyarrhythmia: ventricular tachycardia (VT) and ventricular fibrillation (VF). The sensing circuitry used for detection employs a bipolar electrode configuration (**PACE/SENSE** to **SENSE2**) to maximize rejection of myopotentials, far-field P-waves, and other electrical signals. Separately programmable detection criteria are designed to allow the PCD device to differentiate between VT and VF.

Once either VT or VF is detected, the PCD device will deliver the first programmed VT or VF therapy and up to three additional programmed therapies if the episode persists and is repeatedly detected. Three kinds of VT therapy are available: two different types of overdrive pacing therapy and a synchronized cardioversion therapy. VF therapy consists of high-energy defibrillation shocks; the stored energy level is separately programmable for all four VF therapies.

If required, the PCD device will provide bradycardia therapy with pacing (**PACE/SENSE** to **COMMON**) at the programmed lower rate in the VVI mode.

Figure 1 summarizes the detection and therapy features of the PCD device.

Complete details of these operations are found in the sections that follow:

- Features Used in Sensing and VT/VF Detection
- Ventricular Tachycardia (VT) Detection
- Ventricular Tachycardia (VT) Therapy
- Ventricular Fibrillation (VF) Detection
- Ventricular Fibrillation (VF) Therapy
- VVI Therapy

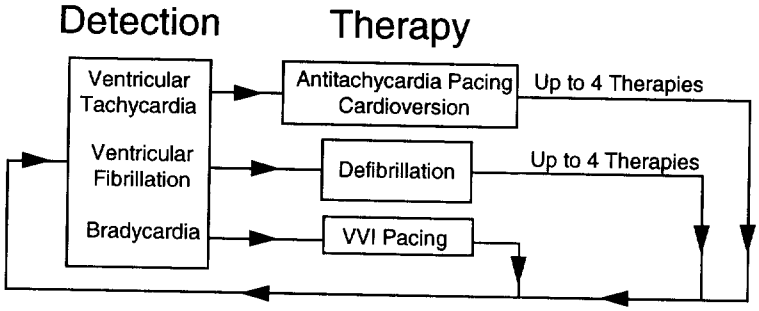


Figure 1. Detection and Therapy in the PCD Device

Features Used in Sensing and VT/VF Detection

Proper sensing is essential for the safe and effective use of the PCD device. The device's sensing function should be regularly verified by means of Marker Channel™ telemetry (see "Telemetry Reports" and Figure 26). If sensing or detection are inappropriate, VT and VF Detection should be programmed OFF until verification studies are performed.

Auto-Adjusting Sensitivity Threshold

The Model 7217B PCD device automatically adjusts its sensitivity following signal detection on the bipolar electrogram (between the **PACE/SENSE** and **SENSE2** electrodes). This feature is designed to prevent the sensing of T-waves when very low sensing threshold levels are used. When the amplitude of the sensed event exceeds the programmed setting, the PCD device notes that a sensed event has occurred. The sensing level is raised to about 75% of the electrogram peak (or about 6 times the programmed setting, whichever is less) and gradually returns to the programmed value with a 560 ms exponential decay time constant. Figure 2 illustrates how the sensing level is changed by increasing or decreasing the Auto-Adjusting Threshold.

NOTE: The Auto-Adjusting Sensitivity level is not increased by pacing, VT therapy, or VF therapy outputs. The physician should be aware that the programmed sensitivity setting and the associated blanking periods are also used to detect a VT or VF episode and, therefore, Auto-Adjusting Sensitivity is active during VT and VF detection.

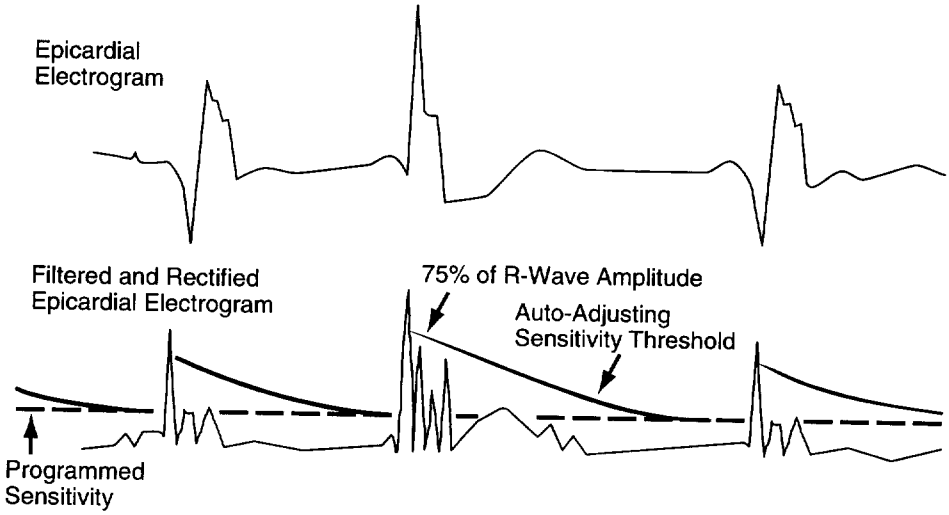


Figure 2. Auto-Adjusting Sensitivity Threshold

Blanking Periods

Nonprogrammable blanking periods follow paced and sensed events, capacitor charging periods, and therapy deliveries. These blanking periods prevent the sensing of device outputs or multiple sensing of the same event. Signals on the sensing electrodes during a blanking period are not used by the PCD device. The blanking period following a pacing output is longer than that following a sensed event. This feature is designed to avoid sensing the polarization signal on the electrodes. There are four blanking periods:

- 120 ms after a sensed event,
- 320 ms after a paced event (i.e., either VVI bradycardia pacing or VT pacing level Burst or Ramp stimuli),
- 300 ms after a cardioversion or defibrillation charging period and also after delivery of a cardioversion or defibrillation therapy, and
- During a charging period.

Refractory Periods

Refractory periods follow some events. The PCD device assumes that signals detected on the sensing electrodes during a refractory period are caused by noise, lead polarization, the trailing edge of an R-wave, or a T-wave. There are five refractory periods:

- 400 ms after a cardioversion or defibrillation charging period,
- 200 ms following sensed events in the automatic cardioversion synchronization period,
- 520 ms following the delivery of any VT or VF therapy,
- 320 to 520 ms after a therapy is aborted, and
- 320 to 480 ms (programmable) after paced events (Refractory After Pace).

No additional refractory period extends beyond the blanking period after sensed events. During VVI operation, **the PCD device will not revert to asynchronous operation in the presence of noise.**

Both the VT and VF detection criteria ignore an event sensed within a refractory period. An event sensed in the refractory period will not inhibit a pacing output. Such an event, however, does restart the sensed event blanking period of 120 ms.

Programming the Refractory After Pace to more than 320 ms may impair the PCD device's ability to detect VT or VF. Events sensed within the refractory period restart a 120 ms blanking period but are ignored by both VT and VF detection criteria and for bradycardia pacing inhibition. Therefore, a short bradycardia escape interval (i.e., a pacing rate greater than 50 ppm) combined with a long Refractory After Pace (360 ms or longer) may prevent a VT event from inhibiting a pacing output. **In such circumstances, the VT could remain undetected.**

To avoid this possibility when the Refractory After Pace is programmed to 360 ms or longer, ensure that at least one of the following is true: (1) the difference between the bradycardia escape interval and the effective refractory period should be greater than the

Tachycardia Detection Interval (TDI); or (2) the bradycardia escape interval must be greater than twice (2X) the effective refractory period. (The effective refractory period for a programmed refractory of 360 ms or longer is the programmed value plus 120 ms.) The following example and table show how programmed refractory periods of 360 ms and greater affect VT detection at various pacing rates above 50 ppm.

For example, if the Refractory After Pace equals 360 ms, then the effective refractory period could be 480 ms. If the escape interval equals 670 ms (90 ppm), then intrinsic rhythms with 190–480 ms intervals may not be detected if the rhythm initiates during VVI pacing.

Programmed Refractory After Pace	VT or VF Interval Lengths That Could Remain Undetected –At 70 ppm (860 ms)	–At 90 ppm (670 ms)
360 ms	380 - 480 ms	190 - 480 ms
400 ms	340 - 520 ms	150 - 520 ms
440 ms	300 - 560 ms	110 - 560 ms
480 ms	260 - 600 ms	70 - 600 ms

In order for the programmed refractory period to have **any** effect on VT detection, the VT episode must initiate during VVI pacing at rates **over** 50 ppm and with the Refractory After Pace **greater** than 320 ms.

Measurement of Intervals

The PCD device measures cardiac cycle lengths in multiples of 10 ms. Intervals are rounded down to the nearest 10 ms multiple (e.g., 457 ms becomes 450 ms). The PCD device uses this rounded interval value when applying the programmed criteria and calculating interval averages.

Ventricular Tachycardia (VT) Detection

Overview of VT Detection

With VT Detection enabled, the PCD device monitors the cardiac cycle length for the fulfillment of the programmed VT detection criteria. When the programmed criteria are fulfilled, the PCD device detects a VT episode and delivers the first programmed VT therapy. If this therapy is ineffective and the VT is again detected, the next programmed VT therapy is delivered. This progression continues until the PCD device confirms VT termination or delivers all programmed VT therapies. VT Detection is suspended if all programmed therapies are ineffective in terminating the arrhythmia. VT Detection is re-enabled when VT termination is confirmed or if VT Detection is manually reprogrammed ON.

All programmed VT detection criteria must be fulfilled for a rhythm to be detected as a VT episode. Whenever VT Detection is enabled (ON) there are three available criteria: the **Interval Criterion** is automatically enabled, the **Interval Stability Criterion** and the **Onset Criterion** are optionally programmable. The number of detected episodes is stored in the device's memory. The data for previously detected VT episodes may be accessed with the programmer.

NOTE: VF Detection must be programmed ON before VT Detection can be programmed ON.

VT and VF Detection may be programmed ON to permit the PCD device to function solely as a tachyarrhythmia monitor with all tachyarrhythmia therapies programmed OFF.

VT Detection Criteria

Interval Criterion

The Interval Criterion is designed to detect a sustained high ventricular rate by measuring each cardiac cycle length and comparing it to the **Tachycardia Detection Interval (TDI)**. If an interval is less than the TDI, then that cycle is potentially a count toward the fulfillment of the **Number of Intervals to Detect (VT NID)**. The Interval Criterion is activated when VT Detection is enabled and, therefore, requires programming both the TDI and VT NID parameters.

The Interval Criterion requires that the measured cardiac cycle length be less than the programmed TDI value and greater than or equal to the programmed Fibrillation Detection Interval (FDI). The VT event counter counts the number of intervals that meet the Interval Criterion. The VT event counter is reset to zero if an interval is greater than or equal to the TDI. The count is not increased nor reset if an interval is less than the FDI. When the cumulative VT event count is equal to the VT NID, the Interval Criterion for VT detection is fulfilled.

Thus, fulfillment of VT Detection when only the Interval Criterion is enabled requires both of the following:

- Measured cardiac cycle lengths be **less than** the programmed Tachycardia Detection Interval (**TDI**), and **greater than or equal to** the programmed Fibrillation Detection Interval (**FDI**), and
- The cumulative number of these intervals be **equal to** the programmed Number of Intervals to Detect (**VT NID**).

Counting is reset to zero when an interval is greater than the programmed TDI and is interrupted when the interval is less than the FDI.

The Relationship Between the TDI and FDI

Figure 3 illustrates how the relationships between the blanking period (120 ms) after a sensed event, FDI, TDI, and bradycardia escape interval determine whether a sensed event is a VF event (B), a VT event (C), or a normal sensed event (D). In addition, all these events inhibit the bradycardia output pulse.

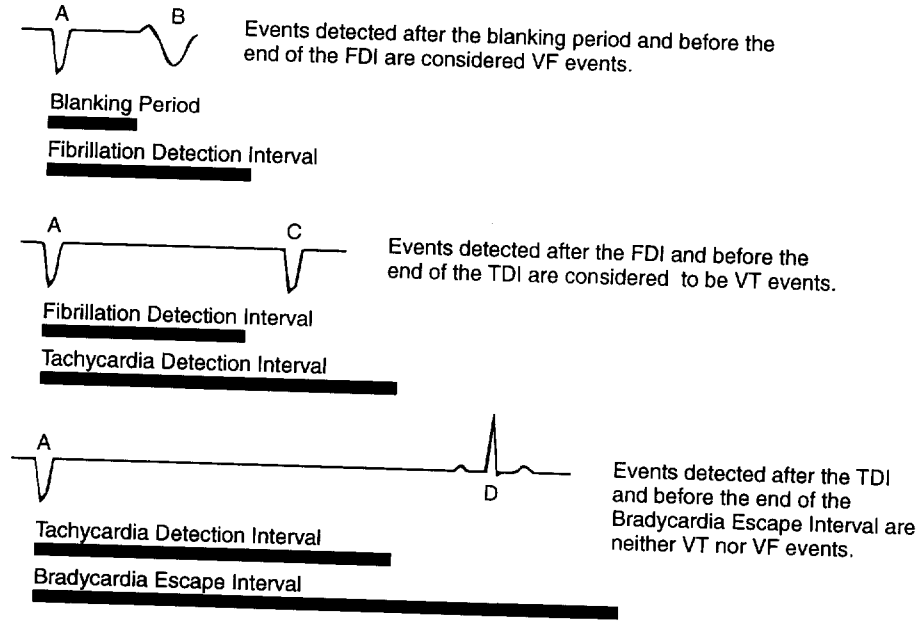
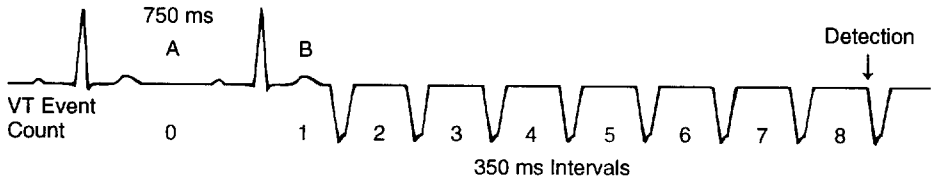


Figure 3. The Relationship of the TDI and FDI

NOTE: Programming the FDI to a value greater than or equal to the TDI effectively disables VT Detection. **When programming these two values, the physician should keep the TDI at least 40 ms longer than the FDI to allow for variability of the clinical VT cycle length.**



Programmed to: TDI = 400 ms; FDI = 250 ms; VT NID = 8

In this example, Interval "B " and the intervals following B increment the VT event counter.

Figure 4. Interval Criterion (Example)

Figure 4 illustrates how the PCD device could use the Interval Criterion to detect a tachycardia. The interval at "B" is 350 ms, i.e., 50 ms less than the programmed TDI value of 400 ms. Because it is less than the TDI and greater than the FDI and since no other VT Detection Criteria are programmed, the VT event count, in this example, begins. When the VT event count reaches 8, VT detection occurs.

NOTE: Some of the timing diagrams provided in this manual depict representative surface ECGs and are illustrative of the operation being discussed. The PCD device actually uses epicardial or intracardiac electrograms (EGMs) for measurement and analysis of the cardiac cycle lengths. Detection and delivery of therapies are based on EGMs, not on surface ECGs.

Interval Stability Criterion

The Interval Stability Criterion is a programmable option that provides an additional restriction to the Interval Criterion. It is intended, for example, to prevent VT detection when rapid ventricular rhythms with irregular intervals due to conduction of atrial fibrillation or flutter would otherwise fulfill the Interval Criterion.

When enabled, this criterion analyzes only those measured cardiac cycle lengths that fulfill the Interval Criterion. A measured cardiac cycle length is considered unstable when the difference between the current measured cycle length and any of the three previous cycle lengths is greater than the programmable Interval Stability value (in milliseconds). Note that the VT event count must be at least "3" before the PCD device can apply the Interval Stability Criterion. If the current cardiac cycle length varies more than the programmed Interval Stability value, then the VT event count is reset to zero. The measurement and counting of cardiac cycle lengths then begins anew.

Thus, with Interval Stability and Interval Criteria enabled, VT Detection requires all of the following:

- Measured cardiac cycle lengths be **less than** the programmed Tachycardia Detection Interval (**TDI**) and **greater than or equal to** the programmed Fibrillation Detection Interval (**FDI**),
- **Each of these measured cardiac cycle lengths** vary from each of the three previous cycles by a value **less than or equal to** the programmed Interval Stability value, and
- The cumulative number of these intervals be **equal to** the programmed Number of Intervals to Detect (**VT NID**).

Counting is reset to zero when an interval is greater than the programmed TDI or is considered "unstable." The count is suspended when the interval is less than the FDI. When this criterion is enabled and a VT therapy is unsuccessful in treating a detected VT, Interval Stability must be fulfilled before the episode can be redetected.

NOTES: Choosing a small Interval Stability value may not allow for normal variation in a VT cycle length.

Decreasing the programmed interval stability increases the specificity of the Interval Stability Criterion to detect the targeted stable tachycardia, but may also decrease the sensitivity of the detection algorithm.

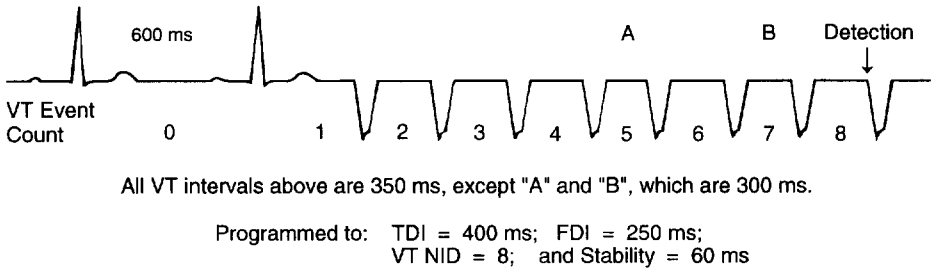


Figure 5. Interval Stability Criterion Fulfilled (Example)

Figure 5 illustrates how the Interval Stability Criterion may be fulfilled. Interval "A" is a "stable" interval, i.e., only 50 ms shorter than the three previous intervals and less than the programmed Stability of 60 ms. Interval "B" similarly qualifies as a stable interval, because it is equal to one of the three previous intervals and is 50 ms shorter than the other two. VT detection occurs when the VT event count reaches the programmed VT NID value (8).

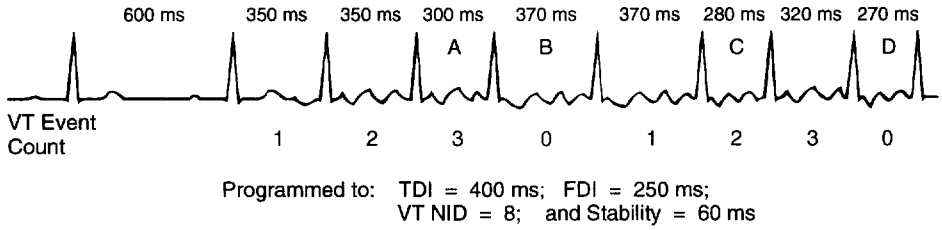


Figure 6. Interval Stability Criterion Not Fulfilled (Example)

Figure 6 illustrates how an "unstable" interval is identified. Interval "B" is 70 ms longer than "A" and therefore exceeds the programmed Stability value by 10 ms. As a result, the VT event count is reset to zero. Interval "C", though 90 ms less than the previous interval and greater than the programmed Stability of 60 ms, does not reset the VT event count, because the counter has not yet reached "3". Interval "D", however, is an unstable interval; it occurs after the event count reaches "3", and thus also resets the VT event count to zero.

Onset Criterion

The Onset Criterion, a programmable option, monitors the cardiac cycle length for a sudden onset of a high ventricular rate. It is intended to avoid VT detection of an episode of sinus tachycardia with gradually increasing (e.g., exercise-induced) high ventricular rates.

This criterion, when enabled, **must first be satisfied** before the device begins counting VT events that otherwise satisfy the Interval Criterion and, if programmed, the Interval Stability Criterion. When the Onset Criterion is enabled, the PCD device evaluates each cardiac cycle for a decrease in cycle length from previous intervals. The Onset Criterion is fulfilled when both of the following conditions are met:

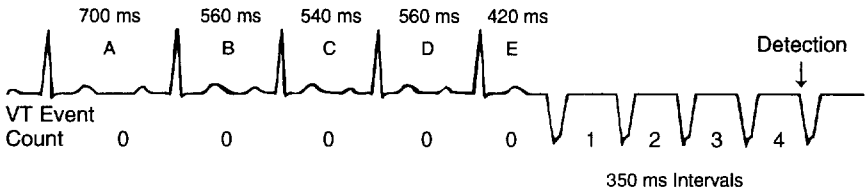
- If the current interval is **less than** a programmed percentage of the average of the previous four intervals, and
- Either the second and/or third interval preceding the current interval is **equal to or greater than** the programmed TDI.

If two consecutive intervals after the Onset Criterion is satisfied are greater than or equal to the TDI, the Onset Criterion is reset and must again be satisfied before a VT can again begin to be detected. When a VT is detected, however, the Onset Criterion is not required again for redetection until the PCD device confirms VT episode termination.

NOTES: If the Onset Criterion is ON and not met at the beginning of a ventricular tachycardia, the VT episode could remain "undetected", such as with an exercise-induced VT. For example, if VT Detection uses the Onset Criterion and is enabled after the start of a VT, the VT may not be detected.

A low programmed onset percentage value will increase the specificity of the Onset Criterion to detect the targeted tachycardia, but may also decrease the sensitivity of the detection algorithm.

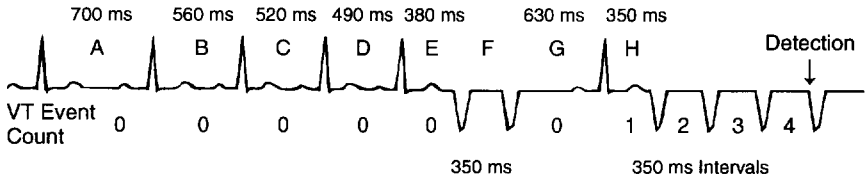
Intervals that are shorter than the programmed FDI may also fulfill the Onset Criterion, even though they are not VT events. Such an interval does not increase nor reset the VT event counter.



Programmed Values: TDI = 400 ms; FDI = 250 ms; VT NID = 4; and Onset = 81%

Figure 7. Onset Criterion Fulfilled (Example)

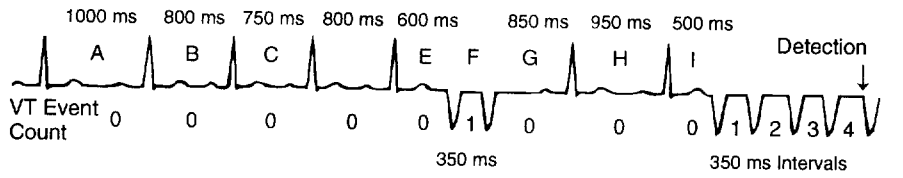
Figure 7 illustrates how the PCD device uses the Onset Criterion to identify a VT episode. Interval "E" meets the programmed Onset Criterion because it is less than 81% of the average of intervals A through D and because B (and/or C) is greater than the TDI. The VT event count begins with the next interval because it is less than the programmed TDI.



Programmed Values: TDI = 400 ms; FDI = 250 ms; VT NID = 4; and Onset = 81%

Figure 8. Onset Criterion Fulfilled (Example)

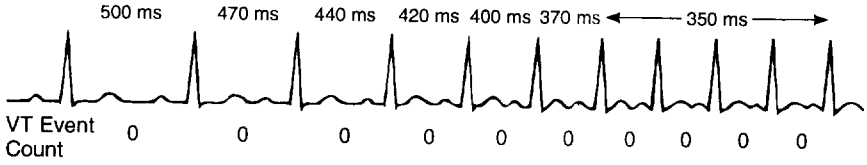
In Figure 8, interval E satisfies the Onset Criterion, i.e., it is less than the programmed 81% of the average of intervals A through D, with interval B (and/or C) greater than the TDI. Interval G by itself, though longer than the TDI, does not reset the Onset Criterion, since two such consecutive intervals are required for a reset of the Onset Criterion. Interval G, however, does reset the VT event count; thus, the event count begins at F, resets to zero at G, and then begins again at H.



Programmed Values: TDI = 400 ms; FDI = 250 ms; VT NID = 4; and Onset = 81%

Figure 9. Onset Criterion Reset and Fulfilled (Example)

In Figure 9, a situation occurs that resets the Onset Criterion, which is first satisfied by Interval E. Two intervals (G and H), longer than the TDI, reset both the Onset Criterion and the VT event count. Thus, a second interval (I) must fulfill the Onset Criterion before the VT event count can begin counting toward VT detection.



Programmed Values: TDI = 400 ms; FDI = 250 ms; VT NID = 4; and Onset = 81%

Figure 10. Onset Criterion Not Fulfilled (Example)

Figure 10 illustrates a sinus rhythm with a gradually accelerating rate. No interval is less than 81% of the average of the four previous intervals. Thus, this rhythm would not be detected by the PCD device as a VT. This example demonstrates how the Onset Criterion may be used to help differentiate between a sinus tachycardia (possibly exercise-induced) and a pathological VT.

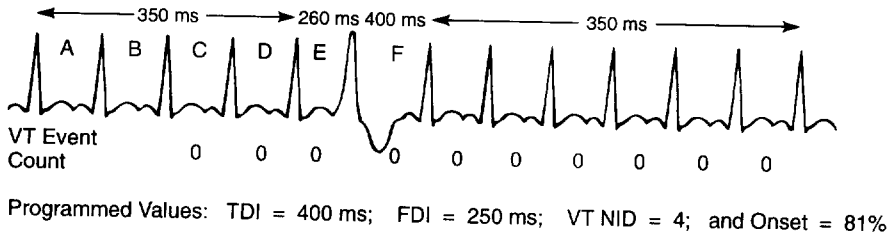


Figure 11. Onset Criterion Not Fulfilled (Example)

In Figure 11, all intervals, except "E" and "F", are 350 ms. Interval E, which is 260 ms, appears to satisfy the Onset Criterion. Although Interval E is indeed less than 81% of the average of Intervals A through D, neither Interval B or C is greater than the TDI. Both requirements must be satisfied to fulfill the Onset Criterion.

Subsequent Reconfirmation/Redetection of an Ongoing VT Episode

After initially detecting a VT episode and delivering the first programmed therapy, the PCD device monitors the cardiac cycle length for the continued fulfillment of the programmed detection criteria. Reconfirmation, i.e., redetection, is required before the next programmed therapy is delivered. **The Onset Criterion is only used for the initial detection of a VT episode and is not used for redetection of the same VT episode.**

VT detection begins immediately with the first cardiac cycle after VT therapy delivery. However, the first event detected may have a longer cycle than the programmed TDI due to the 520 ms refractory period following VT therapy.

NOTE: Programming high VT NID counts will result in correspondingly longer delays between VT therapies (when the previous therapy is ineffective in terminating the VT episode), due to the need to reconfirm the VT episode between therapies. The physician should understand that the programmed VT NID count applies to both initial detection and redetection of an ongoing episode after therapy delivery.

VT Episode Termination and Determination of Therapy Efficacy

The PCD device defines a VT episode as **terminated** when **eight consecutive** cardiac cycles (paced or sensed) all have intervals **greater than or equal to** the TDI.

The PCD device defines a VT therapy "effective" if VT termination occurs prior to any further VT detection. The PCD device is considered "ineffective" if, after **all** programmed therapies, VT detection occurs before VT termination. Once the PCD device detects a VT, it considers the episode as ongoing until a termination occurs. After episode termination, a subsequent VT detection marks the start of a new VT episode. See "Device Reporting Features" in "General Device Information" for information about how effectiveness is reported.

NOTE: A rhythm following a therapy that does not satisfy the VT termination definition is considered part of an ongoing episode. However, the next VT therapy will not be delivered unless the programmed VT detection criteria are again fulfilled.

If all programmed therapies prove ineffective in terminating the arrhythmia, **only a later VT termination (either spontaneous or via a programmer-activated therapy) or manually programming VT Detection ON will restart** the programmed VT detection criteria and automatic therapy delivery.

Suspending and Disabling VT Detection

When the PCD device is "suspended," its detection functions are temporarily inactivated. "Disabled" is a permanently programmed state in which detection and/or therapies are not available (OFF condition). These functions can only be re-enabled via a programming sequence.

The programmed VT Detection criteria are temporarily **suspended** during

- Magnet application (unless a "Cancel Magnet" is programmed),
- Delivery of high rate pacing,
- Capacitor charging, in preparation for the delivery of a cardioversion or defibrillation shock or during a programmed charge period,
- Delivery of VT therapies,
- The period after all programmed VT therapies have proved ineffective (i.e., until VT episode termination is confirmed or VT Detection is again programmed ON),
- Delivery of VF therapies,
- The first 64 ventricular events (pace, sense, and therapy) after VF detection, and
- The period following VT and VF therapies that are manually initiated via the programmer, e.g., following programmed emergency or manual therapies (removing the programming head enables VT Detection).

The programmed VT Detection criteria are **disabled** whenever

- Three consecutive 35-second charge intervals have failed to reach the programmed energy level and the "Charge Circuit Inactive" condition occurs,
- Nominal or VVI option under Emergency VVI is programmed, and
- Power-on reset (an electrical reset) or a detected memory error occurs.

Ventricular Tachycardia (VT) Therapy

The PCD device has three programmable VT therapy types: **Burst, Ramp, and Cardioversion.** Up to four separate therapies may be programmed **in any combination** of the three types. Here are four examples (read across):

Example	Therapy One	Therapy Two	Therapy Three	Therapy Four
No. 1	Ramp	Burst	Cardioversion	Cardioversion
No. 2	Ramp	Ramp	Burst	OFF
No. 3	Cardioversion	Cardioversion	Cardioversion	Cardioversion
No. 4	Cardioversion	OFF	OFF	OFF

NOTES: Programming a therapy OFF disables all subsequent therapies. For example, if the PCD device is programmed to Therapy #1 OFF, Therapy #2 Ramp, Therapy #3 Burst, and Therapy #4 Cardioversion, none of the VT therapies is enabled, and none will be delivered.

The PCD device cannot be programmed to deliver automatic VT therapies without VF detection and therapies programmed ON.

The physician may elect not to program any VT therapy. If VT Detection alone is enabled, the PCD device will only monitor the cardiac rhythm and record the number of detected VT episodes for subsequent interrogation via the programmer.

Burst Therapy[1]

A Burst sequence consists of a **rate-adaptive**, equal-interval set of pulses. A single Burst Therapy consists of one to 15 burst sequences. The physician programs the following: number of S1 pulses, adaptive percentage, number of sequences, millisecond decrement per sequence, and minimum pulse interval.

Burst Therapy is rate-adaptive. The PCD device determines the pulse interval of the first burst sequence as a programmable percentage of the tachycardia cycle length. The cycle length is determined by calculating the average of the last four intervals preceding VT detection.

The first pulse of the Burst sequence is delivered at the calculated "percentage", and is timed from the sensed event at which the VT event count equaled the programmed VT NID. Subsequent pulses in the same sequence are delivered at the same interval.

If a Burst sequence is ineffective in terminating the VT, and VT detection is reconfirmed, the pulse interval for the next sequence will be determined by calculating a percentage of the newly measured tachycardia cycle length and shortening that interval by a programmable value.

1. Certain antitachycardia pacing modes of this device, invented by Dr. Fred Zacouto of Paris, France, fall under one or more patent claims of U.S. Patents 3,857,399 and 4,052,991 and corresponding patents in other countries, which are licensed exclusively to Medtronic, Inc.

The calculated pulse interval can never be less than a programmed "minimum" interval.[1] If the calculated interval is shorter than the programmed minimum, then the pulses will be delivered at the programmed minimum interval.

If the last programmed sequence of a Burst Therapy is ineffective in terminating the VT and the VT is again detected, the PCD device initiates the next therapy (if programmed).

During Burst Therapy, the PCD device operates in the VVI mode, although the programmable Refractory After Pace may affect this operation. R-waves, sensed outside the Refractory After Pace, are counted as individual pulses of the burst train (even though they are not output pulses). Whenever a sensed R-wave inhibits the scheduled pulse, the next pulse is scheduled at the calculated or minimum interval from the time of the sensed event.

A Burst sequence has the following characteristics:

- The pulse width and amplitude for an individual Burst pulse are the same as those programmed for bradycardia pacing output pulses.
- Burst sequences can be programmed as to the number of pulses, from one to 15 (in steps of one).
- The average of the last four intervals leading to VT detection and the resultant rate-adapted burst interval are both rounded to the nearest 10 ms (e.g., 387 ms is rounded to 390 ms).
- Following a Burst sequence, a 300 ms blanking period, a 520 ms refractory period, and a bradycardia escape interval of 1000 ms begin. The circuitry resumes monitoring the cardiac cycle for detection of a new/old VT episode, a VF episode, or bradycardia.

1. The "minimum" pulse interval is the same for all Burst and Ramp therapies.

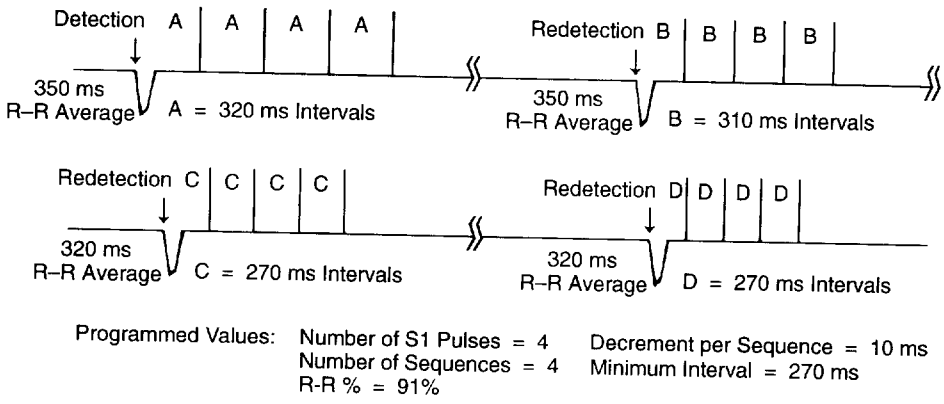


Figure 12. Burst Therapy (Example)

In the example in Figure 12, a VT episode is detected in which the R–R average interval is 350 ms. Note the programmed settings for the example.

The PCD device determines that the calculated pulse interval for the **first Burst sequence (A)** should be 320 ms, i.e., the R–R average interval of 350 ms X 91% (rounded). The first pulse is delivered at 320 ms from the R-wave that fulfilled the programmed VT NID. All subsequent pulses of this sequence are separated by 320 ms intervals.

Assuming the VT is redetected and that the R–R average interval remains at 350 ms, the calculated pulse interval for the **second Burst sequence (B)** is 310 ms (320 ms minus the 10 ms programmed decrement).

Before the **third Burst sequence (C)**, the average R-R interval shortens to 320 ms. Thus, the calculated pulse interval is 270 ms, i.e., (320 X 91%) – 20 ms = 290 – 20 ms = 270 ms (rounded).

The R-R average for the detected VT prior to the **fourth and final Burst sequence (D)** remains at 320 ms. The calculated pulse interval (with a decrement of 30 ms) would have been 260 ms; but, by definition, it cannot be shorter than 270 ms (the programmed minimum interval). Therefore, the pulse interval is 270 ms.

Ramp Therapy

A Ramp sequence consists of a rate-adaptive, set of pulses delivered at decreasing intervals. A single Ramp Therapy consists of from 1 to 15 Ramp sequences.

Ramp Therapy is **rate-adaptive**. The PCD device calculates the interval for the first pulse of the Ramp sequence as a programmable percentage of the average cycle length of the last four cycles prior to VT detection. **Each subsequent interval in the Ramp sequence is shortened from the preceding interval by a programmable value.**

The number of pulses in the first ramp sequence is programmable (up to 15). If additional sequences are programmed and the VT is redetected, the PCD device **automatically increases the number of pulses by one in each successive sequence (to a maximum of 29 in the fifteenth sequence, if programmed to 15 pulses for the first sequence and to the maximum 15 sequences)**.

If a Ramp sequence is ineffective in terminating the VT and the VT is again detected, the first interval of the next sequence will be a programmed percentage of the newly measured tachycardia cycle length. As described above, each subsequent interval is shortened from the preceding interval by a programmable value. After each VT detection that initiates a Ramp sequence, the initial interval of the sequence is recalculated.

NOTE: If the tachycardia cycle length has not changed, the first interval of the next programmed sequence will be the same as the previous sequence. This is in contrast to Burst Therapy, in which the intervals of each sequence are shortened by a programmed value, even when the tachycardia cycle length is unchanged.

If the last programmed Ramp sequence proves ineffective in terminating the VT and the VT is redetected, the PCD device will deliver the next therapy (if programmed).

During Ramp Therapy, the PCD device operates in the inhibited mode, although the programmable Refractory After Pace may affect this operation. This means that R-waves, sensed outside the Refractory After Pace, are counted as individual pulses of the ramp sequence (even though they are not output pulses). Whenever a sensed R-wave inhibits the scheduled pulse, the next pulse is scheduled at the calculated or minimum interval from the time of the sensed event i.e., the interval is shortened (if possible) as if the sensed R-wave was an output pulse. A Ramp Therapy has the following characteristics:

- Each Ramp Therapy can be programmed from 1 to 15 pulses (in steps of one) for the initial sequence. Each successive sequence adds one pulse.
- The pulse width and amplitude for an individual Ramp pulse are the same as those programmed for the pacing output pulses.
- The average of the last four detected intervals and the resultant rate-adapted Ramp interval are both rounded to the nearest 10 ms (e.g., 387 ms is rounded to 390 ms).
- The calculated pulse interval during any Ramp sequence can never be less than the programmed "minimum" interval. If the calculated interval is shorter than the

programmed "minimum", the pulses will be delivered at the programmed "minimum" interval.

- The PCD device operates in the VVI mode during Ramp Therapy. This means that sensed R-waves are counted as individual pulses of the Ramp sequence (even though they are not output pulses). A sensed R-wave inhibits the scheduled pulse, and the next pulse is scheduled at the calculated or minimum interval from the time of the sensed event.
- Following a Ramp sequence, a 300 ms blanking period, a 520 ms refractory period, and a bradycardia escape interval of 1000 ms begin. The circuitry resumes monitoring the cardiac cycle for detection of a new/old VT episode, a VF episode, or bradycardia.

Figure 13 shows a detected tachycardia episode with an R–R interval of 350 ms.

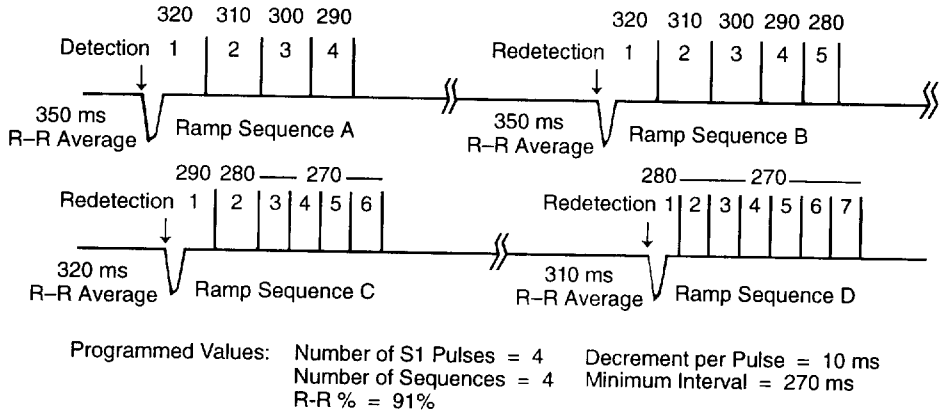


Figure 13. Ramp Therapy (Example)

The PCD device determines that the calculated pulse interval for the **first Ramp sequence (A)** should be 320 ms (i.e., 350 ms X 91% rounded). The first pulse is delivered at 320 ms from the R-wave that fulfilled the programmed VT NID, with each interval thereafter shortened by 10 ms so that the fourth interval equals 290 ms.

Assuming that the VT is redetected and the R–R average interval remains at 350 ms, the calculated initial pulse interval for the **second Ramp sequence (B)** is again 320 ms. Subsequent intervals are shortened as described above. In this sequence, however, a fifth pulse is delivered at 280 ms.

Before the **third Ramp sequence (C)**, the average R-R interval shortens to 320 ms. Thus, the initial interval is 290 ms (320 ms X 91% rounded); due to the 10 ms decrement, intervals three, four, five, and the additional sixth are all delivered at the programmed minimum of 270 ms.

The R–R interval shortens to 310 ms prior to the **fourth Ramp sequence (D)**. In this case, the initial interval is 280 ms. All subsequent intervals (including the additional seventh) are delivered at 270 ms, since this is the programmed minimum value.

VT Acceleration During a Burst or Ramp Therapy

If, after the delivery of a Burst or Ramp sequence, the average cycle length for the four intervals preceding redetection has decreased by a value equal to or greater than 60 ms compared to the average cycle length for the initial VT detection of the episode, the PCD device determines that the VT has accelerated. Subsequent sequences (of a Burst or Ramp therapy) will not be delivered.

For example, assume the programmed therapies were Burst (with multiple sequences), Ramp (with multiple sequences), Cardioversion, and Cardioversion. If the VT were to accelerate after the first sequence of the Burst therapy, the PCD device would cancel the remaining sequences and initiate the programmed Ramp therapy. Similarly, if the VT was still considered accelerated after the initial sequence within the Ramp therapy, the PCD device would go immediately to the next programmed therapy, Cardioversion.

NOTE: This progression to the next therapy applies only when two or more sequences are programmed for a Burst or Ramp therapy. If at any time the detected rhythm satisfies the programmed VF criteria, the PCD device will deliver the first (or next) programmed VF therapy.

Cardioversion Therapy

Overview

Cardioversion therapy may be programmed as any one of the four VT therapies. The pathway for the Cardioversion pulse(s) may be separately programmed for each of the four therapies as:

- a **SINGLE** pulse delivered over one pathway, i.e., from the PULSE2 anode to the COMMON cathode;
- two **SIMULTANEOUS** pulses delivered over two pathways, i.e., one from the PULSE1 anode and the other from the PULSE2 anode, with both flowing to the COMMON cathode;
- two **SEQUENTIAL** pulses, separated by a very short period and delivered over the same two pathways as the **SIMULTANEOUS** pulses.

In all three pathway options, the Cardioversion pulse(s) must be synchronized to a ventricular sensed event.

The physician also separately programs the stored energy[1] and pulse width of the pulse(s) for each of the programmed cardioversion therapies.

When a VT is detected and Cardioversion is the next programmed therapy, the PCD device will initiate a **Charging Period**. During this period, the device charges the high voltage capacitors to the programmed stored energy.

NOTE: The Cardioversion pulse may be programmed to the same range of stored energies as a defibrillation shock used in VF therapy.

Following the completion of charging, the device initiates a **Synchronization Sequence**. During this period the device attempts to confirm the continued presence of the VT (by ensuring that the first interval is less than the TDI) and to synchronize the delivery of the Cardioversion pulse(s) to an R-wave.[2]

1. The Programmer displays stored energy in "Joules" as the programmable value. The cardioversion/ defibrillation output capacitors are charged in the PCD device to a corresponding voltage value. See Table 4 for the conversion of stored energy to volts. The physician should be aware that the delivered energy for both cardioversion and VF therapies depends on the total impedance (of the system and cardiac interface) and the programmed pulse width.
2. Since the Model 7217B cardioversion pulses are synchronized to events sensed on the PACE/SENSE to SENSE2 electrodes, monitoring by surface ECGs will exhibit morphologies and timing that do not necessarily coincide exactly with those taking place at the electrode sites.

The differences between cardioversion and defibrillation in the PCD device are:

- A cardioversion pulse is delivered in response to VT detection, whereas a defibrillation shock is delivered only when VF detection criteria are fulfilled.
- Following the VT charging period, the PCD device reconfirms that the rhythm still has an interval defined as VT. After the VF charging period, no such reconfirmation is attempted.
- Cardioversion requires synchronization to a sensed R-wave for delivery to occur. In VF therapy, the PCD device attempts to deliver the defibrillation shock in synchrony with a sensed event, but does not require such synchronization.
- Current pathways are separately programmable for each programmed cardioversion therapy. All VF therapies must be programmed to the same current pathway.

Charging Period

After a VT detection that is to be followed by cardioversion therapy, there is a Charging Period during which the high-voltage capacitors in the PCD device are charged to the programmed stored energy (leading edge voltage).

Several points should be noted about the Charging Period:

- Electrogram sensing does not occur during this time.
- Bradycardia therapy does not take place.
- Marker Channel and electrogram telemetry are not available.
- Programming is disabled during this period. However, if a magnet is placed over the PCD device and is kept in position until the end of the charging period, the device will recognize the presence of the magnet and the Cardioversion therapy will not be delivered.

The capacitor charging period usually varies from less than one second to ten (10) seconds at beginning-of-life power source status, depending on the programmed stored energy. This time will lengthen as the power source is depleted or as time increases from the last charging period. **If the Charging Period reaches a maximum duration of 35 seconds, charging is terminated**, the cardioversion therapy attempt is aborted, and the device returns to its programmed mode. This situation presents a potential loss of device function (see "Potential Loss of Function Indicators").

Synchronization Sequence

The Synchronization Sequence is designed to ensure the continued presence of the VT after completion of the Charging Period and to synchronize the delivery of the cardioversion pulse(s) to an R-wave, sensed on the implanted electrodes. To do this, the PCD device monitors the cardiac cycle for a sensed R-wave within the timing requirements described below. When these timing requirements are met, the VT is confirmed and the delivery of the cardioversion shock is synchronized to the sensed event.

Following completion of the Charging Period, the Synchronization Sequence requires that the interval from the first non-refractory sensed event to the next sensed event be (1) less than the programmed TDI plus 60 ms and (2) greater than 200 ms.[1]

VT detection is not confirmed and the cardioversion therapy is aborted under the following conditions:

- The timing requirements are not met,
- The initial three events after the Charging Period are sensed during refractory periods, or
- No sensed event occurs within a synchronization period following completion of capacitor charging.

If, after an aborted cardioversion therapy, there is a subsequent VT detection within the same VT episode, the PCD device will again attempt to deliver the same therapy.

If some energy remains on the capacitors after a therapy or because a therapy was aborted, the capacitors are discharged internally when VT episode termination is identified unless they were charged by a programmer-initiated charge command or a VF episode is ongoing.

Timing Periods After Non-Confirmation of VT

If no R-wave is sensed during a synchronization period, the PCD device returns to the programmed settings after a single cycle with a 300 ms blanking period, a 520 ms refractory period, and a 1000 ms escape interval.

If the Synchronization Sequence is terminated by three consecutive refractory sensed events, the PCD device returns to the programmed settings after a single cycle. The single cycle has a 320 ms blanking period, a programmed Refractory After Pace, and the programmed pacing escape interval.

1. When cardioversion is manually initiated via the programmer, the Synchronization Sequence timing requirement simply requires the period from the first non-refractory sensed event to the next sensed event to be less than the programmed bradycardia escape interval.

Cardioversion Timing

Figures 14 through 17 are timing diagrams that illustrate what may occur during the Synchronization Sequence.

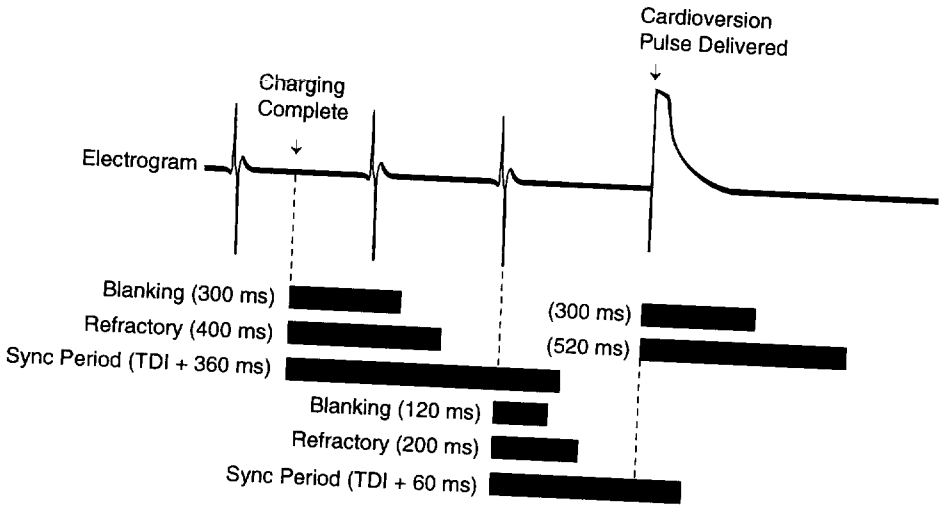


Figure 14. Cardioversion (Scenario "A")

Figure 14 depicts the simplest scenario in which the PCD device delivers the programmed cardioversion pulse(s) at the time of the second non-refractory sensed ventricular event following the Charging Period. The Synchronization Sequence consists of both sets of blanking, refractory, and synchronization periods. During the Synchronization Sequence, the PCD device confirms the continued presence of the tachycardia and identifies the R-wave to which it synchronizes delivery of the programmed cardioversion pulse(s).

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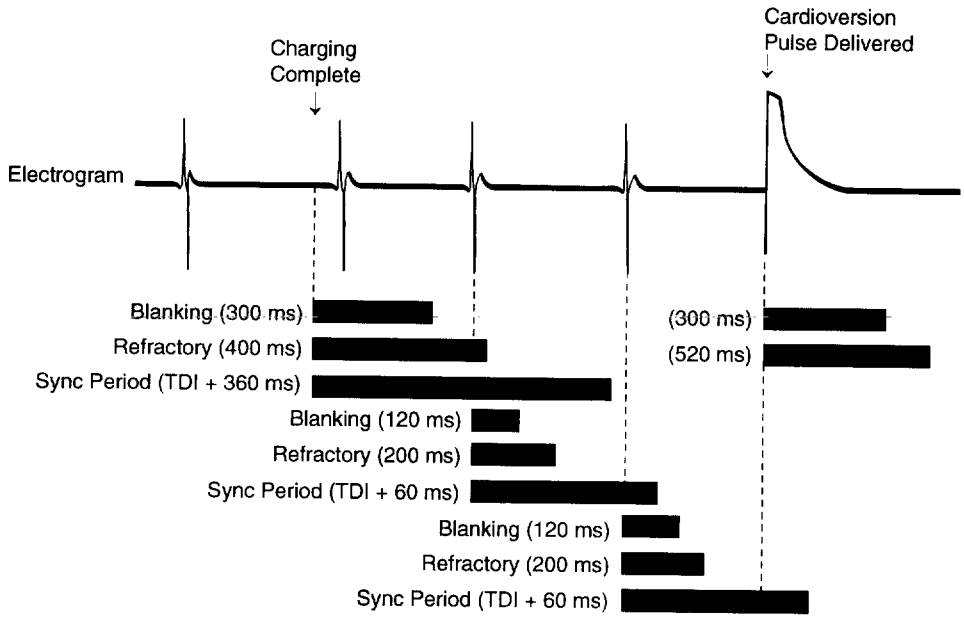

Figure 15. Cardioversion (Scenario "B")

In Figure 15, the first ventricular event after the end of the first blanking period is a refractory sensed event. As a result, the PCD device initiates a second set of periods in an attempt to identify an initial event outside the refractory period. Such an event is sensed and the resulting operation is the same as that in Figure 14. In this case, all three sets of periods comprise the Synchronization Sequence.

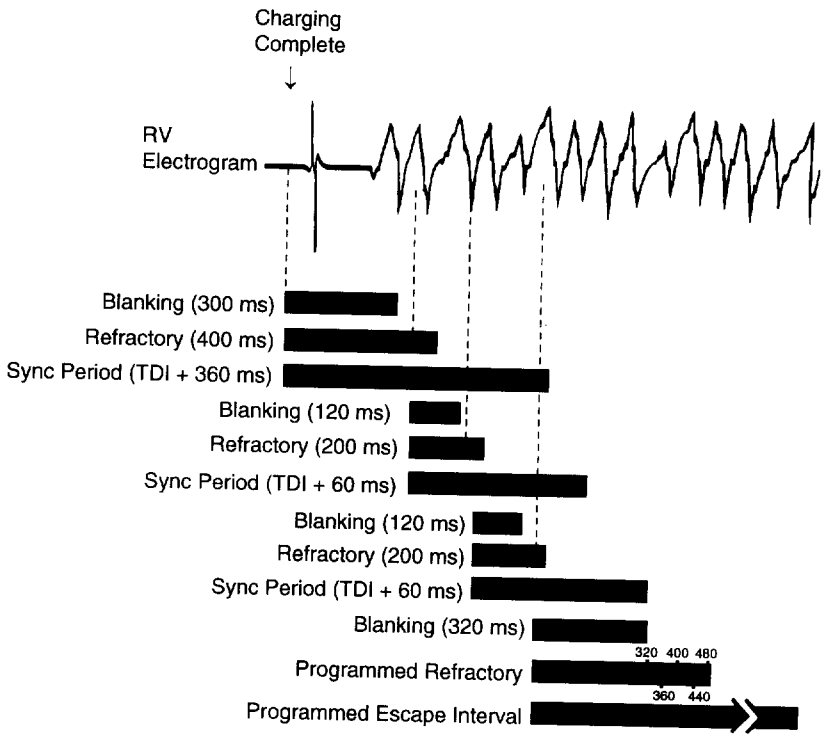

Figure 16. Cardioversion (Scenario "C")

In Figure 16, the PCD device fails to sense any ventricular events outside of a refractory period and, therefore, the VT cannot be confirmed. Thus, the cardioversion cannot be synchronized to a known R-wave. The therapy is aborted. After the third refractory sensed event, a pacing escape interval starts.

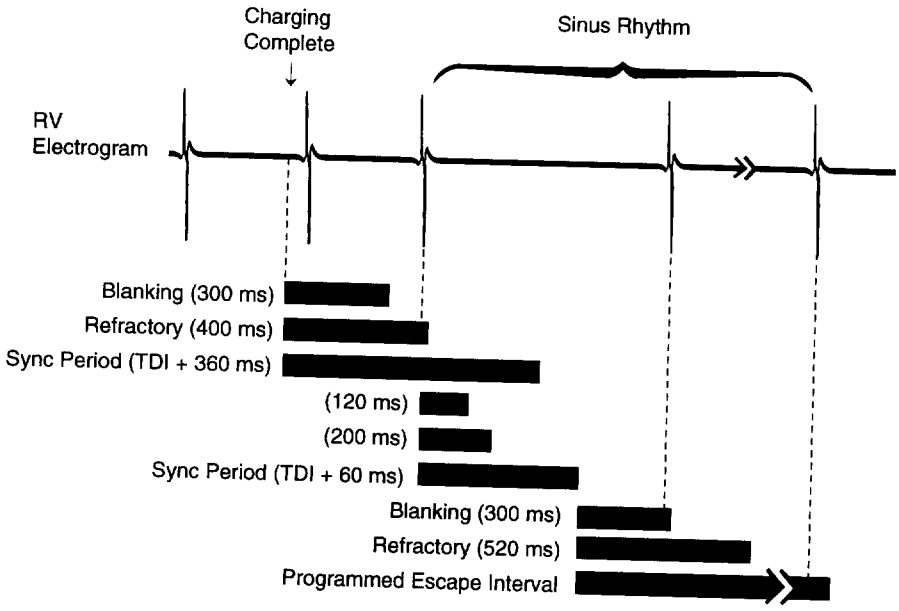

Figure 17. Cardioversion (Scenario "D")

Figure 17 depicts a situation in which the tachycardia terminates spontaneously sometime between VT Detection and completion of the Charging Period. Since the PCD device could not identify two non-refractory sensed ventricular events during the synchronization sequence, it aborted the VT therapy and initiated a bradycardia escape sequence. A sensed R-wave inhibits the bradycardia output.

Delivery of the Cardioversion Pulse

Delivery of the programmed cardioversion pulse(s) is synchronized to the second non-refractory sensed event following completion of charging. The current pathways for the cardioversion therapy are programmable, i.e., single, simultaneous, or sequential.

Following the cardioversion pulse, a 300 ms blanking period, a 520 ms refractory period, and a bradycardia escape interval of 1000 ms begin. The circuitry resumes monitoring the cardiac cycle for detection of a new VT episode, a VF episode, or bradycardia.

Ventricular Fibrillation (VF) Detection

Overview

The PCD device detects ventricular fibrillation using three programmable parameters: Sensitivity of the ventricular sensing circuit, the Fibrillation Detection Interval (FDI), and the Number of Intervals to Detect (VF NID) that must be attained by the VF event counter. Up to four Defibrillation Therapies may be delivered in an attempt to terminate a single VF episode. If the first therapy is ineffective in terminating the arrhythmia and VF is detected again, a second defibrillation shock is delivered. Similarly, a third and fourth shock will be delivered if VF continues to be detected. If all the programmed VF therapies are ineffective, additional VF therapies will not be delivered until the PCD device identifies termination of the VF episode, or if VF detection is manually programmed ON.

NOTE: VT detection must be programmed OFF before VF detection can be programmed OFF.

VF Detection

The VF Detection Criterion is designed to detect a very fast ventricular rate. This criterion requires that 75% or more of the previous intervals are shorter than the programmed FDI. This is done to ensure detection for two reasons: (1) the signal amplitude of events within a VF episode may vary and (2) some intervals may be longer than others.

The Detection Criterion for VF requires that a programmed number of cardiac cycle lengths are less than the programmed FDI. This required number is called the Number of Intervals to Detect (VF NID). The PCD device continuously monitors a number of previous intervals equal to 133% of the programmed VF NID. It analyzes each cycle length to determine if it is shorter than the FDI. If the number of intervals shorter than the FDI equals the number required for VF detection (the VF NID), VF detection occurs.

VF NID	VF Detection Window
6	8
12	16
18	24
24	32
30	40

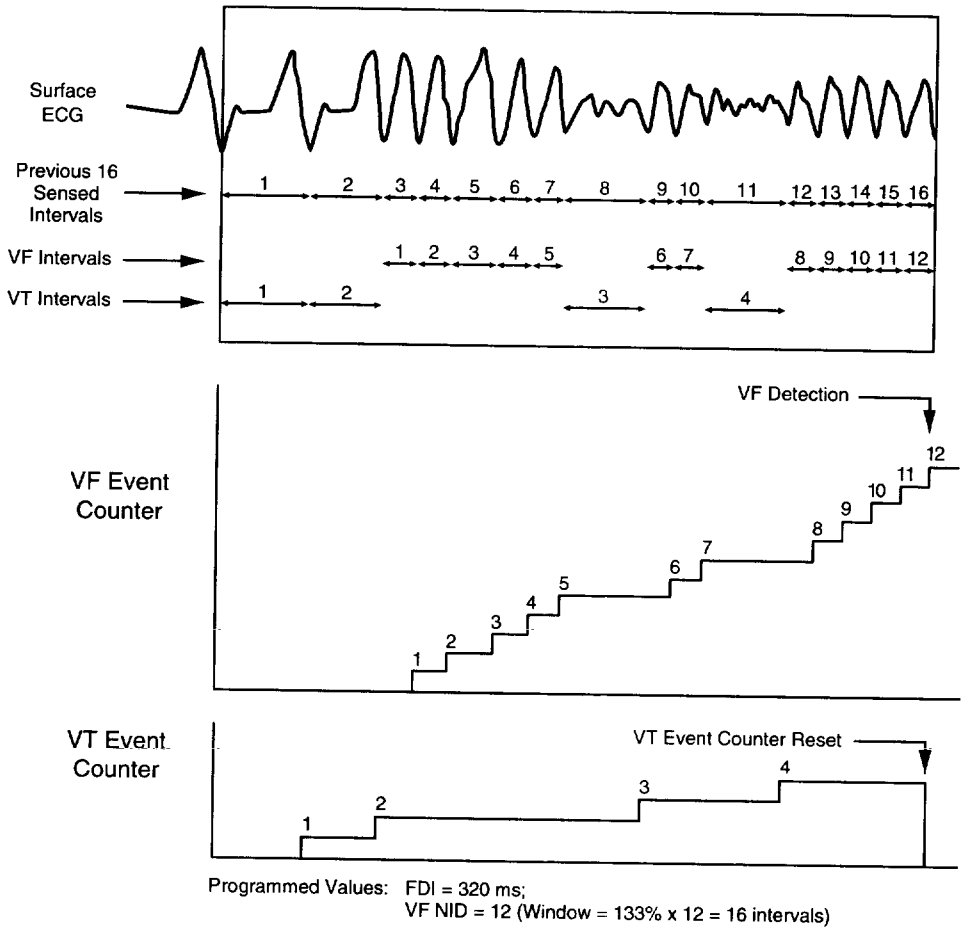

Figure 18. VF Detection (Example)

Figure 18 illustrates how VF Detection may be fulfilled. The PCD device is programmed to a VF NID of 12, which means it will evaluate the 16 intervals preceding the current interval (133% of 12). Since 12 of the intervals within the 16-interval "window" of detection are shorter than the FDI, VF detection occurs.

Relationship of VT and VF Detection

The PCD device separately processes the measured cardiac cycle lengths against the programmed VT and VF Detection Criteria. It is possible that, while a detected VT episode is in progress, a VF episode begins (i.e., to have both an active VT and an active VF episode). In such cases, when VF detection occurs, the PCD device will deliver the next programmed VF therapy.

When VT detection occurs, the fibrillation event count is not reset and interval data that occurred prior to the VT therapy will be used. However, when VF is detected, the VT event count is reset.

VF Episode Termination and Efficacy Determination

The PCD device defines a VF episode as **terminated** when eight consecutive cardiac cycles (sensed or paced) have intervals **greater than or equal to** the FDI.

The PCD device defines a VF therapy "effective" if VF termination occurs prior to any further VF detection. The PCD device is considered "ineffective" if after delivery of the last programmed VF therapy, VF detection occurs before VF termination is detected. See "Device Reporting Features" in "General Device Information" for information about how effectiveness is reported.

NOTE: A rhythm following a therapy that does not satisfy the VF termination definition is considered part of an ongoing episode. However, additional VF therapies will not be delivered unless the VF Detection Criterion is again fulfilled.

If all programmed therapies proved ineffective in terminating the arrhythmia, **only a later VF termination (either spontaneous, or via a programmer-activated therapy or transthoracic defibrillation) or manually programming VF Detection ON** will restart VF detection and automatic therapy delivery.

Suspending and Disabling VF Detection

When the PCD device is "suspended," its detection functions are temporarily inactivated.

"Disabled" is a permanently programmed state in which detection and/or therapies are not available (OFF condition). These functions can only be re-enabled via a programming sequence.

The VF Detection Criterion is temporarily **suspended** during

- Magnet application (unless a "Cancel Magnet" is programmed),
- Capacitor charging (i.e., in preparation for the automatic delivery of a cardioversion or defibrillation shock or during a programmed charge period),
- Delivery of high-rate pacing,
- Delivery of VT therapies,
- Delivery of VF therapies,
- The period after all programmed VF therapies are proved ineffective (i.e., until VF termination is confirmed or VF Detection is programmed ON), and
- The period following VT and VF therapies that are manually initiated via the programmer, e.g., following programmed emergency or manual therapies (removing the programming head enables VT and VF Detection).

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The VF Detection Criterion is **disabled** whenever

- Three consecutive 35-second charge intervals have failed to reach the programmed energy level and the "Charge Circuit Inactive" condition occurs,
- Nominal or VVI option under Emergency VVI is programmed, and
- Power-on reset (an electrical reset) or a detected memory error occurs.

Ventricular Fibrillation (VF) Therapy

Overview

For each detected VF episode, the PCD device can deliver up to four defibrillation therapies. Each therapy consists of a high-energy defibrillation shock separately programmable as to stored energy and pulse width. The current pathway (i.e., single, simultaneous, or sequential) is programmable but must be the same for all VF therapies.

NOTES: A therapy programmed OFF disables all subsequent therapies. For example, if the first VF therapy is programmed OFF, all therapies are effectively disabled.

VF therapy cannot be programmed OFF if the PCD device is programmed to deliver automatic VT therapies.

After detection of a VF episode, the PCD device initiates a charging period for the first programmed therapy. During this period the device charges the high voltage capacitors to the programmed stored energy level. After completion of the charging, the device initiates the Synchronization Sequence. During this sequence, the device attempts to synchronize the defibrillation shock to the leading edge of a sensed event. If synchronization is not possible, an asynchronous shock will be delivered. Defibrillation Therapy, unlike Cardioversion, is "committed", i.e., once the charging cycle has begun, a shock will be delivered[1].

If the first and/or subsequent VF therapies prove ineffective and the VF arrhythmia is again detected after each therapy, the PCD device repeats the above operation up to a total of four times.

NOTE: It is recommended that the physician program the second, third, and fourth VF therapy to the maximum stored energy of 34 joules.

Charging Period

After a VF detection, the high-voltage capacitors are charged to the programmed stored energy (leading edge voltage) level for the next VF therapy. This period has the same function and range of durations as the cardioversion charging period.

1. See the section titled "Cardioversion and Defibrillation Charging Periods" under "Programming Considerations" for a complete description of charging periods.

NOTE: If a cardioversion shock is programmed to a stored energy level higher than that for VF therapy and cardioversion is aborted, leaving the energy stored on the capacitors, the delivered energy of a subsequent VF shock could be higher than the programmed value, if VF is detected prior to the end of the VT episode.

The capacitor charging period usually varies from less than one second to ten (10) seconds at beginning-of-life power source status, depending on the programmed stored energy and the elapsed time since the previous charging cycle. This time will lengthen as the power source is depleted or as time increases from the last charging period. **If the charging period reaches a maximum duration of 35 seconds, charging is terminated,** the VF therapy attempt is aborted, and the device returns to its programmed mode. This situation presents a potential loss of device function (see "Potential Loss of Function Indicators").

Synchronization Sequence

Upon completion of the capacitor charging period, the Synchronization Sequence follows during which the device attempts to synchronize the defibrillation shock to a sensed cardiac event. The defibrillation shock is delivered at the time of the first non-refractory sensed event following completion of the charging period. If there is no non-refractory sensed event within the Synchronization Sequence, then the defibrillation shock is delivered at the end of the Synchronization Sequence.

In Figure 19, a non-refractory event is sensed during the first synchronization period. As a result, the PCD device synchronizes the delivery of the VF therapy to this event.

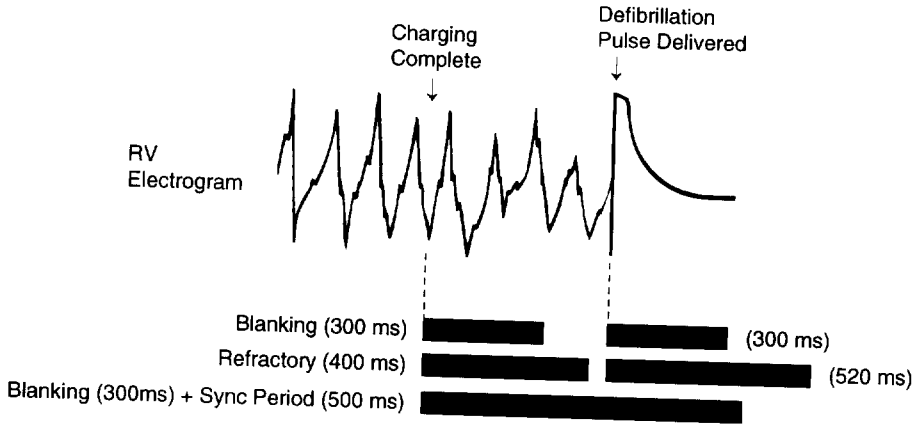

Figure 19. Defibrillation (Scenario "A")

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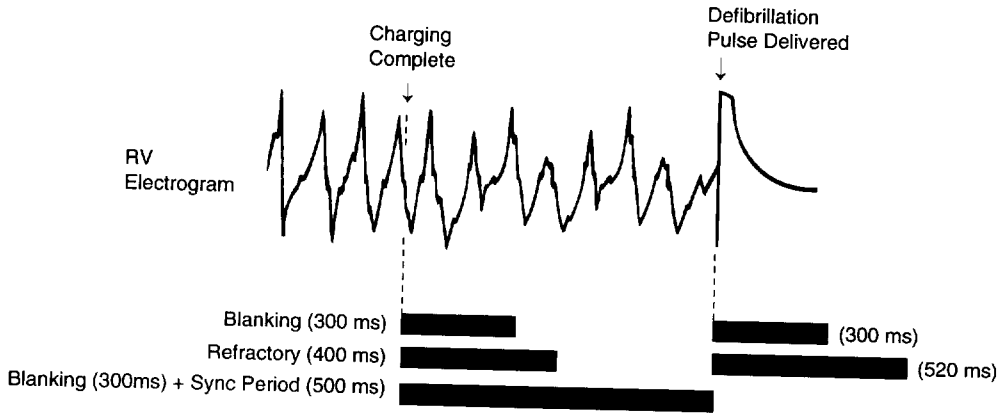

Figure 20. Defibrillation (Scenario "B")

Figure 20 illustrates an absence of sensed events during the synchronization period. As a result, the PCD device delivers the VF therapy at the end of the synchronization period.

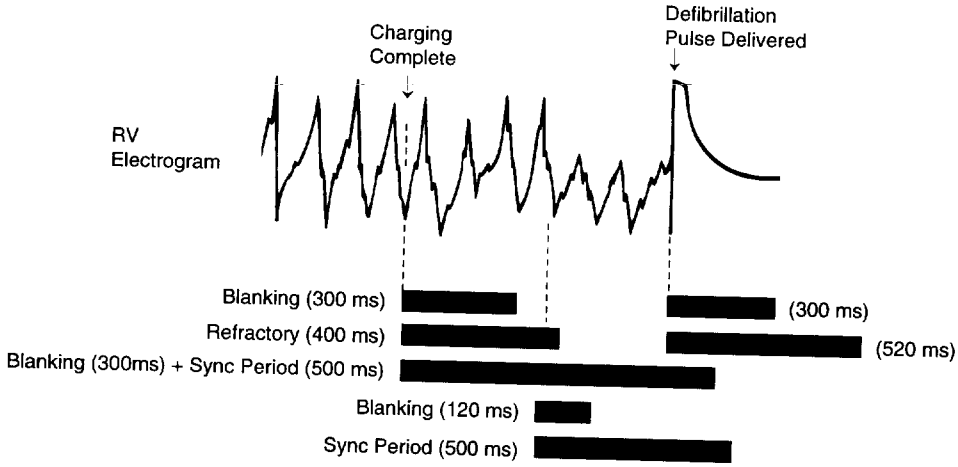

Figure 21. Defibrillation (Scenario "C")

Figure 21 shows how the PCD device might synchronize the delivery of a VF therapy to the second of two sensed events, the first of which is a refractory sensed event. Note the Synchronization Sequence that starts after the charging period. The refractory sensed event starts a second synchronization period as the PCD device attempts to synchronize the VF therapy to a non-refractory sensed event.

Programmable Current Pathways

All four VF therapies must have the same pathway, programmable between:

- a SINGLE pulse delivered over one pathway, i.e., from the PULSE2 anode to the COMMON cathode;
- two SIMULTANEOUS pulses delivered over two pathways, i.e., one from the PULSE1 anode and the other from the PULSE2 anode, with both flowing to the COMMON cathode; or
- two SEQUENTIAL pulses, separated by a very short period and delivered over the same two pathways as the SIMULTANEOUS pulses.

The PCD device delivers sequential and simultaneous pulses with three cardioversion/ defibrillation electrodes. Single pulses can be delivered with two or three electrodes.

The physician also programs the stored energy and pulse width of the pulse(s) for each of the four VF therapies (or as many as are programmed ON).

Operation Following VF Therapy

After a VF therapy, there is a 300 ms blanking period, a 520 ms refractory period, and an escape interval of 1000 ms for one cycle. The device returns to the programmed settings and, if enabled, automatically begins to evaluate the cardiac cycle for the possible detection of VF or bradycardia.

VT detection is automatically suspended[1] for 64 events (including paced events, sensed events, and therapy, except during a Charging Period) after each VF detection that initiates a VF therapy. This operation is designed to avoid detection of a transient VT which may follow such a VF therapy. After 64 events have occurred, the VT detection process is re-enabled and, if the Onset Criterion is programmed ON, then this criterion is considered fulfilled.

If some energy remains on the capacitors after a therapy, the capacitors are internally discharged when VF episode termination is detected, unless they were charged by a programmer-initiated command or a VT episode is ongoing.

1. During the 64 events following an automatic defibrillation therapy, the algorithm for detecting VT episode termination is also suspended.

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VVI Therapy

The Model 7217B PCD device provides backup bradycardia therapy, i.e., pacing in the ventricular inhibited (VVI) mode. Thus, unless a sensed event occurs and resets the pacing interval (the bradycardia escape interval), the PCD device will pace at the programmed rate.

These parameters are programmable:

- **Rate:** rates from 30 to 90 ppm for backup bradycardia pacing.
- **Pulse width:** keep in mind that this programmed setting also applies to VT Burst and Ramp therapies. When programming this parameter, ensure an adequate safety margin above the stimulation threshold.
- **Pulse Amplitude:** choose one of two settings that ensures an adequate safety margin above the stimulation threshold. The setting selected also applies to VT Burst and Ramp therapies.
- **Sensitivity:** this programmed setting will also be used to detect VT or VF. Therefore, program a setting that will sense R-wave and VF wave amplitudes, but not sense P- or T-waves or electromagnetic interference. Sensitivity should be programmed to 0.3 mV to maximize the probability that VF will be detected. A value greater than 1.2 mV may be too insensitive for VF detection. Values less sensitive than 1.2 mV are not recommended except for testing and troubleshooting. If undersensing is observed in normal sinus rhythm, verify that VF sensing and detection are appropriate. Repositioning the lead or implanting a new pacing/sensing lead may be necessary.
- **Refractory period:** the PCD device has a blanking period and Refractory After Pace after a paced event, and only a blanking period after a sensed event. (See "Refractory Periods.") The Refractory After Pace is usually the same duration as the 320 ms blanking period but may be programmed to a longer duration. Events sensed after the 320 ms blanking period are noted on Marker Channel telemetry as refractory sensed events. There is a 120 ms blanking period (nonprogrammable) after sensed events.

Events sensed within the programmed refractory period do not inhibit the pacing output. The PCD device does not revert to asynchronous operation (VOO) in the presence of continuous electrical "noise." Also, placing a magnet over the device does not inhibit VVI therapy.

A combination of wide pacing pulse width, high pacing amplitude, and high sensitivity (low sensing threshold) may cause inappropriate sensing after pacing. Programming a narrower pulse width, a lower amplitude pulse, a longer refractory period after pace, or a higher sense threshold may eliminate this inappropriate sensing. If sensitivity is reprogrammed to eliminate inappropriate sensing, VF should be reinduced and the PCD device should be allowed to automatically detect and treat the arrhythmia to ensure proper sensing and detection.

A long refractory period, coupled with a high programmed pacing rate, may impair the PCD device's ability to detect VT or VF and may cause asynchronous pacing.

IMPLANTING THE PCD DEVICE

Handling and Storage

Dropping the PCD device onto a hard surface (e.g., dropped from a height of 12 inches (30 cm) or more onto a concrete floor) could damage the device. Should this occur, the unit should not be implanted.

Environmental temperature limits for transportation and storage are:

Maximum: +52° C (125° F)
Minimum: –18° C (0° F).

Resterilization

Medtronic has sterilized the PCD device with ethylene oxide prior to shipment. The sterile package is designed to maintain the device in a sterile condition. If the device was not used, it may be resterilized in ethylene oxide.

DO NOT AUTOCLAVE OR STERILIZE THE PCD DEVICE BY GAMMA IRRADIATION. DO NOT ATTEMPT TO CLEAN THE DEVICE IN ULTRA-SONIC CLEANERS.

Avoid the application of certain organic cleaning agents (e.g., alcohol and acetone) prior to resterilization, because they may have a detrimental effect on the device's connector assembly.

When resterilizing, place the device in an ethylene oxide permeable package. Due to the variability between sterilizers, precise resterilization instructions must come from the sterilizer manufacturer. However, the process should not exceed temperatures of 55° C (130° F) nor 15 psi. Use some acceptable method for determining sterility, such as biological indicators.

Prior to implantation of the PCD device, aerate the packaged device to ensure that ethylene oxide residues are no longer present.

Resterilization of a PCD device does not change the "use before" date established at the time of manufacture.

Implantation Procedure

Overview

Patients should undergo the following procedures before implant of the PCD device to help determine if they are appropriate candidates for a PCD system:

- Electrophysiologic evaluation to determine the patient's ventricular arrhythmia and how it responds to different therapies,
- Exercise stress test to determine the patient's maximum sinus rate, and
- Cardiac catheterization to determine if there is a need for concomitant surgery.

If patients do not meet the implant criteria (demonstration of a 10 Joule safety margin) for a transvenous lead system, physicians should consider implanting an epicardial cardioversion/defibrillation lead system. If an epicardial system is to be implanted after testing a transvenous system, consider performing the procedure at a later date. The Transvene® clinical study showed a 9.3% perioperative death rate for patients failing the implant criteria for a Transvene® system and receiving an epicardial system. This compares to 0.7% for those patients receiving a Transvene® system without the additional epicardial surgical procedure.

Implanting the PCD device and corresponding lead system involves seven main steps:

- Operative Set-Up
- Lead System Implantation and Evaluation
- Defibrillation Efficacy Testing
- Connecting the Leads to the PCD Device
- Placing the PCD Device
- PCD System Evaluation
- Closing

During implantation, the PCD system requires an appropriate Medtronic programmer and MemoryMod cartridge and the Medtronic External Tachyarrhythmia Control Device (ETCD) to evaluate and monitor the implanted lead system and therapy efficacy.

Each of the above steps is explained in the following sections. At the end of this chapter, instructions for replacing a PCD device and implanting a PCD device with a chronically implanted lead system are also given.

Operative Set-Up

The preparation and procedures before implanting the lead system are grouped into four main steps: assembling the necessary equipment, setting up the equipment, pre-programming and testing the PCD device, and pre-programming and testing the ETCD and auxiliary equipment.

Necessary Equipment

The equipment listed below should be available for each implant. Duplicates of sterile items should also be on hand.

- Model 7217B PCD device
- External Tachyarrhythmia Control Device (ETCD)
- Appropriate Medtronic programmer and printer
- Appropriate MemoryMod software cartridge
- Cardioversion/defibrillation and pacing/sensing leads
- Appropriate adaptors
- External defibrillator
- Pacing system analyzer (PSA)
- Patient cable for connecting lead system to the ETCD
- EGM cable to connect the programmer to the ETCD
- Cable (and connector pins if necessary) to connect a pacing system analyzer to the ETCD or a surgical cable to connect the PSA directly to the leads
- Test load for discharging high-voltage shocks from the ETCD
- Cables for connecting the EGM output of the ETCD and Marker Channel output of the programmer to a hospital monitor/recorder
- Appropriate batteries for the pacing system analyzer and ETCD
- Extra printer paper for the pacing system analyzer and programmer/printer
- Sterile bag to place over programming head and cable
- Implant documentation forms

Some optional equipment includes an external fibrillation source or stimulator, tape or multi-channel recorder, dual-channel oscilloscope, and appropriate cables.

Equipment Set-Up

Set up the ETCD/programmer with the appropriate MemoryMod cartridge, an external defibrillator, and auxiliary equipment such as monitors, recorders, a fibrillator, and their related cabling. Also, connect the test load to the ETCD.

Pre-Programming and Testing the PCD Device

Check the "use before" date printed on the package. It is recommended that you do not use the product after its expiration date.

Prepare the PCD device for implant by doing the following:

1. Interrogate the device while it is still in its sterile package and print out a full report.
2. Review the battery status. Devices with an initial battery voltage less than 6.1 volts before charging should not be implanted. If the device is charged without obtaining the initial voltage, it should be implanted only if the battery voltage reaches 6.1 volts or more within thirty minutes after charging.
3. Test the charge circuit by charging the capacitors to the maximum output. The charge time must meet the following requirements:
   - If the charge time is less than or equal to 10 seconds, implant the device. If it is greater than 10 seconds, wait 5 minutes, discharge (dump) the capacitors, and then perform a second charge.
   - If the second charge time is less than or equal to 10 seconds, implant the device. If it is greater than 10 seconds, do not implant the device.
4. While still in the sterile package set the device parameters for implant as appropriate for the patient.
5. Ensure that VT and VF Detection are programmed OFF.

Pre-Programming and Testing the ETCD & Auxiliary Equipment

To prepare for lead system evaluation and defibrillation efficacy testing, do the following:

1. Verify that the ETCD's battery status is acceptable.
2. While recording the ETCD's output signals and the Marker Channel output from the printer, calibrate the hospital's monitoring/recording equipment.
3. Test the ETCD's high-energy output capability using the test load.

Lead System Implantation and Evaluation

The PCD lead system uses electrodes designed to carry high current for cardioversion or defibrillation. The cardioversion/defibrillation electrodes (PULSE1, PULSE2, and COMMON) must be specifically suited for this purpose and have a large electrode surface area to reduce cardioversion/defibrillation thresholds and minimize tissue damage possibly caused by the high cardioversion/defibrillation currents.

While the PCD is connected to the leads, no metal portion of any electrode should contact the metal of any other electrode. If the electrodes are in contact during a cardioversion or defibrillation therapy, the current will bypass the heart and may also damage the PCD device.

Pacing occurs between a pacing/sensing lead and one of the cardioversion/defibrillation leads (COMMON). Sensing is accomplished through two pacing/sensing electrodes. Either epicardial or endocardial leads may be used. To reduce the effects of electro-magnetic interference (EMI), the PACE/SENSE and SENSE2 electrodes should be positioned adjacent to each other, and where separate leads are used, the lead wires should be routed together with several loose twists.

Depending on what kind of operative approach is used to implant the leads, the PCD Device can use two different kinds of lead systems: an epicardial lead system or a Transvene® lead system. Each system is described briefly below. See the appropriate Lead Technical Manual for more details.

The physician chooses the lead system that best meets the patient's needs. Patient factors that affect the decision include the following:

- Overall size of the patient's heart,
- Size and location of previous infarcts, aneurysms, or bypass grafts, and
- Surgical approach.

The epicardial lead system uses two or three epicardial patch leads for cardioversion/defibrillation. Three patch sizes allow the physician the flexibility to meet the varying patient conditions. Clinical experience has shown that approximately half of all patients receive a three-patch system; the other half receives two patches. Three patches may be required initially if the physician expects difficulty in meeting defibrillation implant criteria. Adding a third patch to a two-patch system may be required if the implant criteria cannot be met with the two-patch system.

The Transvene® non-thoracotomy lead system can use two or three leads in four different areas:

- A tripolar lead in the right ventricle (RV).
- A unipolar lead in the coronary sinus (CS) and/or superior vena cava (SVC).
- A subcutaneous (SQ) patch lead.

Clinical experience with the Transvene® lead system has shown that most patients (65.6%) received an RV-SVC-SQ system; an additional 29.3% received an RV-CS-SQ system, and the remaining 5.1% recieved an RV-CS-SVC system. The majority of patients were programmed to Sequential Pulse (75.3%), 23.4% were programmed to the Simultaneous Pulse, and 1.3% were programmed to Single Pulse.

Cardioversion/defibrillation occurs between the COMMON electrode (cathode) and one or two anodes. These electrodes can be any of the following: the CS lead, the SVC lead, the RV coil, or the SQ patch. Sensing occurs between the tip and ring of the tripolar RV lead. Pacing occurs between the tip of the RV lead and the COMMON electrode.

The RV electrode was COMMON in the majority (75.3%) of the clinical implants, the SQ patch in 13.9%, the CS in 7.6%, and the SVC electrode in 2.4% of the clinical implants. The overall efficacy in terminating spontaneous episodes of VF was approximately 98% for all pathways, pulsing techniques and choice of cathode.

Lead system implantation and evaluation consists of placing the lead system, connecting the leads for pacing and sensing measurements, performing pacing and sensing measurements, and verifying lead connections. Each step is explained in the following sections. See the appropriate lead technical manual for more details.

Placing the Lead Systems

Placing the Epicardial Lead System

Depending on the physician's preference, a variety of surgical approaches can be used to implant the lead system, such as a limited thoracotomy or median sternotomy.

Placing Pacing/Sensing Leads:
The pacing/sensing leads should be placed close to the ventricular apex to avoid sensing P-waves. Approximately 1 cm should separate the electrodes from each other.

Placing Epicardial Patch Leads:
Suture two or three patch leads to the epicardium or pericardium in locations that produce optimal defibrillation, pacing, and sensing. In all locations, place the leads so that they encompasses the maximum amount of cardiac mass and they have approximately equal amounts of mass between them.

For a two-patch system, a typical approach is to use an anterior right ventricular patch as COMMON and a posterolateral left ventricular patch as PULSE2. For a three-patch system, a typical approach is to use a posterior ventricular septal patch as COMMON, an anterior right ventricular patch as PULSE1, and an anterolateral left ventricular patch as PULSE2. The PULSE1 and PULSE2 patches should be the same size.

Placing Transvene Leads

CAUTION: Given the body diameter of transvenous defibrillation leads, insertion via a subclavian approach should be done as far lateral as possible to avoid clamping the lead body between the clavicle and the first rib. Clamping the lead can eventually cause the conductor to fracture, can cause damage to the insulation, or can cause other damage to the lead. This can result in complications such as loss of detection, loss of pacing therapies, or loss of cardioversion defibrillation therapy. Certain anatomical abnormalities, such as thoracic outlet syndrome, can also precipitate pinching and subsequent fracture of the lead. If the subclavian approach is required, avoid techniques that can damage the lead. Specifically, do not force the lead if significant resistance is encountered. Do not use techniques such as adjusting the patient's posture (i.e., raising the arm or putting a towel behind the person's back) to facilitate the passage of the lead. If resistance is encountered, it is recommended that an alternate venous entry site be used, e.g. the cephalic vein.

There are several possible lead systems that can be evaluated depending on the desired pathway and physician placement preference.

Two Lead System

- Right ventricle, coronary sinus.
- Right ventricle, superior vena cava.
- Right ventricle, subcutaneous patch.

Figure 23 shows a flowchart for lead system evaluation that begins with the two lead system and adds an additional lead if the implant criteria is not met with the two lead system. The decision to evaluate a two lead system is based on the desire to achieve the simplest transvenous defibrillation system.

Three Lead System:

- Right ventricle, superior vena cava, and subcutaneous patch.
- Right ventricle, coronary sinus, and subcutaneous patch.
- Right ventricle, coronary sinus, and superior vena cava.

Clinical results do not indicate superiority of any pulsing technique, lead system, or choice of cathode for transvenous defibrillation. The choice of lead system for initial evaluation can therefore be based on other factors including simplicity (SVC vs CS lead placement) and physician preference.

The RV, CS, and SVC lead should be implanted using standard transvenous implant techniques. Follow the general guidelines below for initial positioning of the Transvene lead system (the final positions will be determined by defibrillation threshold tests):

- Position the RV lead tip in the right ventricular apex.
- Advance the CS lead tip to just under the left atrial appendage, if possible.
- Place the SVC lead tip approximately 5 cm proximal to the right atrium and SVC junction.
- Place the SQ patch lead along the left midaxillary with the center over the fourth-to-fifth intercostal space.

Other positioning recommendations to consider:

- The CS lead position should be considered unacceptable if the proximal end of the CS defibrillation coil is at or outside the CS ostium.
- A cutaneous patch electrode may also be used during acute testing to minimize invasive procedures. Once defibrillation efficacy has been demonstrated, a permanent subcutaneous can be implanted.
- The subcutaneous patch may be placed subcutaneously, submuscularly, or directly on the periosteum of the ribs. The patch may be repositioned on the left lateral chest wall, if necessary, to meet the implant defibrillation efficacy criteria.
- If the Transvene lead system implant criteria cannot be met, an epicardial lead system may be evaluated, as described in this section.
- If the CS lead is proving difficult to position, a temporary pacing catheter can be positioned in the coronary sinus ostium. This can be used as a guide to cannulate the coronary sinus with the permanent lead.

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Connecting the Leads for Pacing and Sensing Measurements

Depending on the physician's preference, two approaches can be used to connect a pacing system analyzer (PSA) to the implanted leads: passing through the ETCD or by direct connection. See the appropriate ETCD or PSA technical manual for connecting instructions.

Performing Pacing and Sensing Measurements

For a Transvene lead system, the pacing connections should be the RV tip electrode as cathode (-) and the defibrillation COMMON electrode as anode (+). Sensing measurements should be made between the RV tip and RV ring electrodes.

For an epicardial lead system, the PACE/SENSE electrode serves as the cathode (-) for pacing and the COMMON patch electrode serves as the anode (+). Measure between this patch electrode and each pacing/sensing electrode to obtain the best pacing threshold. Designate the best pacing/sensing electrode as PACE/SENSE. The other electrode should be SENSE2.

Listed below are the acceptable PCD system implant values for acute and chronically implanted lead systems.

	Acceptable Implant Values	
Measurements Required	**Acute Lead System**	**Chronic Lead System**
Capture threshold (at 0.5 ms pulse width)	≤ 1.5 V - epicardial ≤ 1.0 - endocardial	≤ 3.0 V - epicardial ≤ 3.0 V - endocardial
Impedance	200 - 800 ohms	200 - 800 ohms
Filtered R-wave amplitude	≥ 5 mV (during sinus rhythm)	≥ 3 mV (during sinus rhythm)
Slew rate	≥ 0.75 V/s	≥ 0.45 V/s

Also, check that P- and T-wave oversensing are not occurring by pacing at the maximum output (5.4 V, 1.59 ms) and sensing at the maximum sensitivity (0.3 mV).

Defibrillation Efficacy Testing

Verifying Lead Connections

After connecting all of the leads to the ETCD, confirm that the sensing leads are connected properly by observing sensed events on the Marker Channel telemetry. Verify the cardioversion/defibrillation lead connections to the ETCD by delivering a low-energy shock (0.6 joules) synchronously into sinus rhythm.

The path resistance should be approximately 20 to 100 ohms for epicardial leads, or 40 to 150 ohms for Transvene leads.

If the path resistance measurements (ohms) do not fall within these ranges, check the lead connections and lead placements and tighten or reposition if necessary.

CAUTION: Implanting the PCD device when the path resistance is less than 20 ohms may damage the device.

Performing Defibrillation Efficacy Testing

After checking the lead connections, test defibrillation efficacy to show the ability to properly treat ventricular fibrillation. Before testing defibrillation efficacy, ensure an external defibrillator is charged for a rescue shock. Use the ETCD to perform the following:

1. Program the ETCD to properly detect VF with an adequate safety margin (sensitivity = 1.2 mV, VF NID = 18, FDI = 320 ms).
2. Program the VF therapy parameters (energy, pathway, and pulse width) to the desired settings. See Table 5 in "General Device Information" for information on choosing optimal pulse widths.
3. Induce VF using AC stimulation or the fibrillation induction feature present in the ETCD. See the appropriate programmer manual for specific instructions on inducing VF with the ETCD.
4. Convert the arrhythmia using the ETCD and lead system.

To demonstrate reliable defibrillation efficacy with acute or chronic leads, it is recommended that VF be initiated and terminated three out of four times at a stored output energy of 24 joules or less. The protocol shown in Figures 22 and 23 are suggested. If more than one of the four VF inductions are not terminated by the ETCD and lead system, the decision to implant the PCD device should be re-evaluated.

In order to keep patient morbidity and mortality to a minimum, patients should be rescued promptly with an external device if the lead system and ETCD fails to terminate the VF episode and at least 5 minutes should elapse between VF inductions.

At their option, physicians may also test for ventricular tachycardia therapy efficacy after testing for defibrillation efficacy.

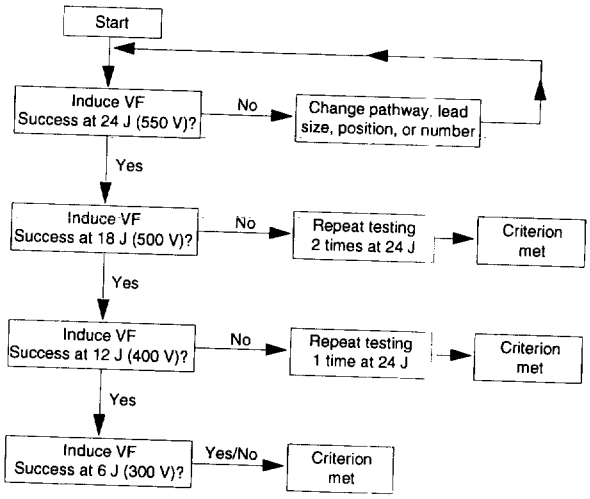

Figure 22. Defibrillation Efficacy Protocol Flowchart

Evaluating VF Sensing

While testing for defibrillation efficacy, evaluate VF sensing by reviewing the Marker Channel symbols and electrograms and checking for post-shock T-wave sensing. If VF sensing is not appropriate, it may be necessary to reposition the leads and repeat the VF inductions.

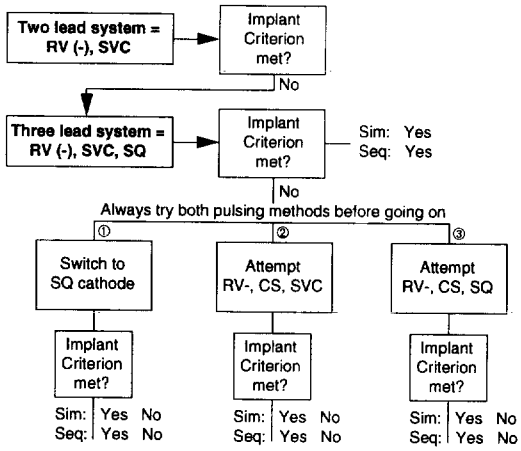

Figure 23. Transvene Lead System Evaluation Protocol Flowchart

Connecting the Leads to the PCD Device

CAUTION: Use of a chest tube is suggested in tunneling the lead connector to the pulse generator to prevent damage to the lead. DO NOT use surgical instruments to grasp the lead or connector pin when tunneling.

The Model 7217B PCD device is connected to a lead system consisting of either two or three cardioversion/defibrillation electrodes. Figures 24 and 25 illustrate these two connection configurations. Both the PULSE2 and COMMON electrodes are used in either configuration. The PULSE1 electrode is required in a lead system that uses the sequential or simultaneous therapy current pathway, but it is not required when the single pulse therapy is used. When the PULSE1 electrode is not used, the 6.5 mm plug provided with the PCD device must be positioned in the lower left port of the connector block.

The COMMON, PULSE2 and PULSE1 lead connectors must be of the 6.5 mm style. If the lead connector is not the correct size, an adaptor designed for use in a 6.5 mm port must be positioned on the lead connector.

In either configuration shown in Figures 24 and 25, both a PACE/SENSE and a SENSE2 electrode are required. The PACE/SENSE and SENSE2 lead connector must be either the Medtronic low-profile bipolar or the IS-1[1] bipolar style. The PACE/SENSE electrode must be on the pin of the lead connector and the SENSE2 electrode must be on the ring of the lead connector. If two unipolar myocardial leads are used for pacing and sensing, insert their connectors into an appropriate adaptor that will fit into the PCD device's bipolar pacing/sensing port. See the appropriate lead technical manual for more details.

1. IS-1 refers to the International Connector Standard (ISO 5841-3; 1992) whereby generators and leads so designated are assured of a basic mechanical fit.

CAUTION: For questions about lead—pulse generator compatibility, consult your Medtronic representative or call Medtronic Technical Services at our 24-hour toll-free number, 1-800-328-2518.

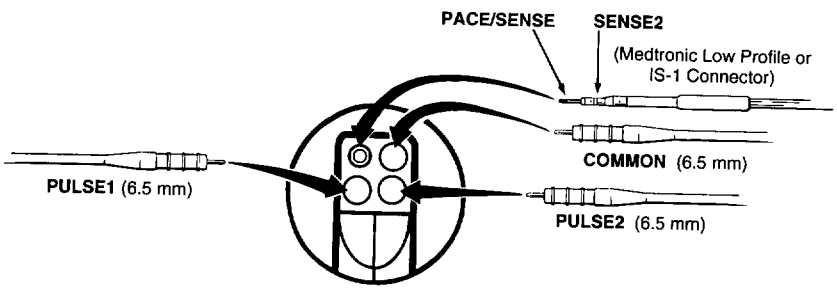

Figure 24. The Three Cardioversion/Defibrillation Electrode System

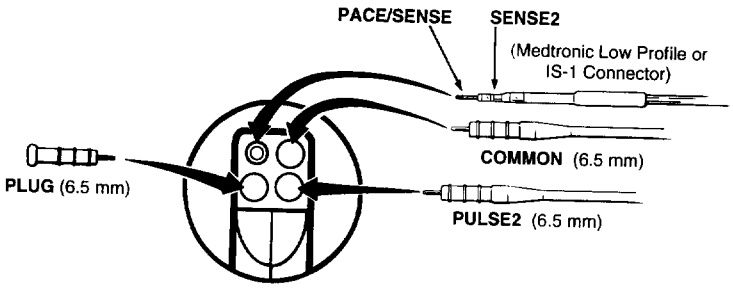

Figure 25. The Two Cardioversion/Defibrillation Electrode System

It should be noted that the insertion depth of an IS-1 lead pin is less than the insertion depth of a low-profile lead pin. The insertion mark for the IS-1 lead connector on the connector module (Figure 26) indicates that the IS-1 lead pin may not be inserted any further than the bar. Since the pin cavity is longer than the IS-1 requirement, the front part of the pin cavity will be empty when using an IS-1 lead.

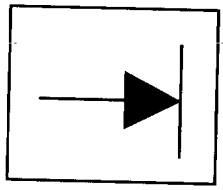

Figure 26

To connect each of the leads and plug, if required, to the PCD device:

1. Place a lead or plug into the appropriate port as shown in Figure 24 or 25.
2. Ensure full insertion of the connector pin by observing it protrude into the pin viewing area (i.e., beyond the metal block of the connector).

3. Pass the hex wrench through the associated grommet and tighten the setscrew securely by turning clockwise until tight. For the PACE/SENSE and SENSE2 connector, tighten both setscrews.

If there is difficulty with lead insertion due to the setscrew obstructing the port, turn the setscrew counterclockwise—but only until the port becomes clear.

CAUTION: Counterclockwise rotation beyond this point may disengage the setscrew from the connector block.

The setscrews must be tightened securely using the hex wrenches provided with the PCD device. The hex wrenches are designed to yield at the handle when overtorqued, thus preventing damage to the socket of the setscrew. **Do not use Medtronic blue handled, right angle, or allen-type wrenches** since they possess torque capabilities far greater than intended for this device.

PCD System Evaluation

After connecting the leads to the PCD device, test the defibrillation efficacy of the PCD system. Before testing defibrillation efficacy, ensure an external defibrillator is charged for a rescue shock. Perform the following:

1. Program the PCD device to appropriately detect and treat the VF episode.
2. If using external fibrillation equipment, place the PCD device in magnet mode (VT and VF Detection are suspended).
3. Induce VF using external fibrillation equipment or the fibrillation feature present in the PCD device. If using external fibrillation equipment, apply the signal between the PACE/SENSE terminal of the PCD and an indifferent electrode attached to body tissue. The SENSE2 terminal may be used instead of the PACE/SENSE terminal with an indifferent electrode. See the appropriate programmer manual for specific instructions on inducing VF with the PCD device.

   CAUTION: When using external fibrillation equipment, make only one connection to the PCD lead system. This connection should be disconnected immediately after VF is induced.

   CAUTION: DO NOT MOVE THE PROGRAMMING HEAD from the beginning of detection through delivery of the shock. If the head is moved, remove it from the PCD device to allow the device to operate automatically. Replacing the head during the sequence may suspend VF Detection or abort the therapy.

4. After verifying sustained VF, press the CANCEL MAGNET key and then the PROGRAM key to allow automatic VF detection and therapy delivery to convert the arrhythmia.[1]

1. When using the fibrillation feature present in the PCD device, pressing the CANCEL MAGNET key and then the PROGRAM key prior to induction of VF will cause VF Detection to be enabled immediately after the end of the fibrillation sequence.

5. Observe the ECG signal and Marker Channel symbols for proper detection and therapy. Proper sensing following therapy delivery must be observed. Wait ten seconds after VF has been terminated before interrogating the device and printing a partial summary report of the data.
6. Program VT and VF Detection OFF before closing.

Placing the PCD Device

To ensure telemetry and programming function post-implant, the Model 7217B PCD device must be placed within 5 cm of the skin and with the engraved side facing toward the skin.

The Model 7217B PCD device has two suture holes located in the connector assembly. Use of these suture holes may help secure the device in the subcutaneous pocket, thus minimizing rotation and/or migration of the device post-implant. Penetration of the holes can be achieved with normally available surgical needles.

Closing

At closing perform or verify the following:

- All leads are sutured or positioned for chronic implant.
- All leads are fully inserted into the PCD device connector and all setscrews are tight.
- Place the PCD device in the pocket within 5 cm of the skin and with the **engraved side toward the skin**.
- Ensure that there are no kinks in the leads.
- Close the pocket.
- Program VF Detection and Therapies ON.
- Interrogate the device and print a full summary to document the post-operative programmed status of the PCD device.

Replacing a PCD Device

To replace a Model 7217B PCD device:

1. Program VT and VF Detection OFF.
2. Carefully dissect the leads and the PCD device free from the surrounding tissues in the pocket. Be especially careful not to nick or breach the lead insulation inadvertently during the process of exposing the PCD system.
3. Insert the proper hex wrench through the slits in the rubber grommet and loosen the setscrew by turning counterclockwise.
4. Gently retract the lead connectors from the connector ports.
5. If any lead pin shows signs of pitting or corrosion, the entire lead should be evaluated and tested to assure the integrity of the system.
6. Take pacing, sensing, and defibrillation efficacy measurements.
7. Connect the leads to the replacement device.
8. Evaluate the defibrillation efficacy of the PCD system.
9. Place the PCD device and close.
10. Interrogate the device and print a full summary to verify and document that the programmed status of the device is as desired.
11. Return the explanted device after cleaning/gas sterilizing to your Medtronic representative for device evaluation.

Implanting a PCD Device With a Chronic Lead System

When implanting a PCD device that connects to a chronically implanted lead system, evaluate the following to ensure the device will detect and treat ventricular arrhythmias appropriately:

1. Integrity of the chronic patch leads. Evaluate by chest X Ray, inspection, or test shock.
2. Chronic pacing and sensing measurements (see "Performing Pacing and Sensing Measurements" in "Implantation Procedure"). Repositioning the chronic leads or implanting new pacing/sensing or patch leads may be necessary.
3. Defibrillation efficacy (see "Defibrillation Efficacy Testing" in "Implantation Procedure"). Repositioning the chronic leads or positioning a third patch lead may be necessary to meet the defibrillation efficacy protocol (Figure 22).
4. VF sensing (see "Evaluating VF Sensing" in "Defibrillation Efficacy Testing"). Repositioning the chronic leads or implanting new pacing and sensing leads may be required.
5. Fit of the connectors in the PCD device (see "Connecting the Leads to the PCD Device" in "Implantation Procedure"). The leads must be properly inserted into the connector block for the device to function properly.

POST-IMPLANT INFORMATION

Programming Considerations

The following suggestions have been developed to assist the physician in programming the Model 7217B PCD device. These suggestions should be used to help program the proper detection and therapy parameters for the patient's clinical arrhythmias. They are **only** considerations based on the review of the clinical experience and are not the result of unanticipated adverse results or complications. The programming choices will also depend on the patient's specific clinical arrhythmia and the results of pre- and post-implant electrophysiologic testing.

NOTE: Always interrogate the device at the beginning and end of each follow-up session and print a full summary to verify and document that the programmed status of the PCD device is as desired.

The suggestions are divided into six main areas: VT Detection, VT Therapy, VF Detection, VF Therapy, VVI Therapy, and General.

VT Detection

The PCD device uses two primary parameters to detect ventricular tachycardia: the Tachycardia Detection Interval (TDI) and the Number of Intervals to Detect (VT NID). The two optional detection methods are the Onset and Stability Criteria. Keep in mind the following when programming VT Detection:

Tachycardia Detection Interval (TDI)

The choice of the TDI is based on the cycle length of the patient's clinical ventricular tachycardia. To provide a safety margin that allows the VT cycle length to vary somewhat and still be appropriately detected, the TDI should be programmed at least 40 ms longer than the clinical VT cycle length (since a single cycle length greater than or equal to the TDI resets the VT event counter to zero). However, it must also be short enough to avoid inappropriate detection of sinus tachycardia and atrial fibrillation or flutter with rapid ventricular response.

Programming the FDI to a value greater than or equal to the TDI effectively disables VT Detection. **When programming these two values, the physician should keep the TDI at least 40 ms longer than the FDI to allow for variability of the clinical VT cycle length.**

Number of Intervals to Detect (VT NID)

The choice of the VT NID is based on the hemodynamic consequences of the clinical VT. Smaller VT NIDs will allow rapid detection of hemodynamically unstable VT. Larger VT NIDs may be indicated in patients with a history of non-sustained but well-tolerated VT. For patients other than these, programming an initial VT NID of 16 is appropriate.

Programming larger VT NID counts will result in correspondingly longer delays between VT therapies (when the previous therapy is ineffective in terminating the VT episode), due to the need to redetect the VT episode after each unsuccessful VT therapy.

The physician should understand that the programmed VT NID applies to both initial detection and redetection of an ongoing episode after each therapy is delivered.

Onset Criterion

Onset Criterion is indicated only if inappropriate detection of sinus tachycardia resulting in inappropriate VT therapy delivery has occurred. Treadmill testing, beginning at 81% Onset, is suggested to evaluate the appropriate function of this algorithm.

This algorithm was used safely in 8.5% of 434 patients in the clinical study. Its use has demonstrated its safety and effectiveness.

If the Onset Criterion is ON and is not met at the beginning of a spontaneous ventricular tachycardia, the VT episode could remain "undetected", such as with an exercise-induced VT. If VT Detection uses the Onset Criterion and detection is enabled after the start of a VT, the VT may not be detected.

A low programmed onset percentage value will increase the specificity of the Onset Criterion to detect the targeted tachycardia, but will also decrease the sensitivity of the overall VT detection algorithm.

Stability Criterion

Stability Criterion is indicated if atrial fibrillation or atrial flutter with a rapid ventricular response has caused inappropriate detection and therapy delivery. A stability value of 60 ms is suggested initially.

This algorithm was used safely in 17.9% of 434 patients in the clinical study. Its use has demonstrated its safety and effectiveness.

Decreasing the programmed interval stability value increases the specificity of the Interval Stability Criterion to detect the targeted stable tachycardia, but may also decrease the sensitivity of the detection algorithm.

Programming VT Detection ON

VT Detection can be programmed ON only after VF Detection has been programmed ON.

VT Therapy

VT Therapy consists of four independently programmable therapies that can be delivered to restore the patient's normal cardiac rhythm. The physician can tailor these four therapies to each patient's needs by choosing from two methods of overdrive pacing (Ramp and Burst) and synchronized Cardioversion. Since the actual programmed parameters used will be patient dependent, the suggestions below may help in programming them appropriately.

The physician should be aware that even when there has been a satisfactory response to VT therapies (i.e., Burst, Ramp, or Cardioversion) during clinically conducted EP studies, underlying or accompanying disease may over time alter the heart's electrophysiologic characteristics. Thus, over time, the programmed automatic therapies may not only be ineffective but also deleterious to the patient (e.g., initiate an atrial tachyarrhythmia or accelerate a ventricular tachycardia to flutter or fibrillation).

Ramp and Burst Therapy

Clinical experience has shown that the most commonly programmed values for Ramp Therapy are the following:

Initial # of S Pulses:	5
First R-S Interval	91%
Per Pulse Decrement	10 ms
# of Sequences	5
Minimum Interval	250 ms

Clinical experience has shown that the most commonly programmed values for Burst Therapy are the following:

# of S1 Pulses:	6
First S1-S1 Interval	84%
Per Sequence Decrement	10 ms
# of Sequences	5
Minimum Interval	250 ms

The values selected for Ramp and Burst Therapies will depend on the patient's clinical VT cycle length, electrophysiologic testing results, and antiarrhythmic drug therapy.

Evaluating VT Therapies

For evaluation of VT therapies, the exact number of inductions and successful terminations that should be completed is primarily dependent on a patient's hemodynamic response to their ventricular tachycardia. In patients with poorly-tolerated VT, it is recommended that at least **ONE** episode of VT be induced and successfully terminated using any of the VT therapies selected. For patients with well-tolerated VT, it is recommended that at least **FOUR** episodes of VT be induced and successfully terminated. This testing should be conducted whenever the following are performed:

- Initial selection of VT therapies,
- Permanent reprogramming of VT therapies, and
- Modification of antiarrhythmic drug therapy.

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Detecting VF as VT

In cases where VF may be detected as VT, consider using one pacing sequence and three high-energy cardioversion shocks for the VT therapies.

VT Therapy #4

The last VT therapy should be high-energy cardioversion.

Programming VT Therapies ON and OFF

VT Therapy cannot be programmed ON unless VF Therapy is also programmed ON. Also, programming one of the four VT therapies OFF will disable all subsequent VT therapies. For example, if VT Therapy #1 is programmed OFF, all VT therapies are effectively disabled.

VF Detection

The PCD device detects ventricular fibrillation using three programmable parameters: the Sensitivity of the ventricular sensing circuit, the Fibrillation Detection Interval (FDI), and the Number of Intervals to Detect (VF NID) that must be attained by the VF event counter. The programming suggestions for VF Detection are the following:

Sensitivity

Sensitivity should be programmed to 0.3 mV to maximize the probability that VF will be detected. Values of 0.6 or 0.9 mV should be used **only** if oversensing (such as P- and T-waves) would cause inappropriate shocks or inhibit pacing therapies. If sensitivity is reprogrammed to eliminate inappropriate sensing, VF should be reinduced and appropriately treated to ensure proper sensing and detection. Repositioning or implanting new pacing/sensing leads may be necessary. Use of values less sensitive (higher threshold) than 1.2 mV are not recommended except for testing and troubleshooting.

In the event of post-pace oversensing, consider increasing the Refractory After Pace if it does not interfere with VT Detection or reducing the pacing pulse width or amplitude if it does not affect proper pacing capture. See "Refractory Periods" in "Principles of Operation" for more information on programming the Refractory After Pace.

Fibrillation Detection Interval (FDI)

FDI should generally be programmed to **at least** 320 ms. If VT therapies are required for faster VTs, then a shorter FDI should be programmed **only** if repeated inductions of true VF are detected as VF at the shorter FDI. Using the Last Episode Detection Sequence memory, the FDI should be lengthened if 3 or more of the intervals from the start of VF detection are greater than or equal to the programmed FDI. Some drugs, such as Amiodarone, may slow the VF intervals to greater than 320 ms, which would require the FDI to be increased.

Number of Intervals to Detect (VF NID)

For most patients a programmed VF NID of 18 should be used. VF NIDs greater than 18 may be indicated for some patients, for example, those with non-sustained rapid tachyarrhythmias. However, in general, VF NIDs greater than 18 should be avoided to prevent prolonged detection and redetection times.

Programming VF Detection OFF

VT Detection must be programmed OFF before VF Detection can be programmed OFF.

VF Therapy

VF Therapy delivers up to four high-energy defibrillation shocks to treat ongoing detected VF episodes. The stored energy and pulse width for each therapy is separately programmable (see Table 5 in "General Device Information" for information on how to program the optimal pulse width); the electric current pathway is also programmable but must be the same for all VF therapies.

Current Pathways

The multiple pathway options the PCD device offers (sequential, simultaneous, and single) allow the physician to provide an adequate defibrillation efficacy safety margin for most patients. For example, the simultaneous pathway may be indicated for patients who have difficulty meeting the defibrillation implant criteria with a different pathway.

Stored Energy

Although the Transvene clinical study provided evidence that defibrillation thresholds remain stable in the study population, individual patients may experience threshold changes relative to changes in their underlying disease state. Therefore, VF therapy number 1 should be programmed to at least twice the lowest energy of defibrillation or 34 Joules.

The second, third, and fourth VF therapies should be programmed to the maximum stored energy of 34 joules.

Programming VF Therapies OFF

VF Therapy cannot be programmed OFF unless VT Therapy is programmed OFF. Also, programming one of the four defibrillation therapies OFF will disable all subsequent defibrillation therapies. For example, if VF Therapy #1 is programmed OFF, all defibrillation therapies are effectively disabled.

VVI Therapy

Pacing Parameters

Rate: VVI pacing may be required for underlying conduction disease and after delivery of cardioversion/defibrillation therapy. Program the rate for appropriate bradycardia support, but allow for contribution of the patient's intrinsic rate.

Pulse Width: keep in mind that this programmed setting also applies to VT Burst and Ramp therapies. When programming this parameter, ensure an adequate safety margin above the stimulation threshold.

Pulse Amplitude: choose from two settings. The setting selected also applies to VT Burst and Ramp therapies; the value selected should ensure an adequate safety margin above the stimulation threshold.

Sensitivity: this programmed setting will also be used to detect VT or VF. Therefore, sensitivity should be programmed to 0.3 mV to maximize the probability that VF will be detected. A threshold greater than 1.2 mV may be too insensitive for VF detection. Values less sensitive than 1.2 mV are not recommended except for testing and troubleshooting. If undersensing is observed in normal sinus rhythm, verify that VF sensing and detection are appropriate. Repositioning or implanting new pacing/sensing leads may be necessary. See also the programming considerations for VF Detection above.

A combination of wide pacing pulse width, high pacing amplitude, and high sensitivity (low sensing threshold) may cause inappropriate sensing after pacing. Programming a narrower pulse width, a lower amplitude pulse, a longer refractory period after pace, or a higher sense threshold may eliminate this inappropriate sensing. If sensitivity is reprogrammed to eliminate inappropriate sensing, VF should be reinduced and the PCD device should be allowed to automatically detect and treat the arrhythmia to ensure proper sensing and detection.

Long Refractory After Pace

A long refractory period (more than 320 ms), coupled with a high programmed pacing rate, may impair the PCD device's ability to detect VT or VF and may cause asynchronous pacing. Events sensed within the refractory period restart a 120 ms blanking period but are ignored by both VT and VF detection criteria and for bradycardia pacing inhibition. Therefore, a short bradycardia escape interval (i.e., a pacing rate greater than 50 ppm) combined with a long Refractory After Pace (360 ms or longer) may prevent a VT event from inhibiting a pacing output. **In such circumstances, the VT could remain undetected.**

To avoid this possibility when the Refractory After Pace is programmed to 360 ms or longer, ensure that at least one of the following is true: (1) the difference between the bradycardia escape interval and the effective refractory period should be greater than the Tachycardia Detection Interval (TDI); or (2) the bradycardia escape interval must be greater than twice (2X) the effective refractory period. (The effective refractory period

for a programmed refractory of 360 ms or longer is the programmed value plus 120 ms.) See "Refractory Periods" in "Principles of Operation" for more information.

General

Estimates of Time to Device Therapy

The time to device therapy depends on several factors including programmed detection parameters, the PCD device's remaining battery life, and the time since the last charge of the device capacitors. For all therapies, the time to device therapy increases with higher programmed NIDs. For cardioversion and defibrillation therapies, the time also increases as the device's battery voltage decreases and as the time since the last charge of the capacitors increases.

The time to device therapy projections found in Table 2 apply under the following conditions:

- The episode interval lengths to be detected are all less than the programmed TDI for VT episodes or FDI for VF episodes,
- A programmed TDI of 400 ms and VT NID of 16,
- A programmed FDI of 320 ms and VF NID of 18
- A beginning-of-life charge time to 34 J of 6.00 seconds,
- A cardioversion or defibrillation therapy of 34 J.

Table 2. Estimated Time to Device Therapy from Onset of Episode

Therapy	Time to Therapy
Ramp or Burst	6.4 seconds
Cardioversion	12.4 seconds
Defibrillation	11.8 seconds

Cardioversion and Defibrillation Charging Periods

The PCD device cannot be programmed during the cardioversion or defibrillation charging periods or during delivery of VT and VF therapies. Positioning (i.e., applying or removing) the programming head during a charging period has no immediate effect on the operation of the PCD device. However, if such positioning changes between the time the charging period begins and ends, the PCD device will abort the scheduled cardioversion or VF therapy.[1]

If the capacitors are not fully charged after three consecutive 35-second charging periods, the PCD device disables all VT and VF detection parameters and charging cycles and all VT pacing therapies.

1. VF therapy is aborted only if a refractory event is sensed at the end of charging.

Permanent Telemetry Enable

This feature, which appears on the 9710 Programmer, is designed for future applications. At that time, it may be used to provide continuous telemetry (after removal of the programming head) for a programmable number of hours, or continuously. **This feature is normally programmed OFF.**

Conditioning the PCD Device Output Capacitors

The cardioversion/defibrillation output capacitors function more efficiently if they periodically receive an electrical charge. The charge conditions and helps maintain the efficiency of the capacitor function. The electrical charge should be used to condition the capacitors at every PCD follow-up visit. See the appropriate MemoryMod cartridge technical manual for charging instructions.

Elective Replacement and Potential Loss of Function Indicators

See Table 3 on the next page for a summary of voltage and charge time requirements at implant, elective replacement, and potential loss of function.

Elective Replacement Indicators

Replacement of the Model 7217B PCD device is recommended when any of the following occur:

- The telemetered voltage for the battery is 4.97 V or less, or
- The capacitor charging time is greater than or equal to 11.00 seconds.

These are elective replacement indicators only. They do not indicate that the PCD device has altered its operation in any way.

Potential Loss of Function Indicators

Whenever any of the following are observed an **immediate replacement** of the PCD device is recommended:

- The potential for altered or loss of function is present when the telemetered voltage for the **Battery** is 4.74 V or less.

  When the telemetered battery voltage is less than this value, the PCD device may be unable to successfully complete a charging cycle to the programmed energy. That is, a charging period may terminate prematurely and result in the "Reset Parameter Value" (see Table 4).

- As the battery depletes, the charging time will generally increase (typically less than 25 seconds), but a single charging period should not exceed 35 seconds. If the output capacitors have not reached their full programmed charge in this time, the charge circuit "times out." (This data is available via telemetry.) After such a timeout, the PCD device will again attempt to confirm VT/VF detection before resuming with an

additional 35-second charging period. If after three successive charging periods the capacitors do not reach their programmed level, the PCD device identifies a "Charge Circuit Inactive" state. (This data is also available via telemetry.) In this state, the PCD device disables the following:

All automatic VT and VF detection and therapies
Programmer-initiated therapies (except emergency Burst Pacing)
Programmer-initiated charging periods

Table 3. Voltage and Charge Time Requirements

	Requirements		
Event	**Voltage**		**Charge Time**
Implant	≥ 6.10 V	and	≤ 10.00 seconds
Elective Replacement	≤ 4.97 V	or	≥ 11.00 seconds
Potential Loss of Function	≤ 4.74 V		*

*Not applicable

Time from Elective Replacement Indicator to Potential Loss of Function

The time from the Elective Replacement Indicator to potential loss of function should be used to determine the frequency of follow-up and the schedule for replacement of the unit.

The time from the Elective Replacement Indicator to potential loss of function is four months (minimum)[1], based on the following conditions:

- 100% pacing at 65 ppm,
- 5.4 V pulse amplitude,
- 0.49 ms pulse width,
- 500 ohm pacing load, and
- two 34-joule high-voltage capacitor charging cycles per month.

This time may be shorter with increased pacing rates, increased pacing pulse widths, lower pacing impedances, or an increase in high-voltage capacitor charging frequency. Potential loss of function means the PCD device may be unable to successfully complete a charging cycle to the programmed energy.

1. The preliminary projection of the time from Elective Replacement to potential loss of function is based on accelerated battery data and device modeling. Minimum projection means that virtually all (i.e. 99.9%) of the modeled production run of PCD devices will attain the values given at the stated conditions.

Pre-Hospital Discharge

Monitor the patient appropriately post-implant and take X rays as soon as possible to document and assess the location of the leads.

While the patient is in the hospital, interrogate the device after each spontaneous episode to assess the appropriateness of the detection and delivered therapy. Depending on the physician's judgment, the clinical tachyarrhythmia should be induced and terminated if no spontaneous episodes have occurred to confirm the appropriateness of the programmed values. Induction can be performed using the noninvasive electrophysiologic study (EPS) features present in the PCD device. See the appropriate MemoryMod cartridge technical manual for instructions.

Pacing and sensing values should also be tested and adjusted if necessary.

CAUTION: The physician should be aware that even when there has been a satisfactory response to VT therapies (i.e., Burst, Ramp, or Cardioversion) during clinically conducted EP studies, underlying or accompanying disease may over time alter the heart's electrophysiologic characteristics. Thus, over time, the programmed automatic therapies may not only be ineffective but also deleterious to the patient (e.g., initiate an atrial tachyarrhythmia or accelerate a ventricular tachycardia to flutter or fibrillation).

Patient Follow-Up

Regular patient follow-up testing should be scheduled every three months post-implant to confirm that the programmed parameter values are appropriate and to monitor the condition of the implanted system and of the device's battery. After the battery voltage falls below 5.25 volts, patient follow-up should be scheduled every month.

Perform the following during each follow-up visit:

- Evaluate the patient's clinical status.
- Interrogate the device at the beginning and end of each follow-up session and print a full summary to verify and document that the programmed status of the PCD device is as desired.
- Observe the battery voltage before charging the device's capacitors.
- Review device experience and status.
- Evaluate pacing and sensing performance.
- Perform a programmer-initiated 34-joule charge of the capacitors and interrogate for the charge time[1]. Do not "dump" the energy from the capacitors so as to allow them to reform.

If the charge time is greater than or equal to 11.00 seconds, wait five minutes before dumping the energy on the capacitors and then perform another programmer-initiated 34-joule charge and interrogation. If the second charge time is again greater than or equal to 11.00 seconds or if the initial battery voltage is 4.97 volts or less, the device should be replaced.

If the battery voltage is not observed before the device's capacitors are charged, it must reach its required value within thirty minutes after charging.

The patient should have X-rays and pacing/sensing thresholds taken every three months for the first year after implant and every six months thereafter to verify proper lead position and check for conductor fractures.

See the section titled "Elective Replacement and Potential Loss of Function Indicators" for more information about when to replace the PCD device.

1. Under unique conditions, a charge time of 2.33 seconds or its multiple may be reported as 2.33 seconds less than its actual value (e.g. a reported charge time of 0.00 seconds could actually be 2.33 seconds). If this occurs, wait five minutes before dumping the energy on the capacitors and perform another programmer-initiated 34 J charge and interrogation.

GENERAL DEVICE INFORMATION

Magnet/Programming Head Operation

Applying and holding a magnet (Part No. 174105) and/or programming head over the device temporarily suspends the automatic detection and therapy capabilities. Using the "Cancel Magnet" function on the programmer will restore these detection capabilities while the magnet/programming head is in position.

CAUTION: Telemetry communication with the PCD device may cause inappropriate sensed events resulting in brief inhibition of bradycardia therapy. These sensed events may also count toward detection of VT or VF. Removing the programming or transtelephonic monitor head restores the device to normal function.

Placing a magnet over the PCD device does **not** inhibit VVI therapy.

Turning Off the PCD Device

To turn OFF the VT and VF capabilities of PCD device, press the "Nominal VVI" key and then the "Program" key on the programmer. This turns OFF VT and VF Detection and programs other parameters to the values listed in Table 4 below. This programming takes effect after any therapies in progress are delivered. This keystroke sequence can be used at any time after the device model number has been selected or a successful interrogation has been performed. The physician should interrogate the device after pressing the key to ensure that VT and VF Detection have been turned OFF.

To turn the PCD device back ON, follow the usual programming steps.

The table below lists the settings the PCD device is programmed to at the following events:

- At factory shipping,
- When "Nominal VVI" is programmed,
- When the VVI option under "Emergency VVI" is programmed,and
- When a "power-on reset" (an electrical reset) occurs.

Table 4. Nominal VVI Settings, Reset Parameter Values, Emergency VVI Option Settings, and Factory Shipped Settings

Parameter	Value
Mode	VVI
Pulse Width	0.49 ms
Sensitivity	0.6 mV
Amplitude	5.4 V
Refractory After Pace	320 ms
Pacing Rate	65 ppm
VT Detection & Therapies	OFF
VF Detection & Therapies	OFF

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Device Reporting Features

The PCD device has a number of reporting features that provide current programmed settings of pacing, sensing, and VT and VF Detection and Therapy. It also provides current functional status of the device and information about previous detected and treated VT and VF episodes.[1]

Programmed Parameters

Pacing and Sensing

The PCD device reports the pacing mode, rate, pulse width, and amplitude. It also gives the programmed sensitivity and refractory after pace.

VT Detection and Therapy

The PCD device reports the following about VT Detection and Therapy:

- VT Detection ON or OFF
- Interval Criterion settings (TDI and VT NID)
- Interval Stability Criterion ON or OFF
- Interval Stability Criterion settings
- Onset Criterion ON or OFF
- Onset Criterion settings
- Onset Counter ON or OFF
- VT Therapy types (Ramp, Burst, or Cardioversion) and their respective settings.

PACING AND SENSING	
PACING MODE	VVI
PACING RATE	65 PPM
PACING PULSE WIDTH	0.49 MS
PACING AMPLITUDE	5.4 V
SENSITIVITY	0.3 MV
REFRACTORY AFTER PACE	320 MS
VT DETECTION AND THERAPIES	
VT DETECT:	
VT DETECTION ENABLE	ON
# INTERVALS TO DETECT	16
VT DETECTION INTERVAL	400 MS
INTERVAL STABILITY	OFF MS
ONSET CRITERIA ENABLE	OFF
ONSET VALUE (R-R%)	81 %
ONSET COUNTER ENABLE	OFF
VT THERAPY #1:	
THERAPY TYPE	RAMP%
VT THERAPY ENABLE	ON
INITIAL # OF S PULSES	5
FIRST R-S INTERVAL	97 %
PER PULSE DECREMENT	10 MS
# OF SEQUENCES	8
MINIMUM INTERVAL	200 MS
VT THERAPY #2:	
THERAPY TYPE	BURST%
VT THERAPY ENABLE	ON
# OF S1 PULSES	6
S1-S1 INTERVAL	84 %
PER SEQUENCE DECREMENT	10 MS
# OF SEQUENCES	5
MINIMUM INTERVAL	200 MS
VT THERAPY #3:	
THERAPY TYPE	CARDIOVERSION
VT THERAPY ENABLE	ON
CV PULSE WIDTH	3.9 MS
CV ENERGY (JOULES)	3.0 J
CV CURRENT PATHWAY	SEQ
VT THERAPY #4:	
THERAPY TYPE	CARDIOVERSION
VT THERAPY ENABLE	ON
CV PULSE WIDTH	3.9 MS
CV ENERGY (JOULES)	34.0 J
CV CURRENT PATHWAY	SEQ

1. The data strips shown are examples.

VF Detection and Therapy

The PCD device reports the following about VF Detection and Therapy:

- VF Detection ON or OFF
- VF Detection settings (FDI and VF NID)
- Defibrillation Therapy settings

VF DETECTION AND THERAPIES	
VF DETECT:	
VF THERAPY ENABLE	ON
VF DETECTION INTERVAL	320 MS
# INTERVALS TO DETECT	18
VF DEFIBRILLATION THERAPY #1:	
VF THERAPY ENABLE	ON
DEFIB PULSE WIDTH	3.9 MS
DEFIB ENERGY (JOULES)	34.0 J
DEFIB CURRENT PATHWAY	SEQ
VF DEFIBRILLATION THERAPY #2:	
VF THERAPY ENABLE	ON
DEFIB PULSE WIDTH	3.9 MS
DEFIB ENERGY (JOULES)	34.0 J
DEFIB CURRENT PATHWAY	SEQ
VF DEFIBRILLATION THERAPY #3:	
VF THERAPY ENABLE	ON
DEFIB PULSE WIDTH	3.9 MS
DEFIB ENERGY (JOULES)	34.0 J
DEFIB CURRENT PATHWAY	SEQ
VF DEFIBRILLATION THERAPY #4:	
VF THERAPY ENABLE	ON
DEFIB PULSE WIDTH	3.9 MS
DEFIB ENERGY (JOULES)	34.0 J
DEFIB CURRENT PATHWAY	SEQ

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Status and Data

These reports provide the physician with the capability to acquire data on the device's activities/operations between office visits.

- The PCD device will determine and report its own internal status, e.g., what it has retained in memory, error messages, battery status, last charging time, and charging circuit status.
- The **VT Onset Counter** reports the number of instances when the Onset Criterion associated with VT detection was fulfilled. It only counts when VT Detection is also ON and either the Onset Criterion or Onset Counter is enabled.
- Following detection of a VT episode, the PCD device's **VT Episode Counter** adds one. This counter does not increase for subsequent detection(s) of the same VT episode. It keeps track of the number of detected VT episodes.
- If the PCD device determines the VT therapy was effective (see "VT Episode Termination and Determination of Therapy Efficacy"), the **VT Therapy Success Counter** (corresponding to the last delivered therapy) is increased by one. A counter exists for each of the four possible programmed therapies.[1]
- The **Number of VTs That the PCD was Ineffective** (in terminating) increases by one each time all programmed VT therapies are ineffective in terminating a detected VT episode.

DATA

PCD STATUS:	
MEMORY RETENTION	OK
CHARGE CIRCUIT	OK
LAST CHARGE TIME	3.12 SEC
BATTERY VOLTAGE	6.19 V
VT ONSET COUNTER	14
VT EPISODE AND THERAPY DATA:	
EPISODE COUNT	6
VT THERAPY #1 SUCCESS COUNT	3
VT THERAPY #2 SUCCESS COUNT	2
VT THERAPY #3 SUCCESS COUNT	1
VT THERAPY #4 SUCCESS COUNT	0
# OF VT'S PCD INEFFECTIVE	0
PCD EFFICACIOUS ON LAST VT	YES
LAST THERAPY USED	#3
# SEQ IN LAST PACE THERAPY	5
R-R AVG FOR LAST PACE THRPY	370 MS
VF EPISODE AND THERAPY DATA:	
EPISODE COUNT	5
VF THERAPY #1 SUCCESS COUNT	3
VF THERAPY #2 SUCCESS COUNT	2
VF THERAPY #3 SUCCESS COUNT	0
VF THERAPY #4 SUCCESS COUNT	0
# OF VF'S PCD INEFFECTIVE	0
PCD EFFICACIOUS ON LAST VF	YES
LAST THERAPY USED	#2

LAST EPISODE DETECTION SEQUENCE:
-19. R-R INTERVAL-920 MS
-18. R-R INTERVAL-910 MS
-17. R-R INTERVAL-230 MS
-16. R-R INTERVAL-210 MS

-0. R-R INTERVAL-210 MS
-0. VF DETECTED

EVENTS AFTER LAST THERAPY:
+0 VF THERAPY #2 DELIVERED
+1 R-R INTERVAL-650 MS
+2. R-R INTERVAL-920 MS
+3. R-R INTERVAL-920 MS

+10. R-R INTERVAL-920 MS
+10. THERAPY WAS SUCCESSFUL

1. This counter is also incremented if the VT therapy accelerated the rhythm to VF and the corresponding VF therapy is successful in terminating the VT episode prior to the next VT detection.

The number of effective therapies plus the number of VT episodes in which the PCD was ineffective should equal the VT episode count. Exceptions to this may occur if a therapy is aborted (e.g., by a magnet application or by spontaneous termination of the VT episode during the first therapy's charging period), if therapies are initiated by the programmer during the episode, or if the device is interrogated prior to identification of VT termination.

- The **PCD Efficacy on the Last VT Episode** is also available, that is, whether the device was successful (8 consecutive paced or sensed beats greater than or equal to the TDI) on the last detected VT episode.
- The **Last VT Therapy Used** notes which programmed therapy was delivered last.
- The **Number of Sequences in the Last Pacing Therapy** reports which sequence within the last Burst or Ramp Therapy was delivered last. This information is useful because, from it (and with the next report), the physician can determine the interval and number of pulses of the last delivered therapy.[1]
- The **R–R Average for the Last Pacing Therapy** discloses the average of the last four intervals prior to delivery of the last Burst or Ramp sequence. When this information is coupled with knowledge of the programmed settings for the last pacing therapy and sequence counter of the therapy, the physician can determine the pulse intervals delivered during the last pacing therapy.[1]
- Following detection of a VF episode, the PCD device's **VF Episode Counter** is increased by one. This counter does not increase for each detection within the same VF episode.
- If the PCD device determines a VF therapy was effective (see "VF Episode Termination and Efficacy Determination"), **the Successful VF Therapy Counter** corresponding to the last delivered therapy is incremented by one. A counter exists for each of the four possible therapies.
- The **Number of VF Episodes in which the PCD device was Ineffective** is incremented by one each time all programmed VF therapies are delivered and determined to be ineffective in terminating a detected VF episode.

  The number of effective therapies plus the number of VF episodes in which the PCD device was ineffective should equal the total VF episode count. Exceptions to this may occur if a therapy is aborted by a magnet application, if therapies are initiated manually by the programmer during a VF episode, or if the device is interrogated prior to identification of VF termination.
- The **PCD Efficacy on the Last VF Episode** is also available from the PCD device.
- The **Last VF Therapy Used** notes which programmed VF therapy was last delivered.
- The **Last Episode Detection Sequence** retains data from 20 intervals just prior to the last detected VT/VF episode.
- The **Events After Last Therapy** section retains data from 10 intervals following the last VT/VF therapy of the last VT/VF episode.

1. These two counters are also updated by a manually-programmed Burst or Ramp therapy.

Electrophysiological Study (EPS) Features

With programmer-initiated commands, the PCD device will produce up to four independently programmable premature stimuli. These stimuli may be used to induce a tachycardia for determining the patient's susceptibility to ventricular tachyarrhythmias and the efficacy of the device's programmed therapies (i.e., Burst, Ramp, or Cardioversion) to treat the induced tachycardia.

Also, a ramp or burst pacing sequence with very short intervals for more aggressive stimulation may be used to establish the efficacy of Defibrillation Therapy.

The PCD device has these manually controllable therapies:

- **Emergency therapies,** including Defibrillation, Cardioversion, Burst, and VVI nominal pacing parameters,
- Defibrillation therapy (**VFRx**), programmable as to pulse width, stored energy, and current pathway, and
- VT therapies (**VTRx**), programmable as to Burst, Ramp, or Cardioversion.

Telemetry Features

The physician can acquire information about the present and past operation of the PCD device.

- Programmed Parameter Report, i.e., the programmed values to which the PCD device is currently set. See "Device Reporting Features" in "General Device Information" for more information on reports.
- Continuous, Real-Time Marker Channel™ telemetry, including the timing and categorization of sensed, paced, and therapeutic events (i.e., VF/VT/Normal). Refer to Figure 27 and the programmer technical manual for additional details.
- Continuous, Real-time Electrograms from either of two different sets of leads. EGM-Near-Field is taken from the PACE/SENSE to SENSE2 leads and EGM-Far-Field is taken from the PULSE1 to COMMON leads. (Far-Field electrograms are not available in two-electrode cardioversion/defibrillation systems because a plug is used in the PULSE1 connector port.)

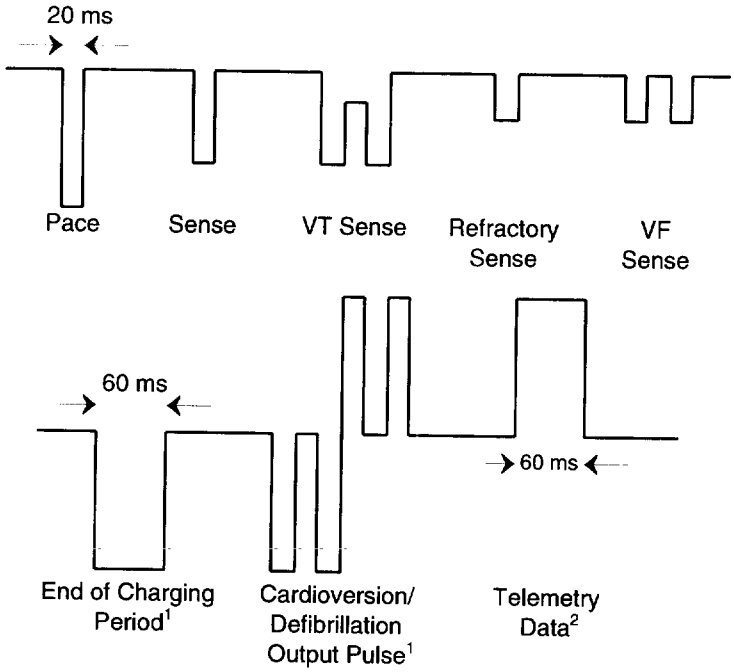

Figure 27. Representative Marker Channel Symbols

1. Interference generated during charging or pulse delivery may occasionally prevent these markers from appearing.

2. This indicates data transmission other than Marker Channel telemetry. Other markers may not appear or may falsely appear within 300 ms either side of this Telemetry Data marker.

Permanent Telemetry Enable

This feature, which appears on the 9710 Programmer, is designed for future applications. At that time, it may be used to provide continuous telemetry (after removal of the programming head) for a programmable number of hours, or continuously. **This feature is normally programmed OFF.**

Radiopaque Identification

A radiopaque code block is visible on a standard X Ray as black characters on a white background. This code block may be used to identify the PCD device, Model 7217B, as follows:

Manufacturer:	Medtronic
Model Identification:	ZB (Model 7217B)
Engineering Series Number:	Follows the Model Identifier

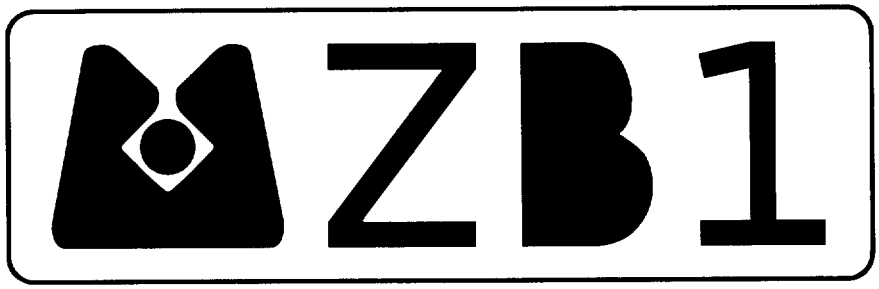

Figure 28. Radiopaque I.D.

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Output Voltage and Delivered Energy

Programming Output Voltage For Cardioversion/Defibrillation

Table 5 converts stored energy (joules) to pulse amplitude (volts), based on a 75 ohm load.

Table 5. Converting Joules to Volts

Programmed Stored Energy (Joules)	Pulse Amplitude (Volts)	Programmed Stored Energy (Joules)	Pulse Amplitude (Volts)
34.0	753 (± 5%)	9.0	387 (± 5%)
32.0	732 (± 5%)	8.0	366 (± 5%)
30.0	708 (± 5%)	7.0	342 (± 5%)
28.0	684 (± 5%)	6.0	315 (± 5%)
26.0	660 (± 5%)	5.0	288 (± 5%)
24.0	633 (± 5%)	4.0	258 (± 5%)
22.0	606 (± 5%)	3.0	225 (± 5%)
20.0	579 (± 5%)	2.0	183 (± 5%)
18.0	549 (± 5%)	1.8	174 (± 16%)
16.0	516 (± 5%)	1.6	162 (± 16%)
15.0	501 (± 5%)	1.4	153 (± 16%)
14.0	483 (± 5%)	1.2	141 (± 16%)
13.0	465 (± 5%)	1.0	129 (± 16%)
12.0	447 (± 5%)	0.8	114 (± 16%)
11.0	429 (± 5%)	0.6	99 (± 16%)
10.0	408 (± 5%)	0.4	81 (± 16%)
		0.2	57 (± 16%)

Programming Pulse Width For Defibrillation

To achieve the most effective defibrillation therapy for the most patients, the output pulse should have approximately a 65% "tilt", which means the amplitude at the end of the pulse should drop 65% of the initial amplitude. Tilt values are dependent on the pulse width and pathway resistance. Table 6 below suggests what the pulse width should be programmed to as a function of the pathway resistance to obtain a 65% tilt. For example, when programming for SEQUENTIAL pulses where the two path resistances are 80 and 60 ohms, calculate the mean resistance (70 ohms) and use the SEQUENTIAL table to choose a pulse width of 4.4 ms. If programming for SIMULTANEOUS pulses where the path resistances are 90 and 70 ohms, approximate the resistance by using the product of the two path resistances divided by their sum ($6300 \div 160 \approx 39\ \Omega$). Then look at the SIMULTANEOUS/SINGLE table for 39 ohms and choose 4.9 ms. For a SINGLE pulse with a path resistance of 40 ohms, for example, use the SIMULTANEOUS/SINGLE table, look under 40 ohms, and choose 4.9 ms.

Clinical experience has shown that the most commonly used defibrillation pulse width is 3.9 ms for SEQUENTIAL pathway and 6.3 ms for SIMULTANEOUS and SINGLE pathways.

Table 6. Pulse Widths for 65% Tilt

SEQUENTIAL		SIMULTANEOUS/SINGLE	
Resistance (ohms)*	Pulse Width (ms)	Resistance (ohms)**	Pulse Width (ms)
20-34	2.0	<19	2.0
35-42	2.4	20-21	2.4
43-50	2.9	22-25	2.9
51-58	3.4	26-29	3.4
59-66	3.9	30-33	3.9
67-74	4.4	34-37	4.4
75-82	4.9	38-41	4.9
83-89	5.4	42-45	5.4
90-97	5.9	46-48	5.9
98-102	6.3	49-52	6.3
103-110	6.8	53-56	6.8
111-118	7.3	57-59	7.3
119-126	7.8	60-63	7.8
—	8.1	64-100	8.1

*Use the mean of the two path resistances.
**For simultaneous, approximate the resistance—use the formula $\frac{R_1 \times R_2}{R_1 + R_2}$

Stored and Delivered Energy

Cardioversion and defibrillation therapies have three programmable parameters: stored energy, pathway, and pulse width. The stored energy determines the pulse amplitude (as shown in Table 5). The percentage of programmed stored energy that is applied to the lead system (that is, the delivered energy) depends on the programmed pathway, the programmed pulse width, and the pathway impedance. The percentage of programmed stored energy that is delivered increases when the programmed pulse width increases or the pathway impedance decreases.

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The percentage of delivered energy vs. programmed stored energy may be seen by referring to Figures 29 and 30. Increasing the programmed stored energy will have a proportional effect on the delivered energy. For example, if the pulse width, pathway, and pathway impedance are unchanged, doubling the stored energy doubles the delivered energy.

Figures 29 and 30 demonstrate the effect on the delivered energy with respect to the programmed stored energy, pulse width, pathway, and pathway impedance. One should not conclude, however, that two different settings delivering the same energy have the same effectiveness. Always verify the effectiveness of the new settings when reprogramming pulse width or current pathway.

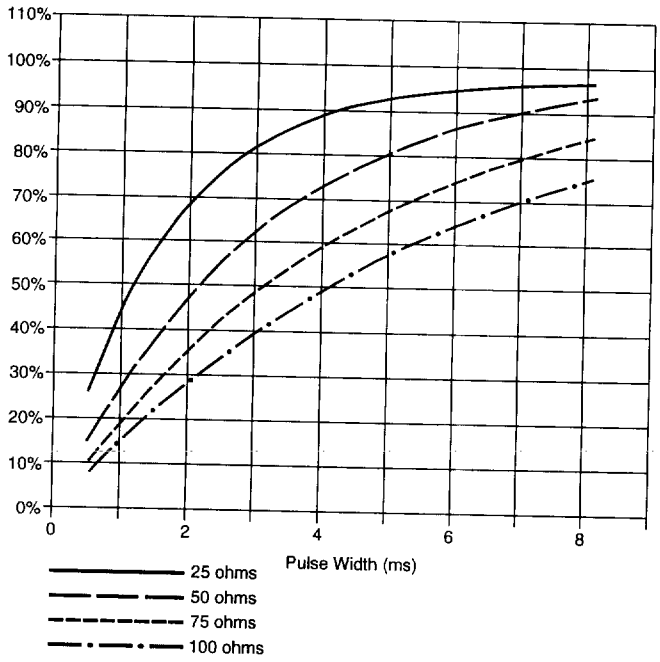

Figure 29. Percentage of Programmed Stored Energy Delivered Over a Single Pathway

If, for example, the programmed pulse width is 3.9 ms and the pathway impedance is 50 ohms, the percentage of delivered energy (compared to programmed stored energy), is about 72%. Increasing the pulse width to 6.3 ms with the same impedance will result in about an 88% delivered energy figure.

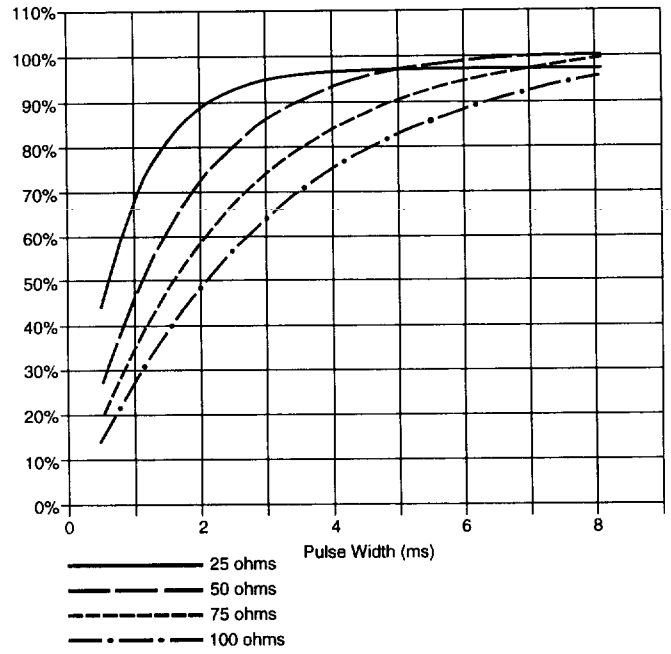

Figure 30. Percentage of Programmed Stored Energy Delivered Over Sequential or Simultaneous Pathways

Programming a sequential or simultaneous pathway may change the percentage of delivered energy. With the same examples as were used to illustrate Figure 29 where each pathway is 50 ohms, the percentages are about 93% and 99% respectively.

Output Waveforms

The illustrations that follow depict examples of waveforms that can be delivered by the PCD device during its programmable VT and VF therapies. Figures 31-33 represent the three programmable waveforms delivered during Cardioversion and Defibrillation Therapy. Figure 34 displays the waveform for Burst and Ramp therapies and bradycardia therapy, which are delivered at pacing energy levels. (Dashed voltage waveforms represent detected potentials generated from other leads. The examples assume 75 ohms as the resistance for cardioversion and VF pathways.).

Cardioversion and Defibrillation
Sequential Current Pathway

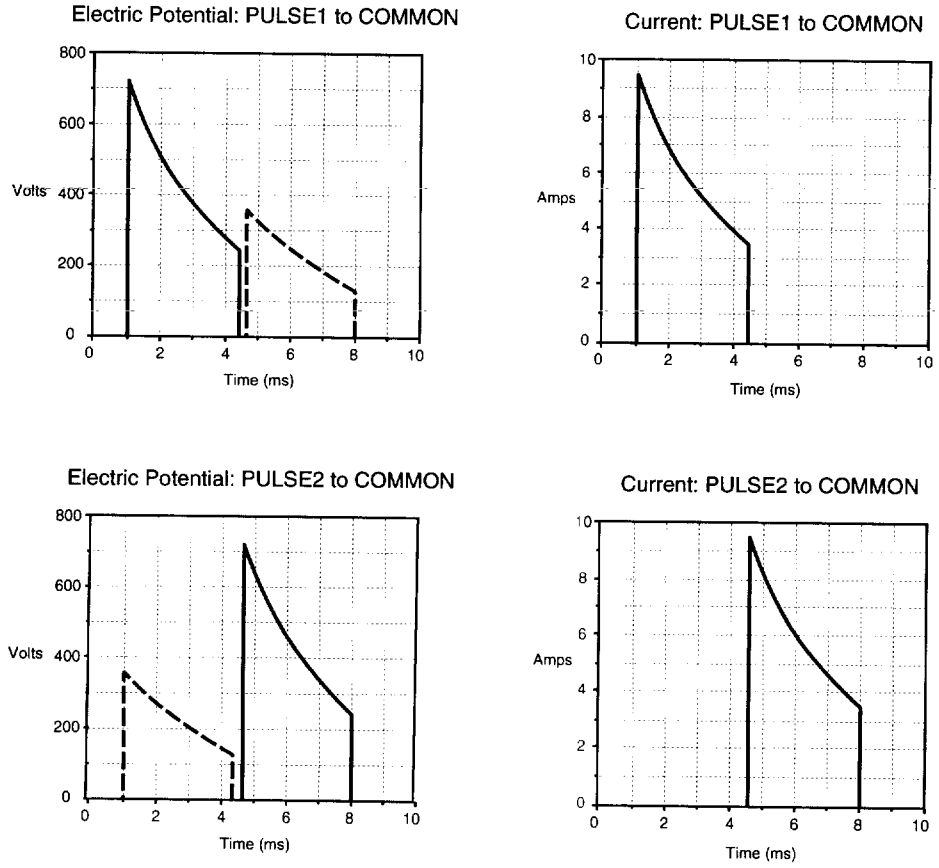

Figure 31. Output Waveforms (Sequential)

NOTES: 1. Dashed waveforms indicate potential reflected through the heart from the active electrode.

2. Current through the PACE/SENSE and SENSE2 electrodes will normally be less than 10 mA.

Cardioversion and Defibrillation
Simultaneous Current Pathway

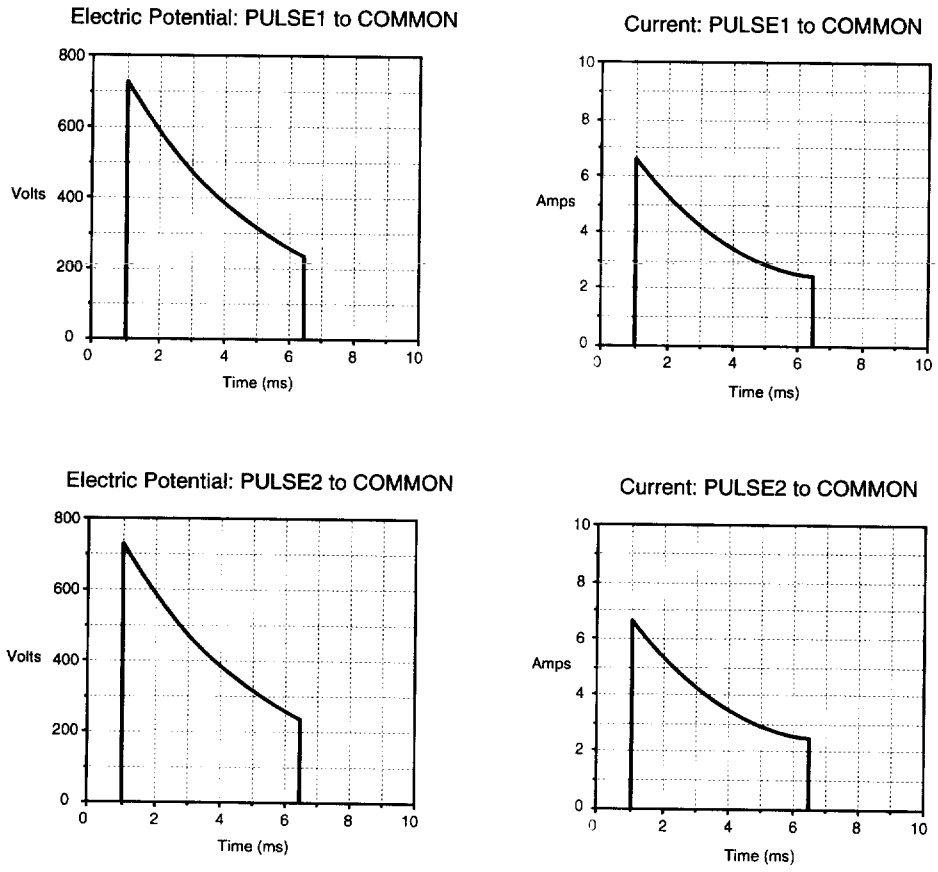

Figure 32. Output Waveforms (Simultaneous)

NOTE: Current through the PACE/SENSE and SENSE2 electrodes will normally be less than 10 mA.

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Cardioversion and Defibrillation
Single Current Pathway

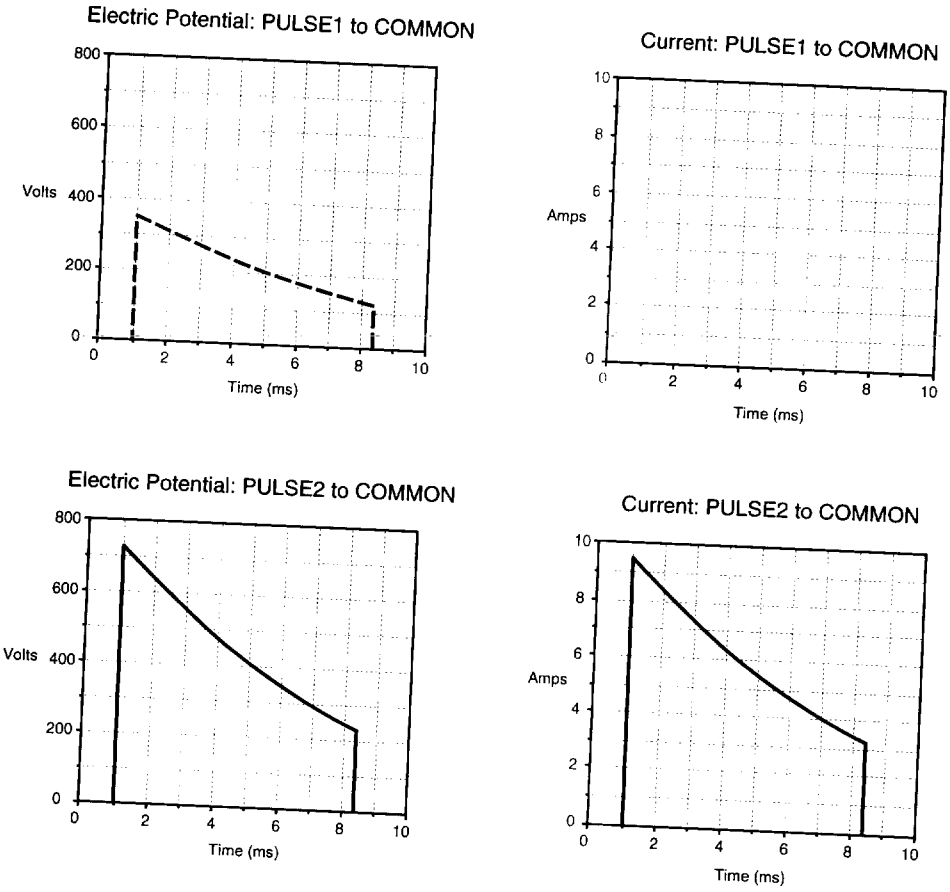

Figure 33. Output Waveforms (Single)

NOTES: 1. Dashed waveforms indicate potential reflected through the heart from the active electrode.

2. Current through the PACE/SENSE and SENSE2 electrodes will normally be less than 10 mA.

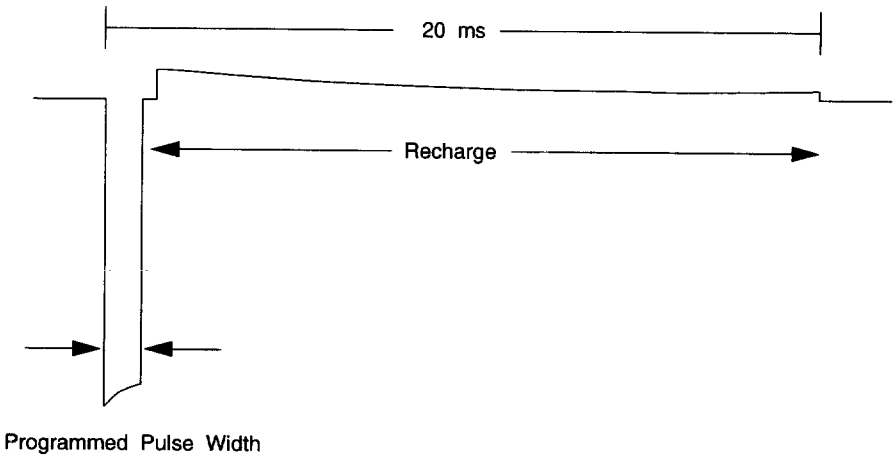

Figure 34. Output Waveform (Pacing)

WARNINGS AND PRECAUTIONS

Lead Systems

The Medtronic 7217B has been proven safe and effective when combined with Medtronic epicardial patch electrodes, Medtronic Transvene non-thoracotomy leads, or commercially available electrodes manufactured by Cardiac Pacemakers Incorporated (i.e. C10). No claims of safety and efficacy can be made with regard to other acutely or chronically implanted lead systems.

Disease Progression, Detection and Automatic VT and VF Therapies

The physician should be aware that even when there has been a satisfactory response to VT or VF therapies (i.e., Burst, Ramp, Cardioversion, or Defibrillation) during clinically conducted EP studies, underlying or accompanying disease or change in antiarrhythmic drug therapy may over time alter the heart's electrophysiologic characteristics. Thus, over time, the programmed automatic therapies may not only be ineffective but also deleterious to the patient (e.g., initiate an atrial tachyarrhythmia or accelerate a ventricular tachycardia to flutter or fibrillation). In addition, changing cardiac electrical characteristics may prevent detection of a tachyarrhythmia or may cause the pulse generator to misinterpret a normal rhythm as a clinically significant arrhythmia.

Implanted or Temporary Pacemakers

Previously implanted bradycardia pacemakers, tachyarrhythmia devices and leads should be explanted. The output pulses of an implanted device may adversely affect the tachyarrhythmia detection capabilities of the PCD device. If leads must be abandoned rather than removed, they should be capped to ensure they will not become a pathway for currents to or from the heart. If a patient requires a separate atrial or dual chamber pacemaker for hemodynamic reasons, either permanent or temporary, consider the following to minimize potential interaction between the pacemaker and the PCD:

- Use only bipolar pacemakers that remain bipolar after exposure to high voltage shocks;
- Use pacemaker leads with close interelectrode spacing;
- Allow adequate space between the pacing lead electrodes and the defibrillation lead electrodes;
- Test the PCD device to determine if output pulses from the pacemaker are sensed by the PCD;
- Induce all the patients ventricular tachyarrhythmias and ventricular fibrillation with the pacemaker programmed to an asynchronous mode at maximum output to evaluate possible inhibition of detection by the PCD due to pacing artifacts;
- Program the pacemaker to the lowest amplitude allowable for capture chronically, the maximum sensitivity, and the minimum rate acceptable to the patient.

Electromagnetic Interference (EMI)

Exposure to EMI may, under certain circumstances, prevent VT/VF detection or cause the PCD device to falsely detect a VT or VF and deliver an unneeded VT or VF therapy. The delivery of the therapy could, in turn, provoke an actual VT or VF. Additionally, since the PCD device communicates with the programmer by means of radio frequency telemetry, EMI may cause short telemetry interruptions. Under unique circumstances, EMI may cause an electrical reset of the device (see **Power On Reset**). **Keep PCD patients away from EMI sources, when and as long as any detection criteria are enabled.** Physicians should carefully weigh their decision to program the device to maximum sensitivity (0.3 mV), as it will increase the susceptibility to EMI sources. EMI sources include, but are not limited to, the following:

- Nuclear Magnetic Resonance Imaging (MRI) equipment
- Therapeutic diathermy
- Defibrillation equipment
- Electrocautery
- High-voltage systems
- Radio transmitters
- Theft prevention equipment
- Current-carrying conductors
- High-powered electromagnetic fields

Preventing Accidental Exposure to Maximum Voltage

To prevent an accidental discharge during implantation or explantation, the Model 7217B PCD device should be programmed so that VT and VF detection are both OFF.

In the event of a patient's death while the Model 7217B PCD device is implanted, the device should be explanted and returned to Medtronic. Prior to the explant procedure, **both VT and VF detection must be programmed OFF** to prevent the delivery of potentially hazardous shocks to medical or mortuary personnel. Medtronic requests that such individuals INTERROGATE THE PCD DEVICE AND PRINT A FULL REPORT BEFORE TURNING OFF DETECTION AND EXPLANTING THE DEVICE.[1]

Supraventricular Tachyarrhythmias

Depending on programmed detection and therapy settings, patients with supraventricular tachyarrhythmias (despite a drug regimen) may be inappropriately paced, cardioverted, or defibrillated. If the PCD device cannot distinguish such rhythms from ventricular tachyarrhythmias with available criteria, the physician must judge whether the use of the PCD device is advisable.

1. Consult the Technical Manuals for the Programmer and MemoryMod for details on turning OFF VT and VF detection.

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Because of the nature or frequency of conducted rapid atrial rhythms, the physician should carefully evaluate such rhythms and weigh the patient's needs against the benefits before implanting the PCD device. If the determining factor hinges on which therapies must be used, the physician should be aware that the total designed capacity for cardioversion and VF therapies is finite. The use of pacing level therapies, i.e., Burst and Ramp, will not appreciably alter the device's longevity.

Repeated, Multiple VT/VF Episodes

The physician must weigh the risks versus the benefits for patients who display a history of repeated and multiple VT episodes. Use discretion in the treatment of such episodes, since it may quickly deplete the battery of the PCD device.

The PCD device has a finite capacity for its high-energy therapies, i.e., cardioversion and defibrillation. The use of pacing level therapies, i.e., Burst and Ramp, will not appreciably alter the device's longevity.

Diathermy

Therapeutic diathermy should not be used at the implant site on patients who have a PCD device because of possible damage to the circuitry due to heating effects on the device.

Defibrillation

The Model 7217B PCD device may be damaged by direct or transthoracic defibrillatory discharges. When performing direct heart defibrillation, do not directly contact the exposed metal surface of any electrode with the paddles. When performing transthoracic defibrillation, do not place a paddle directly over the PCD device. Interrogate the PCD device after the use of direct or transthoracic defibrillation to determine the functional integrity of circuits and programmed parameters. Reprogramming may be necessary.

Patch electrodes, because they "insulate" a portion of the heart tissue, may unavoidably reduce the effectiveness of transthoracic defibrillation.

Use of a Magnet

Use only a Medtronic magnet (Part No. 174105) or programming head over the PCD device.

Positioning a magnet or the programming head of the Programmer over the Model 7217B PCD device temporarily suspends VT and VF Detection and makes the device subject to programming. Placing a magnet over the PCD device does **not** inhibit VVI therapy.

Electrocautery

Electrosurgical units should **never be used in the vicinity (i.e., six inches [15 cm] or closer)** of a Model 7217B PCD device and its associated lead system. Currents generated from electrosurgical units may cause permanent loss of output, induce ventricular

fibrillation, or reset programmed parameters in these units (see "Effects of Electrosurgical Cautery and Defibrillation"). Where alternatives to electrocautery are available, these should be used.

Power On Reset

Certain conditions, (including but not limited to: exposure to EMI, electrocautery or transthoracic defibrillation) may lead to an electrical reset of the device. The table below lists the settings the PCD is reset to when a "power on reset" (POR) occurs. **Always interrogate the PCD device at the beginning and end of each follow-up session to verify and document that the programmed status of the device is as desired.** The device may be reprogrammed to desired parameters after the source of interference is removed.

If a POR has occurred, then the POWER ON RESET message should be cleared from the PCD device memory and the device reprogrammed to desired parameters. To clear the POWER ON RESET message, use the DATA key on the main menu of the programmer to display and clear the STATUS group.

Table 7. Power On Reset Parameter Values

Parameter	Value
Mode	VVI
Pulse Width	0.49 ms
Sensitivity	0.6 mV
Amplitude	5.4 V
Refractory After Pace	320 ms
Pacing Rate	65 ppm
VT Detection & Therapies	OFF
VF Detection & Therapies	OFF

Nonsterile Package

The sterile package should be inspected prior to opening. If the seal or package is damaged, contact your local Medtronic representative.

Damage to a PCD Device Prior to Implantation

The Model 7217B PCD device should not be implanted if dropped on a hard surface from a height of 12 inches (30 cm) or more.

Random Failures

All devices will ultimately cease to function due to normal depletion of the battery and may also fail at any time due to random component or battery failure which cannot be predicted prior to their occurrence. Also, the system may cease to function at any time due to lead-related problems such as dislodgement, fracture, fibrotic tissue formation, elevated thresholds, or medical complications.

Infrequent Charging of the High-Voltage Capacitors

Infrequent charging of the high-voltage capacitors may cause the charging period to be longer than desired. **The use of the programmer-initiated charging command should be performed to 34 joules at every PCD follow-up visit.**

SIDE EFFECTS

Possible side effects include, but are not limited to, the following: body rejection phenomena including local tissue reaction; muscle and nerve stimulation; pericarditis; infection; lead dislodgement; erosion of the PCD device, leads, or adaptor through the skin; and adverse psychological effects, which may include psychologic intolerance to the PCD device, imagined pulsing, dependency, fear of inappropriate pulsing, and fear that pulsing capability may be lost.

POTENTIAL ADVERSE EFFECTS

The following potential adverse effects may arise during and after implantation of a PCD device: myocardial irritability at implant, which might cause premature ventricular contractions (PVCs), supraventricular tachycardia, or fibrillation; cardiac tamponade or loss of sensing due to perforation of the myocardium at implant; acute hemorrhage due to venous perforation; infection; thrombus formation and subsequent pulmonary embolization caused by the presence of intravascular leads; loss of system function due to battery failure or other component failure; inability to reprogram the pulse generator because of programmer failure; false sensing, inappropriate pulsing, and/or inhibition of normal electrical conduction due to dislodged or fractured leads, case fracture, or electronic component failure; interruption of desired function due to electrical or magnetic interference, including nuclear magnetic resonance (NMR) and diathermy and lithotripsy when used near the site of the pulse generator and leads, and system failure due to ionizing radiation; erosion or extrusion of the pulse generator; fibrotic tissue growth; fluid accumulation; keloid formation; and formation of hematomas or cysts.

EFFECTS OF ELECTROMAGNETIC INTERFERENCE

The Model 7217B PCD device is designed to limit the effects from most common sources of electromagnetic interference (EMI). Because many forms of EMI exist, it is impossible to characterize all of them here. In general, VT and VF Detection should, if possible, be programmed OFF before subjecting the patient to procedures that induce strong electromagnetic fields.

Paired sensing between the PACE/SENSE and SENSE2 leads makes the Model 7217B PCD device relatively insensitive to signals of non-cardiac origin. It is important to maintain a distance no greater than one (1) cm between the two electrodes to minimize EMI effects. The patient should be advised to avoid strong electromagnetic fields such as those listed in Table 8. Such signals could be interpreted by the device as being of cardiac origin and be detected as a tachyarrhythmia with subsequent delivery of VT or VF therapies.

Table 8. Potential Complications

Source	Effects/Precautions
Standard fluoroscopy radiation for imaging	No Effect
Microwave diathermy/ovens	No Effect[1]
Therapeutic diathermy	Heating of circuitry. Must be avoided directly over the device; program VT/VF Detection OFF.
Transthoracic defibrillation	Effectiveness of transthoracic defibrillation may be affected by the implanted PCD system; possible circuit damage or loss of output if ≥ 400 J or < 15 cm from the PCD device; increased pacing threshold; decreased R-wave amplitude; resetting of programmed parameter values (see "Power On Reset" on page 82).
Direct defibrillation	Effectiveness of direct defibrillation may be affected by the implanted PCD system; potential circuit damage to the PCD device, loss of output, increased pacing threshold, decreased R-wave amplitude, resetting of programmed parameter values. Avoid direct contact of the paddles with the exposed coils of the patch electrodes.
Electrosurgical cautery	Possible triggering of VT/VF detection and/or therapies; within 15 cm of the PCD system, the complications may include: potential circuit damage to the PCD device, loss of output, increased pacing threshold, decreased R-wave amplitude, or resetting of programmed parameter values. Program VT/VF Detection OFF to avoid inadvertent detection.
Ionizing radiation	Possible damage to circuitry. Should be avoided or device shielded; see "Hospital or Medical Environment." May mimic R-waves and inhibit output or initiate VT/VF detection and therapies. Program VT/VF Detection OFF to avoid inadvertent detection.
Domestic electrical equipment, car engine, airport screening equipment	No adverse effect with conventional, properly grounded and operating devices. However, excessive levels of EMI may cause VT/VF detection.
Pulsed energy; leakage current	May mimic R-waves and inhibit output or cause VT/VF detection.

1. Up to 200 Volts peak/meter.

Potential Complications (Continued)

Source	Effect/Precautions
Continuous strong interference	May mimic R-waves and inhibit output or cause VT/VF detection.
Continuous strong magnetic field	Undesired suspension of VT/VF detection; possible damage to PCD circuitry, if charging occurs.
Metal portions of the electrodes touching each other	A short circuit may occur during defibrillation or cardioversion resulting in permanent damage to the device's high-energy output circuitry.

Effects of Electrosurgical Cautery and Defibrillation

The use of electrocautery (within 15 cm) or direct defibrillation may cause permanent damage to the device.

Under certain conditions, the use of direct defibrillation or electrosurgical cautery in the vicinity of a Model 7217B PCD System (i.e., device and lead/electrodes) may cause the device to be set to its reset parameter values (see Table 4 in "General Device Information").

Program VT/VF Detection OFF during electrosurgical cautery to avoid triggering of VT/VF therapy.

Following the use of direct or transthoracic defibrillation or electrosurgical cautery, interrogate the device and print a full summary to verify and document that the programmed status of the device is as desired.

NOTE: Always interrogate the device at the beginning and end of each follow-up session and print a full summary to verify and document that the programmed status of the PCD device is as desired.

Hospital or Medical Environment

Exposure to normal diagnostic levels of x-ray and fluoroscopic radiation should not affect the Model 7217B PCD device.

The Model 7217B PCD device SHOULD NOT BE DIRECTLY IRRADIATED by therapeutic levels of ionizing radiation (such as produced by cobalt or linear accelerators used for cancer treatment) because of risk of permanent damage to the device's circuitry. If such therapy is required in the vicinity of the device, the device should be shielded (with VT/VF detection OFF) and its operation and various functions confirmed following treatment.

Home or Job Environment

The Model 7217B PCD device should not be affected by the normal operation of electrical equipment such as household appliances, electrical machine shop tools, microwave ovens, spark-ignited internal combustion engines, radio frequency transmitting systems, or microwave frequency transmitting systems.

NOTE: Such effects will normally not be observed if proper electrode spacing (i.e., no greater than 1 cm between the PACE/SENSE and SENSE2 electrodes and with the corresponding leads routed together) is provided at implant.

Medtronic should be consulted when device wearers will be in areas where contact with current-carrying conductors is possible or when they must come near high-powered, electromagnetic fields radiated by arc-welding units, induction furnaces, resistance welders, etc.

GENERAL WARNING

The Medtronic® Implantable Pacer Cardioverter Defibrillator Device (the "Device") and the Medtronic Implantable Leads (the "Leads") are implanted in the extremely hostile environment of the human body. This environment places severe limitation on the design and function of the Device and Leads. These limitations unavoidably reduce the effectiveness and longevity of the Device and Leads despite the exercise of due care in design, component selection, manufacture, and testing prior to sale.

The Device includes a nonseparable power source that will ultimately cease to function due to exhaustion or premature failure thereby necessitating removal of the Device. The Leads are necessarily very small in diameter and very flexible, which unavoidably increases the likelihood of breakage or breach of their insulation. Other reasons for failure of the Device or Leads include, but are not limited to: body rejection phenomena; physiological variations in patients; medical complications, including antiarrhythmic drugs; Lead displacement; Lead fracture; fibrotic tissue formation; erosion of the Device or Lead through body tissue; infection; perforation of an artery or heart; random component failure; or interference from transmitters, tools, appliances, instruments, equipment, electrocautery, external defibrillators or other devices that use electricity, ionizing radiation, or electromagnetic wave transmission.

Complications that may be associated with the use of the Device and Leads include, but are not limited to: failure to detect ventricular tachycardia or ventricular fibrillation; failure to terminate ventricular tachycardia or ventricular fibrillation; delivery of a pacing or shock therapy when no ventricular arrhythmia is present, which could precipitate an episode of ventricular tachycardia or ventricular fibrillation; acceleration of a ventricular arrhythmia; failure to capture after a shock delivery; constrictive pericarditis; discomfort or pain during or following the delivery of electrical shock; or tissue or muscle burns at the site of the electrodes.

Consequently, no representation or warranty is made that failure or cessation of function of the Device or Leads will not occur, that the body will not react adversely to the implantation of the Device or the Leads, that medical complications will not follow the implantation of the Device or the Leads, that the Device and Leads will effectively restore adequate cardiac function, or that implantation of the Device and Leads will prevent sudden death. See the Medtronic Warranty packaged with the product for the terms and conditions of the warranty.

SERVICE

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GLOSSARY OF TERMS

The following definitions and/or descriptions are used in this manual.

Anode: Positive "pole" of the current pathway. PULSE1 and/or PULSE2 are the anodes for delivery of cardioversion and defibrillation therapies.

Auto-Adjusting Sensitivity: The device automatically adjusts the programmed sensitivity to a less sensitive value following signal detection on the sensing leads. This prevents the sensing of T-waves when sensitive thresholds are used.

Acceleration: The criteria for determination that a VT has accelerated after delivery of a therapy. Acceleration is defined as a decrease by 60 ms or more in the average cardiac cycle length from the initial VT detection cycle length.

Automatic: When the desired detection and therapy are programmed ON, the device delivers the therapy (without manual intervention) after all detection criteria are met.

Blanking Period: The period during which the PCD device does not sense events. Blanking periods occur after each paced, sensed, or therapy event and during and after a charging period is completed.

Burst: A VT therapy in which the device delivers a sequence of rate-adaptive, equal-interval pulses. The first pulse in the sequence is delivered at a programmable percentage of the tachycardia cycle length. Subsequent pulses in the same sequence are delivered at this same interval.

Cancel Magnet: A programming command that overrides the effect (on VT and VF Detection) of positioning a programming head over the device. This command reinstates automatic VT and VF Detection while the programming head is in place.

Cardioversion: Describes the VT therapy type in which the PCD device delivers a programmable pulse that is synchronized to a ventricular sensed event.

Cathode: Negative "pole" of the current pathway. COMMON is the cathode for delivery of cardioversion and defibrillation therapies.

Charge: A programming command that allows the manual initiation of the capacitor charging cycle. The length of this cycle is an indication of the condition of the PCD device battery.

Charge Circuit Inactive: A change in device function after three consecutive Charging Periods are equal to 35 seconds. In this state, the device disables:

- All automatic VT and VF Detection and Therapies,
- Programmer-initiated therapies (except Emergency Burst Pacing),
- Programmer-initiated EPS, premature stimuli, and fibrillation stimuli,
- Programmer-initiated Charging Periods.

Charging Period: The period during which the PCD device stores the programmed energy (charge) in capacitors so that it can rapidly deliver a cardioversion or defibrillation therapy.

Committed: Once a charging cycle is initiated for defibrillation therapy, a shock will be delivered. The therapy may be aborted by applying a magnet; however, timing of magnet application will determine whether therapy is aborted.

COMMON: The electrode that serves as the cathode for cardioversion and defibrillation therapies, and as the anode for pacing therapies.

Current Pathway: The path followed by a Cardioversion or Defibrillation pulse(s) when discharged across cardiac tissue, i.e., between an anode and cathode.

Defibrillation: A therapy consisting of electrical shock to terminate ventricular fibrillation. The device attempts to synchronize the shock to a ventricular depolarization, and if unsuccessful, delivers the shock asynchronously. Automatic VF Therapy can be programmed up to a series of four attempts to terminate a VF episode.

Detection: The condition in which the device has determined the presence of electrical events that fulfill all programmed VT or VF criteria.

Disabled: A permanently programmed state in which detection and/or therapies are not available (OFF condition). These functions can only be re-enabled via a programming sequence.

Dump: A programming command that discharges the manually-charged capacitor into a load circuit in the device.

Effective Therapy: The PCD device considers a VT or VF therapy effective if, after the therapy, the device recognizes the termination of the episode prior to redetection, i.e., the continuation of the original arrhythmia.

EGM (Electrogram): The signal, transmitted via telemetry, of an electrogram taken from the device's lead system.

Elective Replacement Indicator: The telemetered battery voltage at which replacement of the device is recommended. It does not indicate that the device has altered its operation in anyway.

Emergency-VVI: A programming step that allows quick access to manual initiation of Defibrillation, Burst, Cardioversion, or VVI Nominal Therapy.

Enable: Allows or turns ON the function: e.g., allows VT and VF Detection and Therapies to carry out the designed capacity for detecting and terminating VT/VF episodes.

ETCD: External Tachyarrhythmia Control Device.

Fibrillation Detection Interval (FDI): The interval in milliseconds that measured cardiac intervals must be less than or equal to in order to meet the ventricular fibrillation detection criteria.

Interval Criterion: The programmable VT Detection Criterion that is designed to detect a sustained high ventricular rate by measuring each cardiac cycle length and comparing it to the programmed Tachycardia Detection Interval.

Interval Stability Criterion: The programmable VT Detection Criterion that allows the PCD device to screen out irregular ventricular rhythms and/or unstable VTs.

Marker Channel: A programmer-generated set of symbols that allows real-time visualization of sensing, pacing, detection, and therapy events occurring within the device.

Number of Intervals to Detect (NID): The programmable number of measured cardiac intervals that must meet the FDI or TDI criteria for detection to occur. Displayed on the programmer screen as #INT.

Non-Committed: Post completion of charging for cardioversion, the device attempts to confirm the presence of VT and synchronize to an R-wave; if this is not possible, therapy will not be delivered.

Onset Criterion: The programmable VT Detection Criterion that permits the PCD device to differentiate between a sudden or abruptly starting tachycardia and one with a gradually increasing rate such as sinus tachycardia.

Paced Events: Output pulses (of pacing energy levels) from the PCD device.

Pacing Therapies: Two VT therapies, Burst and Ramp, are pacing therapies designed to deliver pulses at pulse widths and amplitudes the same as those programmed for bradycardia therapy.

PCD Ineffective: The PCD device is considered ineffective for VT or VF if, after all therapies have been delivered, the device redetects the arrhythmia prior to recognition of the episode's termination.

Potential Loss of Function Indicator: The telemetered voltage at which immediate replacement of the PCD device is recommended. In this situation the potential for altered or loss of function is present.

PULSE1, PULSE2: The defibrillation electrodes that serve as anodes for cardioversion and defibrillation therapy.

Ramp: A VT Therapy in which the device delivers a sequence of rate-adaptive, decreasing-interval pulses. The first interval is a programmable percentage of the detected VT cycle length. Each subsequent interval is decremented from the preceding interval by a programmable value. For each sequence the device automatically increases the number of pulses by one.

Redetection: After the delivery of VT/VF Therapy the device monitors the cardiac cycle length for continued fulfillment of the programmed detection criteria. Fulfillment of this criteria (redetection) is required before the next therapy will be delivered.

Refractory Period: The period after paced, sensed, or therapy events during which events are not used for detection, synchronization, etc., but are used to restart a blanking period. The PCD device can sense events during this time, but not during the related blanking period. Events sensed during the refractory period are called "refractory sensed events."

Rounding: When attempting to detect a tachyarrhythmia, the PCD device rounds down to the nearest 10 ms while measuring the cardiac cycle length. However, it rounds up or down to the nearest 10 ms interval when using the measured interval to average or calculate percentages of intervals, e.g., during Burst or Ramp Therapies or when the Onset Criterion is active.

Sensed Event: The recognition by the PCD device circuitry of electrical activity on the paired leads (PACE/SENSE to SENSE2) that exceeds the programmed sensitivity threshold. Sensed events are either refractory sensed events or non-refractory sensed events, i.e., events sensed outside a refractory period. Non-refractory sensed events may also be categorized as VT, VF, or normal sensed events.

Sequence: The programmable feature that indicates the number of attempts that will be made by a given Ramp or Burst therapy to terminate the tachycardia.

Sequential Pulse Cardioversion or Defibrillation: The programmable therapy designed to terminate a VT/VF episode, consisting of two high-voltage pulses delivered one after the other across two different pathways.

Simultaneous Pulse Cardioversion or Defibrillation: The programmable therapy designed to terminate a VT/VF episode, consisting of two high-voltage pulses delivered at the same time across two different pathways.

Single Pulse Cardioversion or Defibrillation: The programmable therapy designed to terminate a VT/VF episode, consisting of one high-voltage pulse delivered across one pathway.

Suspend: Temporary inactivation of detection functions by placing the programming head over the device. Cancel Magnet or lifting the programming head reactivates detection if it was previously programmed ON. Detection functions are also suspended after all therapies are delivered.

Synchronization Sequence: In both Cardioversion and Defibrillation Therapy, the process conducted after the completion of charging when the PCD device attempts to identify the leading edge of an R-wave or ventricular event with which to synchronize the delivery of a high-energy output. In Cardioversion therapy, this period is also used to confirm the continued presence of the VT.

Tachycardia Detection Interval (TDI): The interval in milliseconds that measured cardiac intervals must be less than to meet the ventricular tachycardia detection criteria. Note: The intervals must also be greater than the FDI.

Termination: The PCD device considers a VT of VF episode "terminated" whenever it detects eight consecutive cardiac cycles longer than the TDI or FDI, respectively.

Therapy Type: Defines the kind of delivered therapy, i.e., Burst, Ramp, Cardioversion, or Defibrillation.

Therapy Sequence: A single attempt to terminate a VT with pacing level stimuli. The term applies to VT therapy types in which a single therapy can consist of a programmable number of Burst or Ramp sequences.

Therapy: The device operation to treat a detected VT or VF. A single therapy consists of a cardioversion or defibrillation shock or a sequence of pacing level treatments, i.e., Burst or Ramp.

VF Episode: The period during which the device considers VF in progress, i.e., from the time of initial VF detection until the criteria for VF termination are recognized by the PCD device.

VT Episode: The period during which the device considers VT in progress, i.e., from the time of initial VT detection until the criteria for VT termination are recognized by the PCD device.

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SPECIFICATIONS[a,b]

Programmable Functions	Capability	Increments	Programmer Default[c]	Tolerance	Other Notes
Sensing/Pacing					
Mode	VVI				Only mode available
Pacing Rate[d]	30-64, 65, 66-82, 85, 86, 88, 90 ppm	2 ppm	65 ppm	± 1 ppm	
Pulse Width	0.03–1.59 ms	0.03 ms	0.49 ms	– 0.0, + .03 ms	
Sensitivity[e,f]	0.3–2.4 mV	0.3 mV	0.3 mV	± 0.15 mV ± 0.20 mV ± 0.25 mV ± 0.40 mV	For 0.3 mV For 0.6 mV For 0.9–1.5 mV For 1.8–2.4 mV
Pulse Amplitude	2.8 and 5.4 V		5.4 V	2.5 & 5.2 V min	
Refractory After Pace	320–480 ms	40 ms	320 ms	– 20, + 0 ms	
VT Detection					
Enable	ON/OFF		OFF		
VT Detection Interval[g]	280–600 ms	10 ms	400 ms	± 1 ms	TDI should be at least 40 ms longer than FDI
Number of Intervals to Detect	4-52	4	16		NID value applies to all VT Detections
Onset Criterion	ON/OFF		OFF		
R-R Percent[g]	56–62, 66–87, 91–97%	3%	81%	± 0.5%[h,i]	
Onset Counter	ON/OFF		OFF		
Interval Stability[g]	OFF, 30–130 ms	10 ms	OFF	± 1 ms[h]	

a. Due to Medtronic's continuing deveopment, it is not possible to list all currently available programming configurations. See the appropriate Medtronic programmer manual for specific details.
b. Parameter and tolerance values apply at 37° C and 510 ohm load at time of manufacture. Values may vary depending on the specific test procedures used.
c. Programmer default values are associated with the Model 9788 MemoryMod.
d. Escape interval equals pulse interval (–10, + 50 ms).
e. With a 40 ms sine^2 waveform.
f. When using the Cenelec waveform, the rated sensing threshold value will be 1.5 times the rated sine^2 sensing threshold value.
g. With a periodic (constant amplitude and wave shape) signal.
h. Does not include an additional (-0, +10 ms) rounding tolerance associated with each interval measurement.
i. Does not include an additional ± 5 ms rounding tolerance associated with an R-R average calculation.

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Programmable Functions	Capability	Increments	Programmer Default	Tolerance	Other Notes
VF Detection					
Enable	ON/OFF		OFF		
VF Detection Interval[a,b]	240-400 ms	10 ms	320 ms	± 1 ms	FDI should be at least 40 ms less than TDI
Number of Intervals to Detect	6-30	6	18		
VT Therapies	0-4				
Burst					
Enable	ON/OFF		OFF		
Number of S_1 Pulses	1–15	1	6		
S_1–S_1 Interval	50–62, 66–87, 91–97%	3%	84%	± 0.5%[c]	
Number of Sequences	1–15	1	5		
Decrement per Sequence	0–40 ms	10 ms	10 ms	± 1 ms	
Minimum Pulse Interval[d]	150–300 ms	10 ms	200 ms	± 1 ms	
Ramp					
Enable	ON/OFF		OFF		
Initial Number of S_1 Pulses	1-15	1	5		
First R–S Interval	50–62, 66–87, 91–97%	3%	97%	± 0.5 %[c]	
Decrement per Pulse	0–40 ms	10 ms	10 ms	± 1 ms	
Number of Sequences	1–15	1	8		
Minimum Pulse interval[d]	150–300 ms	10 ms	200 ms	± 1 ms	

a. With a periodic (constant amplitude and wave shape) signal.
b. When VF Detection is enabled, the programmed setting for this parameter serves as the minimum interval to identify a VT event.
c. Tolerance does not include rounding tolerances associated with the R–R interval measurement (–0,+10 ms), R–R average calculation (± 5 ms), and the stimulation interval calculation (± 5 ms).
d. The Minimum Pulse Interval selected applies to both Burst and Ramp therapies and is used for all programmed therapies and sequences.

Programmable Functions	Capability	Increments	Programmer Default	Tolerance	Other Notes
Cardioversion					
Enable	ON/OFF		OFF		
Current Path	Single, Simultaneous, or Sequential		Sequential		
Pulse Width	0.5–2.0 ms	0.5 ms	6.3 ms	+0.2, –0.1 ms	
	2.4–5.9 ms	0.5 ms		+0.2, –0.1 ms	
	6.3–7.8 & 8.1 ms	0.5 ms		+0.2, –0.1 ms	
					Peak voltage with 75 ohm load:
Energy (Stored)	0.2–1.8 joules	0.2 J	0.6 J[a]	± 35%	± 16%
	2.0–15.0 joules	1.0 J		± 15%	± 5%
	16.0–34.0 joules	2.0 J		± 15%	± 5%
VF Therapy	0–4				
Enable	ON/OFF		OFF		
Current Path	Single, Simultaneous, or Sequential[b]		Sequential		
Pulse Width	2.0 & 2.4–5.9 ms	0.5 ms	6.3 ms	+0.2, –0.1 ms	
	6.3–7.8 & 8.1 ms	0.5 ms		+0.2, –0.1 ms	
					Peak voltage with 75 ohm load:
Energy (Stored)	0.2–1.8 joules[c]	0.2 J	34 J	± 35%	± 16%
	2.0–9.0 joules[c]	1.0 J		± 15%	± 5%
	10.0–15.0 joules	1.0 J		± 15%	± 5%
	16.0–34.0 joules	2.0 J		± 15%	± 5%
VT Manual Prescriptions					Programmer-in itiated therapies (Manual Prescriptions) do not involve the automatic detection criteria. Only one pacing sequence or therapy per command.
Burst	See Above				
Ramp	See Above				
Cardioversion	See Above				
VF Manual Prescriptions					
Defibrillation	See Above				
Electrophysiological Studies[d]					Delivered:
S_1–S_1	300–2000 ms	10 ms	600 ms	± 2 ms	in VVI Mode
S_1–S_2	150–600 ms	10 ms	400 ms	± 1 ms	Asynchronously
S_2–S_3	150–600 ms	10 ms	OFF	± 1 ms	Asynchronously
S_3–S_4	150–600 ms	10 ms	OFF	± 1 ms	Asynchronously
Number of S_1	1–20	1	8		
	20–95	5			

a. Default setting is 34.0 J for therapy #3 and #4
b. The programmed current path applies to all four VF therapies.
c. Energy range available only for Therapies #1 and #2.
d. Specifications may vary with the specific Medtronic programming system used.

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Programmable Functions	Capability	Increments	Programmer Default	Tolerance	Other Notes
Electrophysiological Studies (continued)					
High Rate Pacing (Fib)					
Manual–Interval	100-400 ms	10 ms	400 ms	± 1 ms	
Automatic					
Interval Limit	100–200 ms	10 ms	200 ms	± 1 ms	
	210–250 ms	20 ms		± 1 ms	
	300–400 ms	50 ms		± 1 ms	
Telemetry					
Permanent	OFF, 1-63 hrs Continuous	1 hr	OFF		Based on 4,000 events per hour
Type	Marker Channel		Marker Channel		
	EGM–Near Field				PACE/SENSE to SENSE2
	EGM–Far Field				PULSE1 to COMMON
Manual Capacitor Charging					Peak voltage with 75 ohm load
	0.2–1.8 J	0.2 J		± 35%	± 16%
	2.0–15.0 J	1.0 J		± 15%	± 5%
	16.0–34.0 J	2.0 J		± 15%	± 5%

Nonprogrammable Functions	Capability	Tolerance	Other Notes
Blanking	120 ms[a,b]	–20, +0 ms[c]	After sensed event
	320 ms	–20, +0 ms[c]	After paced event
	300 ms	–20, +90 ms[c]	After Charging Period
	300 ms	–20, +0 ms[c]	After VT/VF therapy or failure to synchronize
Refractory	200 ms	–20, +0 ms[c]	After sense, during CV Synchronization Sequence
	400 ms	–20, +90 ms[c]	After Charging Period
	520 ms	–20, +0 ms[c]	After VT/VF therapy or failure to synchronize
VF Synch Period	500 ms	± 1 ms	If no sensed event, the defibrillation shock is delivered
Escape Interval	1000 ms	±2 ms	After VT/VF therapy
Maximum Allowable Charging Period	34.95 seconds	+20, –10 ms	For cardioversion and VF therapy

a. Using a periodic (constant amplitude and waveform) signal.
b. Measured from the time of the previous sensed event.
c. Based on a 40 ms sine^2 waveform at twice the programmed sensitivity threshold.

Nonprogrammable Functions	Capability	Tolerance	Other Notes
Time Between Sequential Pulses	244 µsec	± 225 µsec	
Disabling of VT Detection	64 events		After a VF detection
Rate Limit (Protective Feature)	120 ppm	± 20 ppm	Does not apply during therapies or programmed high rates
Input Impedance (min)	50 Kohms		

Data	Range	Tolerance	Other Notes
PCD Status			
Memory Retention	OK, Reset (by **P**ower Inadequate, **M**emory Loss, **B**oth)		
Charge Circuit	OK, Timeout, Inactive		
Last Charge Time	10 ms – 34.95 seconds	+ 20, – 10 ms	
Battery Voltage	Measured Voltage	± 200 mV	
VT Onset Counter	0–65,535		
VT Episode and Therapy Data			
Episode Count	0–255[a]		
VT Therapy Success Count	0–255[a]		Reports for each of 4 therapies
Number of VTs PCD Ineffective	0–255[a]		
PCD Efficacious on Last VT	YES/NO		
Last Therapy Used	0–4		
Number of Sequences in Last Therapy	1–15		Applies to Burst and Ramp therapies only
R-R Average for Last Pace Therapy	None, 150–600 ms		Applies to Burst and Ramp therapies only

a. An increment to a counter that causes the value to exceed the maximum will cause the counter to go to the minimum value.

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Nonprogrammable Functions	Capability	Tolerance	Other Notes
VF Episode and Therapy Data			
Episode Count	0–255[a]		
VF Therapy Success Count	0–255[a]		Reports for each of 4 therapies
Number of VFs PCD Ineffective	0–255[a]		
PCD Efficacious on Last VF	YES/NO		
Last Therapy Used	0-4		
Last Episode Sequence	20 intervals		Prior to last VT or VF episode detection
Cycle Length Intervals	100 – 2000 ms	+ 12, –2 ms	
Last Therapy Sequence	10 intervals		Following last VT or VF therapy delivered during last episode
Mechanical Dimensions			
Size: Height	101 mm		
Length	70 mm		
Width	20 mm		
Mass	197 grams		
Displacement Volume	113 cc		
External Shield	Titanium		
Battery	Lithium Silver Vanadium Oxide		(6.4 V nominal)
Factory Preset Parameters	As indicated on Package Labeling		

a. An increment to a counter that causes the value to exceed the maximum will cause the counter to go to the minimum value.

Europe

Medtronic Europe S.A./N.V.
Woluwe Office Garden
Woluwedal 26
1932 St. Stevens Woluwe
Belgium
Telephone: (32-2) 716 88 11
FAX: (32-2) 716 88 15

Asia-Pacific

Japan
Medtronic Asia-Pacific
Shuwa Kioi-cho Park Building, 5F
3-6 Kioi-cho, Chiyoda-ku
Tokyo 102, Japan
Telephone: (81-3) 3230-2701
FAX: (81-3) 3230-0446

Australia
Medtronic Australasia Pty. Ltd.
22 Clarke Street
Crows Nest, Sydney, N.S.W., 2065
Australia
Telephone: (61) 2 437-6066
FAX: (61) 2 437-6869

Asia
Medtronic International Ltd.
2002 CC Wu Building
308 Hennessey Road, Wanchai
Hong Kong, B.C.C.
Telephone: (852-5) 891-4068
FAX: (852) 891-6830

Latin America

Medtronic, Inc.
450 Fairway Drive
Suite 103
Deerfield Beach, FL 33441
USA
Telephone: (305) 428-8556
FAX: (305) 428-8984

North America

Canada
Medtronic of Canada Ltd.
6733 Kitimat Road
Mississauga, Ontario L5N 1W3
Canada
Telephone: (905) 826-6020
FAX: (905) 826-6620
Toll-free: 1-800-268-5346
(24-hour consultation service)

United States
Medtronic, Inc.
7000 Central Avenue, NE
Minneapolis, MN 55432-3576
USA
Telephone: (612) 574-4000
FAX: (612) 574-4879
Toll-free: 1-800-328-2518
(24-hour consultation service)

Medtronic

December 1993
UC9203800bEN 195828-003

02

STERILE
PAK
LABEL

Medtronic

PCD™

7217B

CONTENTS **(STERILE)** : Implantable Tachyarrhythmia Control Device/Accessories
CONTENU **(STERILE)** : Appareil Implantable de Contrôle de la Tachyarythmie/Accessoires
INHALT **(STERIL)** : Implantierbares Tachyarrhythmie-Steuergerät/Zubehör
CONTENIDO **(ESTERIL)** : Aparato Implantable para Control de Taquiarritmias/Accesorios
CONTENUTO **(STERILE)** : Apparecchio Impiantabile per Controllo di Tachiaritmias/Accessori

CAUTION : Federal Law (USA) restricts this device to sale by or on the order of a physician
ATTENTION : La réglementation américaine (FDA) n'autorise la vente de ce produit que sur prescription médicale
ACHTUNG : Ein US-Bundesgesetz schränkt den Verkauf dieses Produkts auf Ärzte oder auf Anordnung durch einen Arzt ein
PRECAUCION: Les Leyes Federales (EE.UU.) restringen la venta de este dispositivo únicamente a médicos o por prescripción médica
ATTENZIONE : La Legge Federale (U.S.A.) limita la vendita di questo prodotto esclusivamente ai medici o su richiesta del medico.

STERILIZATION : ETHYLENE-OXIDE GAS
STERILISATION : GAZ D'OXYDE D'ETHYLENE
STERILISATION : ÄTHYLENOXYDGAS
ESTERILIZACION : GAS OXIDO DE ETILENO
STERILIZZAZIONE : GAS OSSIDO DI ETILENE

EXPOSURE TEMPERATURE
TEMPERATURE D'EXPOSITION
ZULÄSSIGE TEMPERATUR
TEMPERATURA DE EXPOSICION
TEMPERATURA DI CONSENTITA
-18° C...52° C

TECHNICAL SPECIFICATIONS : (Manufacturer's settings at 37° C and 510 Ω Load)
CARACTERISTIQUES TECHNIQUES : (Préréglées par le fabricant à la température de 37 °C et pour une charge de 510 Ω)
TECHNISCHE DATEN : (Herstellerangaben bei Körpertemperatur und 510 Ω Lastwiderstand)
ESPECIFICACIONES TECNICAS : (Parámetros fijados en fábrica a temperatura corporal y 510 Ohmios de resistencia)
SPECIFICHE TECNICHE : (Valori del fabbricante misurati a temperatura corporea ed un carico del valore di 510 Ohm)

VF DETECTION / DETECTION VF / VF ERKENNUNG / DETECCION DE VF / RIVELAZIONE DI FV: Off / Désactivée / Aus / Parada / Desinserita

VF THERAPIES / THERAPIES VF / VF THERAPIEN / TERAPIAS DE VF / TERAPIE PER FV: Off / Désactivées / Aus / Paradas / Desinserite

VT DETECTION / DETECTION VT / VT ERKENNUNG / DETECCION DE VT / RIVELAZIONE DI TV: Off / Désactivée / Aus / Parada / Desinserita

VT THERAPIES / THERAPIES VT / VT THERAPIEN / TERAPIAS DE VT / TERAPIE DI TV: Off / Désactivées / Aus / Paradas / Desinserite

MODE / MODE / BETRIEBSART / MODO / MODO: VVI

PULSE AMPLITUDE / AMPLITUDE D'IMPULSION / IMPULSAMPLITUDE / AMPLITUD DEL IMPULSO / AMPIEZZA DELL'IMPULSO: 5,4 V

SENSITIVITY / SENSIBILITE / EMPFINDLICHKEIT / SENSIBILIDAD / SENSIBILITÀ: 0,6 mV

PACING RATE / FREQUENCE DE STIMULATION / STIMULATIONSFREQUENZ / FRECUENCIA DE ESTIMULACION / FREQUENZA DI STIMOLAZIONE: 65 ppm / min⁻¹ / min⁻¹ / min⁻¹ / min⁻¹

PULSE WIDTH / DUREE D'IMPULSION / IMPULSDAUER / ANCHURA DEL IMPULSO / DURATA DELL'IMPULSO: 0,49 ms

NON REUSABLE
NON REUTILISABLE
NICHT WIEDERVERWENDBAR
INTERIOR DESECHABLE
MATERIALE STERILE INVOLUCRO NON RIUTILIZZABILE

Serial No./No. de Série/
Seriennummer/
Número de Serie/Numero di Serie

Use before/Utiliser avant/
Zu implantieren vor dem/
Fecha de Caducidad/Data di Scadenza

Sterile Lot No./Lot de Stérilisation No./
Sterilisationsnummer/Lote Estéril Número/
Numero di Lotto Sterile

Sterilization Date/Date de Stérilisation/
Sterilisationsdatum/
Fecha de Esterilización/Data di Sterilizzazione

192976-002

203

SHELF
BOX
LABEL

Medtronic

PCD™

7217B

Connector Configuration: 3x Unipolar 6.5 mm and 1x Bipolar Connector 3.2 mm Low-Profile (IS-1 Lead Compatible) * Special Leads required / Configuration du Connecteur: 3x Unipolaire 6,5 mm et 1x Connecteur Bipolaire Profile 3,2 mm (Compatible avec Sonde IS-1) * Sondes Spéciales nécessaires / Stecker Konfiguration: 3x unipolarer 6,5 mm und 1x Bipolar 3,2 mm nektor (kompatibel mit IS-1-Elektrode) * Spezielle Elektroden notwendig/Configuración del Conector: 3x Unipolar 6,5 mm y 1x Conector Bipolar de Perfil Bajo 3,2 mm (Compatible [illegible] * Necesita Cables Especiales / Configurazione del Connettore: 3x Monopolare 6,5 mm e 1x Connettore Bipolare a Basso Profile 3,2 mm (Compatible con il Elettrocatetere IS-1 [illegible] trocateteri Speziali

CONTENTS : One Implantable Tachyarrhythmia Control Device/Product Literature/Accessories
CONTENU : Un Appareil Implantable de Contrôle de la Tachyarythmie/Documentation/Accessoires
INHALT : Ein Implantierbares Tachyarrhythmie-Steuergerät/Dokumentation/Zubehör
CONTENIDO : Un Aparato Implantable para Control de Taquiarritmias/Documentación/Accesorios
CONTENUTO : Un Apparecchio Impiantabile per Controllo di Tachiaritmias/Documentazione/Accessori

The contents **(STERILE)** of the inner package have been sterilized by ethylene-oxide gas
Le contenu **(STERILE)** du paquet interne a été stérilisé au gaz d'oxyde d'éthylène
Der Inhalt **(STERIL)** der inneren Verpackung ist in Äthylenoxidgas sterilisiert
El contenido **(ESTERIL)** del paquete interior ha sido esterilizado con gas óxido de etileno
Il contenuto **(STERILE)** della confezione interna è stato sottoposto a sterilizzazione con gas ossido di etilene

CAUTION : Federal Law (USA) restricts this device to sale by or on the order of a physician.
ATTENTION : La réglementation américaine (FDA) n'autorise la vente de ce produit que sur prescription médicale.
ACHTUNG : Ein US-Bundesgesetz schränkt den Verkauf dieses Produkts auf Ärzte oder auf Anordnung durch einen Arzt ein.
PRECAUCION: Las Leyes Federales (EE.UU.) restringen la venta de este dispositivo únicamente a médicos o por prescripción médica.
ATTENZIONE : La Legge Federale (U.S.A.) limita la vendita di questo prodotto esclusivamente ai medici o su richiesta del medico.

STERILIZATION VALIDITY PERIOD	4 Years	STORAGE TEMPERATURE	
DUREE DE VALIDITE DE STERILISATION	4 Ans	TEMPERATURE DE STOCKAGE	
WIRKSAMKEIT DER STERILISATION	4 Jahre	ZULÄSSIGE LAGERTEMPERATUR	4° C...38° C
PERIODO DE VALIDEZ DE LA ESTERILIZACION	4 Años	TEMPERATURA DE ALMACENAMIENTO	
PERIODO DI VALIDITA DELLA STERILIZZAZIONE	4 Anni	TEMPERATURA DI IMMAGAZZINAGGIO	

TECHNICAL SPECIFICATIONS : (Manufacturer's settings at 37° C and 510 Ω Load)
CARACTERISTIQUES TECHNIQUES : (Préréglées par le fabricant à la température de 37° C et pour une charge de 510 Ω
TECHNISCHE DATEN : (Herstellerangaben bei Körpertemperatur und 510 Ω Lastwiderstand))
ESPECIFICACIONES TECNICAS : (Parámetros fijados en fábrica a temperatura corporal y 510 Ohmios de resistencia)
SPECIFICHE TECNICHE : (Valori del fabbricante misurati a temperatura corporea ed un carico del valore di 510 Ohm

VF DETECTION	Off	VF DETECTION	Off
DETECTION VF	Désactivée	DETECTION VF	Désactivée
VF ERKENNUNG	Aus	VF ERKENNUNG	Aus
DETECCION DE VF	Parada	DETECCION DE VF	Parada
RIVELAZIONE DI FV	Desinserita	RIVELAZIONE DI FV	Desinserita
VF THERAPIES	Off	VF THERAPIES	Off
THERAPIES VF	Désactivées	THERAPIES VF	Désactivées
VF THERAPIEN	Aus	VF THERAPIEN	Aus
TERAPIAS DE VF	Paradas	TERAPIAS DE VF	Paradas
TERAPIE PER FV	Desinserite	TERAPIE PER FV	Desinserite
PACING RATE FREQUENCE DE STIMULATION STIMULATIONSFREQUENZ FRECUENCIA DE ESTIMULACION FREQUENZA DE STIMOLAZIONE	65 ppm / min^{-1}	SENSITIVITY SENSIBILITE EMPFINDLICHKEIT SENSIBILIDAD SENSIBILITA	0,6 mV
PULSE AMPLITUDE AMPLITUDE D'IMPULSION IMPULSAMPLITUDE AMPLITUD DEL IMPULSO AMPIEZZA DELL'IMPULSO	5,4 V	MODE MODE BETRIEBSART MODO MODO	VVI	PULSE WIDTH DUREE D'IMPULSION IMPULSDAUER ANCHURA DEL IMPULSO DURATA DELL'IMPULSO	0,49 ms

192976-002

END
LABEL

Medtronic

PCD™ 7217B

Tachyarrhythmia Control Device;
Pacer-Cardioverter-Defibrillator

Serial No./No. de série/
Seriennummer/
Número de Serie/Numero di Serie

Use before/Utiliser avant/
Zu implantieren vor dem/
Fecha de Caducidad/Data di Scadenza

Sterile Lot No./Lot de Stérilisation No./
Sterilisationsnr./Lote Esteril Número/
Numero di lotto Sterile

Sterilization Date/Date de Stérilisation/
Sterilisationsdatum/
Fecha de Esterilización/Data di Sterilizzazione

pages 1020
↓
1097

Medtronic

Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576
Telephone: (612) 574-4000
Cable: Medtronic Telex: 29-0598
FAX: (612) 574-4879

August 26, 1992

Part 1

Office of Device Evaluation
PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

FDA/CDRH/ODE
27 Aug 26 00
RECEIVED

Re: Response to OCS Request for Additional Manufacturing Information for the Medtronic® PCD™ Transvene™ System (Document Control Number P920015) ACIVI

This Amendment addresses deficiencies in the above referenced PMA that were described in your letter dated May 14, 1992 (Attachment A). The response to each deficiency follows this cover letter.

This information is submitted in triplicate in accordance with 21 CFR Part 812. This submission contains confidential or commercial trade secret information and we request that it be given the maximum protection provided by law. If further information is required, please contact the undersigned.

Sincerely yours,

MEDTRONIC, INC.

C. Whitacre

Chip Whitacre
Cardiac Pacing Business
Product Regulation Manager
(612) 574-8656
(612) 574-8424 FAX

Attachment

One Place Your Text Could Go (See Documentation Section 6)

1. **The Design Assurance Plan, Project [(b) (4)] dated 2/7/91 for the new helix electrode, part 136250-001, is not representative of the manufacturing operations. The qualification report dated 4/16/91 does not address the effects of the sterilization process on the integrity of the helical electrode. [vol. 2, pp. 153-156]**

RESPONSE:

The Design Assurance Plan and subsequent Design Assurance Report presented in Volume 2, pp.153 - 156 was intended to be representative of the validation of the steps in the manufacturing process. In this case the assurance plan and the results of the crimping of the helix coil to the conductor coil was presented as an example of the validation of a single step in the manufacturing process, which did not involve any materials or other changes that would effect the function of the lead. Since the dimensions of the helix that pass through the seal were not changed, there was no need to readdress the possible effects of the sterilization process on the helix electrode.

The effects of the sterilization process on the integrity of the lead were examined in the original design assurance evaluation for the Model 6884/6966. Results of design assurance testing, i.e., electrical, mechanical, and environmental testing on [(b) (4)] complete leads, following sterilization, are presented in Volume 4, pp. 464 - 481 of the PMA application (copy provided in Attachment B of this submission for reference). All [(b) (4)] leads were subjected to multiple, [(b) (4)] hour cycles of EtO sterilization, examined for visual defects and then subjected to the functional testing regime (see Attachment B). All [(b) (4)] leads met the specifications in the design assurance plan.

2. **Provide the locations of the biological indicators used during the sterilization validation and routine production for the 6966 lead. [vol. 2, p. 207]**

RESPONSE:

For the sterilization validation of the Model 6884/6966, test samples (innoculated leads) were evenly distributed among the locations in the sterilizer as shown in Figure 1. Tests were carried out using a fully loaded sterilizer chamber, which consisted of [B 4] each containing [(b)(4)] Each [(b)(4)] was fully loaded with [B 4] The test samples were loaded into the [(b)(4)] as shown in Figure 2.

FIGURE 1

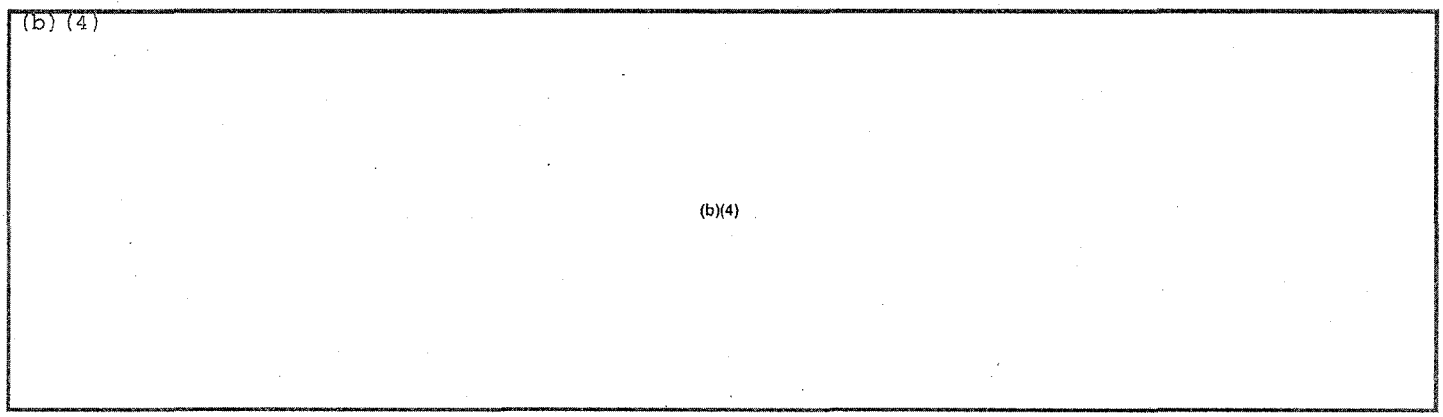
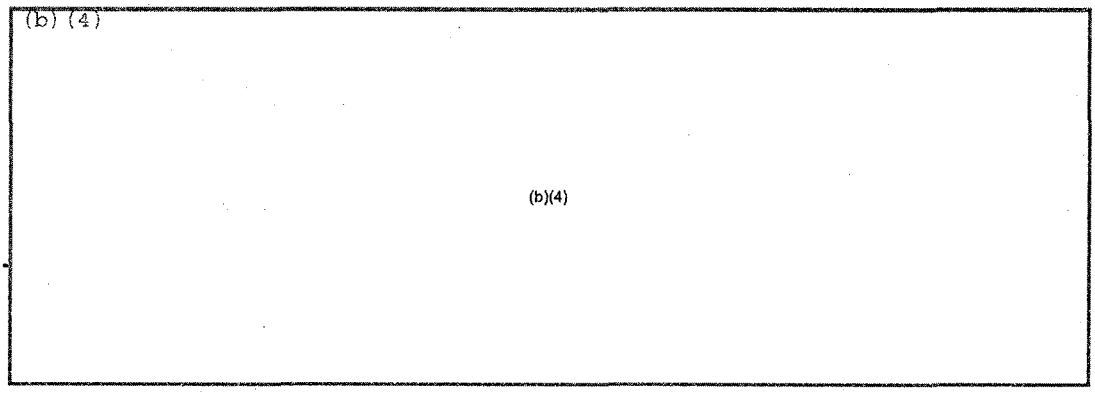


FIGURE 2

Location of Test Samples Within [(b)(4)]



3. **Provide the product density and configuration pattern for the 6966 sterilization cycle. [vol. 2, p. 207]**

RESPONSE:

The 6884/6966 sterilization cycle includes (b) (4)(b)(4) (see Figure 1, Deficiency #2), each containing (b) (4) (b)(4) leads packaged in standard lead trays. The product density is (b) (4)(b)(4)

4. **Provide the maximum parameter of the humidity specification for the sterilization cycle of the 6966 lead. [vol. 2, p. 211]**

RESPONSE:

The range of humidity specified for the exposure period in the sterilization process is (b) (4)(b)(4) The humidity during exposure is typically between (b) (4)(b)(4)

5

5. **The finished device evaluation for the 6966 lead does not address the effect of sterilization on device performance. [vol. 2, p. 174]**

RESPONSE:

The effect of the sterilization process on the performance of the Model 6884/6966 has been evaluated in the original design assurance testing. Results show that the lead continues to perform to design specifications after multiple, [b4] exposures to EtO. Results of the design assurance testing, following sterilization, on [(b) (4)(b)(4)] Model 6966 leads are presented in Volume 4, pp. 464 - 481 of the PMA application (copy provided in Attachment B of this submission for reference).

6. **The validation plan for 6963 lead does not address the effects of the sterilization cycle on device performance. [vol. 3, p. 327]**

RESPONSE:

The effect of the sterilization process on the performance of the Model 6881/6963 was evaluated in the original design assurance testing. Results show that the lead continues to perform to design specification after multiple, [5] exposures to EtO. Results of design assurance testing, following sterilization, on the lead are presented in Volume 4, pp. 446-463 of the PMA application (copy provided in Attachment C of this submission for reference).

7. **The process qualification report, [(b) (4)(b)(4)], does not address the effects of the sterilization cycle on the performance of the 6999 lead. [vol. 3, p. 335]**

RESPONSE:

The process validation plan, [(b) (4)(b)(4)] was intended to describe the plan for validating the processes in the manufacture of the 6897/6921/6999 leads.

The effect of the sterilization process on the performance of the Models 6897/6921/6999 was addressed in the Design Assurance Plan for those leads. The results of design qualification testing for the Models 6897/6921/6999 are presented in Volume 4, pp. 482-498 of the PMA application (see copy of the applicable pages in Attachment D of this submission for reference). [(b) (4)(b)(4)] leads were subjected to multiple, [84] hour cycles of EtO. All the leads were then tested for electrical, mechanical and environmental performance. All leads performed within established specifications.

8. **Provide the product location of biological indicator and spore inoculation for the validation and production sterilization cycles of the 6963 and 6999 leads. [vol. 3, p. 372]**

RESPONSE:

All sterilization cycles are validated and monitored with the inoculated product and biological indicators. Figure 1 shows the locations of inoculated product in the load. Figure 2 shows the locations of biological indicators in the load.

FIGURE 1

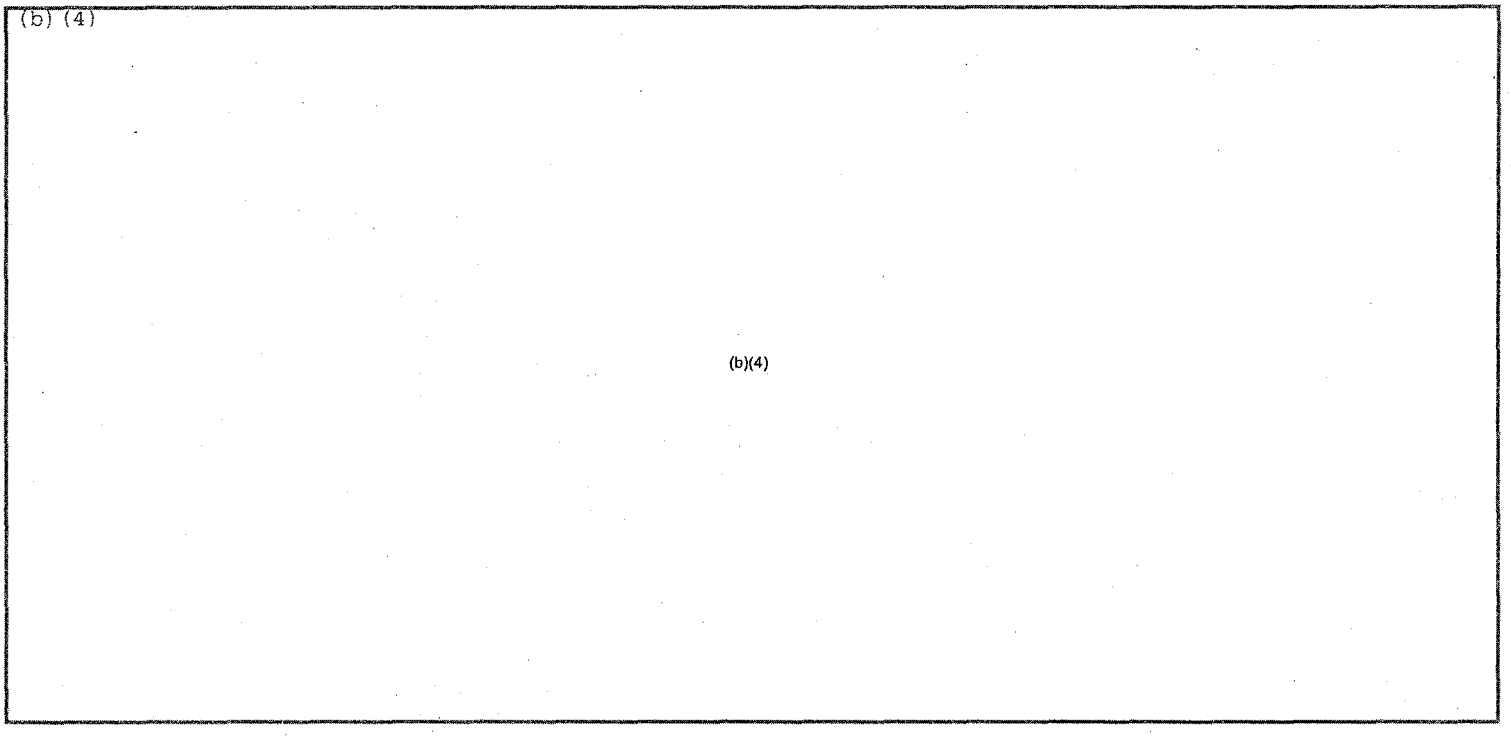
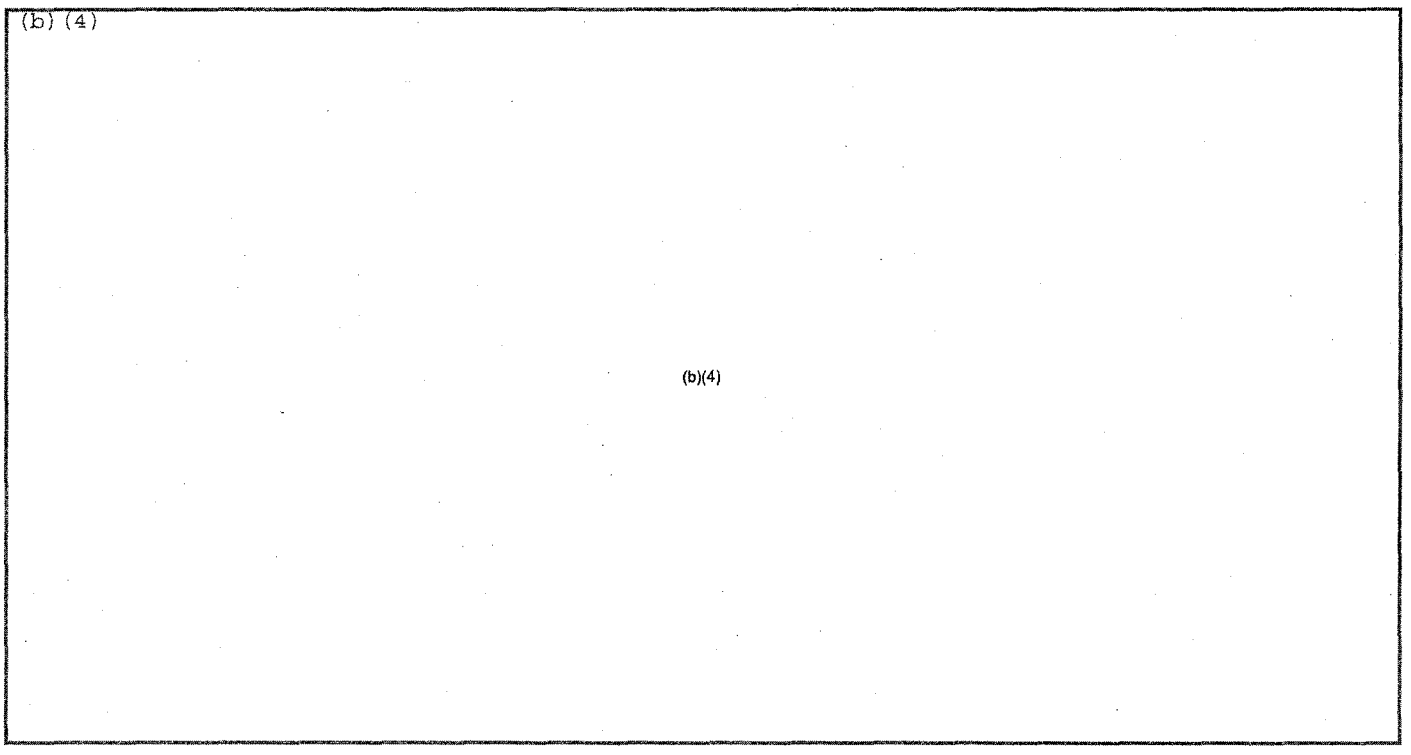


FIGURE 2



9. **Provide the maximum parameter of the 12/88 ethylene oxide gas exposure for the 6999 lead. [vol. 3, p. 376]**

RESPONSE:

The maximum exposure time is [60] minutes for the 6897/6921/6999 lead. The range of time necessary to assure an [(4)(4)] minutes.

10. Explain the difference in the sterilization gas exposure parameters of the (b)(4) Control Device between the two manufacturing facilities. The gas exposure parameter at the Rice Creek facility is (b)(4) minutes; the gas exposure parameter at the Kerkrade facility is (b)(4) minutes minimum. The Kerkrade facility does not specify a maximum gas exposure. [vol. 4, p. 415 and p. 432]

RESPONSE:

The difference in the sterilization gas exposure times is due to the difference in the use of the sterilization chambers at the two facilities. At the Rice Creek facility as many as (b)(4) product families may be in the chamber at one time. Therefore, the exposure time is determined by the requirements of the product family that is most difficult to sterilize. And for Rice Creek product the exposure parameter is (b)(4) minutes. The gas exposure time for the Kerkrade facility is (b)(4) minutes. However, a review of the results of the lethality testing for the (b)(4) (Table 1) shows that the mean D - value for the process at the two facilities is identical.

TABLE 1

COMPARISON OF D-VALUES FOR PULSE GENERATOR FAMILY

Plant	Exposure time (minutes)	Inoculation level (# spores/ml)	Mean D-Value (minutes)
Kerkrade	(b)(4)		
Rice Creek			

11. Provide the manufacturing methods, controls, and evaluation procedures for the facility identified as Medtronic Milaca, 900 6th Avenue N.E. Milaca, MN 56353. [vol. 4, p. 437]

RESPONSE:

Production and Process Controls - Milaca Facility

The manufacturing processes for the Model 5355 printed circuit boards are similar to all other printed circuit boards manufactured at Milaca. Written assembly processes are utilized which also contain the necessary quality requirements. In-line inspection steps are intended to verify the previous operators' work and these steps are specified within the process. Manufacturing assembly and inspection operations are performed by certified operators. Below is a summary of the primary manufacturing steps utilized in manufacturing a printed circuit board (PCB) assembly.

Manufacturing: PCB

[B4]

[B4]

(b) (4)(b)(4)

[B4]

[B4]

[B4]

[B4]

(b)(4)

[B4]

[b(4)]

[(b)(4)]

Manufacturing process procedures (work instructions) are written and controlled to assure the device/component conforms to the original design.

[b(4)]

Responsibilities and requirements for initiation, review, approval, distribution, retrieval, and disposal of process are defined in Milaca's Policies/Procedure manual.

All process changes are reviewed and approved by the [B4 (b)(4)]

Process development format, identity, distribution and maintenance are defined in the Manufacturing Documentation Standards Manual and Milaca's Policies and Procedures Manual. Each process and each page within a process is issue-level controlled, as well as the traceform

(b)(4)

Variances are noted on the product traceform (Device History Record).

(b)(4)

. RRI's are noted on the Device History Record for product with rework performed.

(b)(4)

Non-conforming assemblies which can not readily be reworked by the operator are submitted to the (b)(4) The non-conforming assembly is reviewed and dispositioned by the responsible

(b)(4)

for corrective action and completeness. PRR's are also noted on the Device History Record.

Non-conforming assemblies are recorded on the (b)(4) which is reviewed by the product assembly team, engineering, and management for corrective action and effectiveness of that corrective action.

Attachment A

A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

MAY 14 1992

Ms. Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576

Re: P920015
PCD Transvene System

Dear Ms. Marrone:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) is continuing to process the above named premarket approval application (PMA). Simultaneously with a review by the Office of Device Evaluation (ODE), the Office of Compliance and Surveillance (OCS) must review the manufacturing information in your PMA to determine that it is sufficiently complete and appropriately organized to permit FDA to determine whether your firm (or your contract manufacturer) has the capability of manufacturing your PMA device in accordance with (1) the conditions specified in the PMA application and (2) the requirements of the medical device GMP regulation.

The Division of Compliance Programs (DCP) of OCS has reviewed the manufacturing section of your PMA and believes that it lacks the information necessary to effectively complete a review and determine whether to initiate a PMA inspection (see enclosed). While the deficiencies outlined in the enclosure do not preclude further review of your PMA, if left uncorrected they may delay or preclude evaluation of your manufacturing process and final approval of your PMA application. We request that you respond as indicated. Please be advised that continued review by ODE of your application (including the manufacturing section) may identify additional deficiencies. Also, the OCS review of your response to this letter may identify additional deficiencies.

For your information a Guidance for Preparation of PMA Manufacturing Information was published on March 22, 1991 (a notice of availability was published in the August 20, 1991 Federal Register). It is also available as part of the PMA Manual Supplement which may be obtained from the Division of Small Manufacturer's Assistance at 1-800-638-2041.

Information supplied in response to the enclosed request should be submitted in the form of an amendment AND BE CLEARLY IDENTIFIED AS A RESPONSE TO AN OCS REQUEST IN YOUR REFERENCE BLOCK. FDA will consider the PMA to have been withdrawn voluntarily if you fail to respond in writing to this request for an amendment within 180 days of the date of this letter as provided under 21 CFR 814.44(g). You may, however, amend the PMA within the 180 day period to request an extension of time to respond. Any such request is subject to FDA approval and must justify the need

Part 1 - Page 1036

Rec'd 5/19/92

for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180 day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180 day period will be considered a resubmission of the PMA and will be assigned a new number. A resubmission should be complete and self-contained without reference to earlier submissions because of potential difficulties in assembling files from storage.

All correspondence regarding this PMA should be submitted in three (3) copies in the form of a PMA amendment to the address below and reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)
ATTN: MQAB
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

This letter reflects the current progress of our review of your application. Please be advised, however, that continued review of your application or questions arising from any response to this letter, may result in additional deficiencies being identified.

If you have any questions concerning this deficiency letter, please contact Frank Twardochleb at (301) 427-1128.

Sincerely yours,

for Deborah Lewis

Philip J. Phillips
Director, Program Operations Staff
Office of Device Evaluation
Center for Devices and
Radiological Health

Deficiency List

The Office of Compliance and Surveillance (OCS) in the Center for evices and Radiological Health (CDRH) has completed an initial review f your premarket approval application (PMA), P920004, with regard to the Good Manufacturing Practice (GMP) regulations. Please address the following issues and provide the requested documentation:

1. The Design Assurance Plan, (b)(4) dated 2/7/91 for the new helix electrode, part (b)(4) is not representative of the manufacturing operations. The qualification report dated 4/16/91 does not address the effects of the sterilization process on the integrity of the helical electrode. [vol.2, pp.153-156]

2. Provide the locations of the biological indicators used during the sterilization validation and routine production for the 6966 lead. [vol.2, p.207]

3. Provide the product density and configuration pattern for the 6966 sterilization cycle. [vol.2, p.207]

4. Provide the maximum parameter of the humidity specification for the sterilization cycle of the 6966 lead. [vol.2, p.211]

5. The finished device evaluation for the 6966 lead does not adress the effect of sterilization on device performance. [vol.2, p.174]

6. The validation plan for 6963 lead does not address the effects of the sterilization cycle on device performance. [vol.3, p.327]

7. The process qualification report, (b)(4) does not address the effects of the sterilization cycle on the performance of the 6999 lead. [vol.3, p.335]

8. Provide the product location of biological indicator and spore inoculation for the validation and production sterilization cycles of the 6963 and 6999 leads. [vol.3, p.372]

9. Provide the maximum parameter of the (b)(4) exposure for the 6999 lead. [vol.3, p.376]

10. Explain the difference in the sterilization gas exposure parameters of the (b)(4) Control Device between the two manufacturing facilities. The gas exposure parameter at the Rice Creek facility is (b)(4) minutes; the gas exposure parameter at the Kerkrade facility is (b)(4) minutes minimum. The Kerkrade facility does not specify a maximum gas exposure. [vol.4, p.415 and p. 432]

11. Provide the manufacturing methods, controls, and evaluation procedures for the facility identified as Medtronic Milaca, 900 6th Ave. N.E. Milaca, MN 56353. [vol.4, p. 437]

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ATTACHMENT B

Copy from PMA Application
dated March 31, 1992, Volume 4, pp. 464-481.

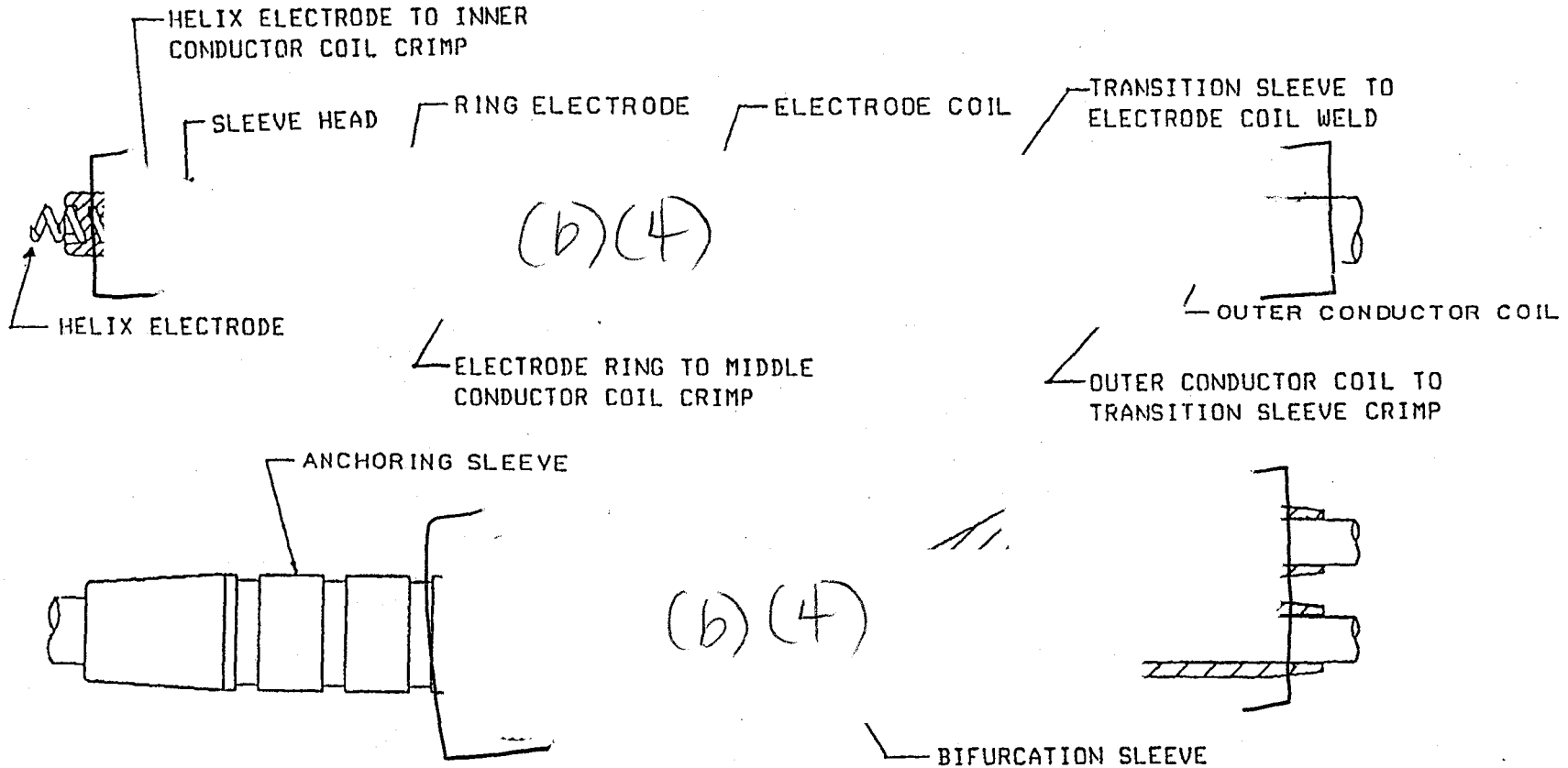
Design Assurance Testing
Model 6884/6966

2. Model 6966

The Model 6966 is a permanent, tripolar, endocardial, pacing, sensing and defibrillation lead intended for use in the right ventricle. The lead has a distal, extendable/retractable helix electrode and a medial ring electrode for bipolar sensing. The lead also has a single, 5 cm long coil electrode just proximal to the pacing ring that is intended for defibrillation. The lead circuits are of coaxial design insulated with (b) (4)(b)(4) tubing over each coil. See the figures on the following pages for illustration of the Model 6966.

Parameter	Model 6966
Lead length:	110 cm
Lead diameter:	11 French
Body diameter:	10 French (3.3 mm)
Fixation:	2 mm helix (pacing cathode)
Connector:	
Pacing	3.2 mm in-line bipolar
Defibrillation	6.5 mm unipolar
Insulation:	
Inner	(b) (4) (b)(4)
Middle	
Outer	

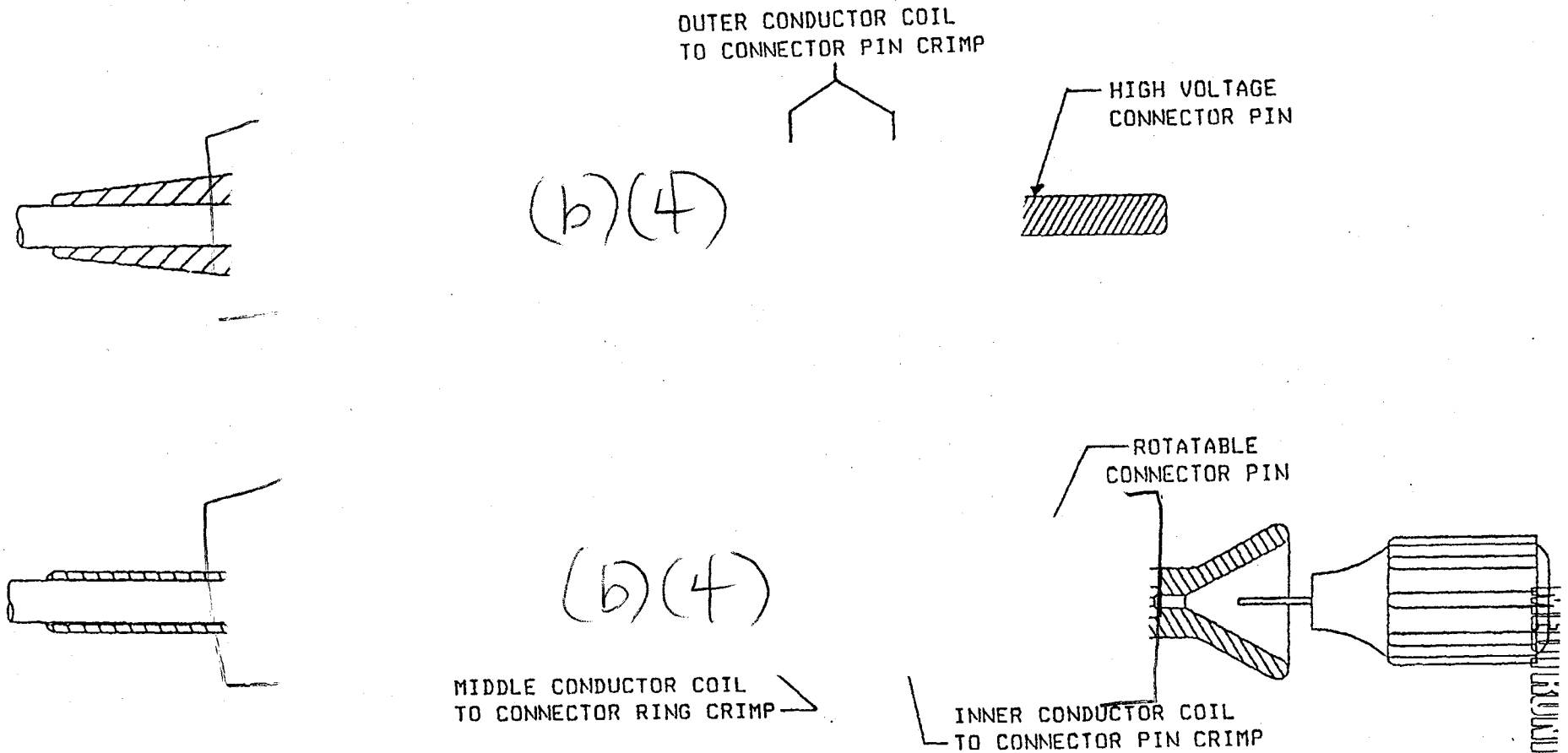
Parameters	Model 6966
Conductors:	
Inner	(b) (4)
Middle	
Outer - Defib.	(b)(4)
Electrode Material:	
Pacing Helix	
Sensing Ring	
Defibrillation Coil	
Conductive Surface Area	



MODEL 6966 RIGHT VENTRICULAR LEAD
DISTAL END

MEDTRONIC CONFIDENTIAL

Part 1 - Page 1044



MODEL 6966 RIGHT VENTRICULAR LEAD
PROXIMAL END

a. Model 6966 Electrical Testing

Electrical Testing

1) D.C. Resistance

a) Test Method

Electrode resistance is measured between the connector pins and each electrode. The high voltage circuit is measured between the connector pin and the proximal end of the defibrillation electrode coil.

b) Rationale

Electrical D.C. resistance is measured to ensure proper functioning of the Model 6966 lead.

c) Test Equipment

(b) (4)

(b)(4)

d) Samples Tested

(b) (4) (b)(4) complete leads were measured for electrical resistance.

e) Results

Inner Coil Assembly (pacing helix)

Specification: (b) (4) (b)(4)

(b) (4)

(b)(4)

Middle Coil Assembly (sensing ring)

Specification: (b) (4) (b)(4)

(b) (4)
(b)(4)

Outer Coil Assembly (defibrillation coil)

Specification: (b) (4) (b)(4) maximum

(b) (4)
(b)(4)

The results are within the specified limit and therefore are considered acceptable.

b. Environmental Testing

1) Thermal Shock

a) Test Method

Leads were subjected to (b)(4) cycles from (b) (4) (b)(4) with a soak time of (b)(4) minutes at each extreme and a maximum transfer time of one minute.

b) Rationale

Thermal shocking is used to determine the resistance of the lead system to alternate exposure extremes of high and low temperatures as when transported from extremes of climate.

c) Test Equipment

(b) (4)
(b)(4)

d) Samples Tested

(b)(4) complete Model 6966 leads were subjected to thermal shock.

e) Results

There were no visual defects. The electrical D.C. resistance, Hipot and intermittency were tested and all samples met specification.

c. Mechanical Testing

The purpose of the mechanical testing was to determine the mechanical integrity of the Model 6966 to ensure that the devices are suitable for their intended use and conform to design specifications.

1) Flex Testing of Insulated Conductor Coils and Non-insulated Electrode Coils*

a) Test Method

Samples are mounted in lead flex fixtures, then flexed under ambient room conditions at (b)(4) over specified radii at the rate of (b)(4) Samples are flexed until failure.

b) Rationale

Insulated conductor coils and non-insulated electrode coils are flex tested to assess longevity under accelerated use conditions.

c) Test Equipment

Medtronic Lead Flex Test Fixture.

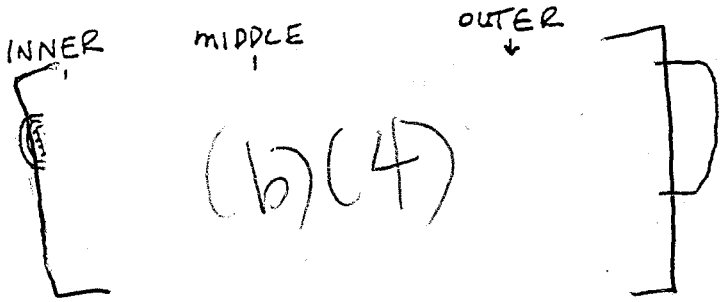
* See Appendix 2 for additional information regarding development of the Medtronic flex test and information relative to the Transvene lead system.

d) Insulated Conductor Coils

i. Samples Tested

(b)(4) samples of lead bodies (inner, middle and outer insulations and coils) were tested. See figure below.

Model 6966
Insulated Conductor Coil



ii. Results

At (b)(4) inch radius,
Median = (b)(4) cycles
Spec = (b)(4) cycles

Individual failure times are:

1.	(b)(4)	7.	(b)(4)
2.		8.	
3.		9.	(b)(4)
4.	(b)(4)	10.	
5.		11.	
6.			

Flex life measurements exceed specification and therefore are considered to be satisfactory.

e) Electrode Coil

i. Samples Tested

[(b)(4)] samples of the electrode coil [(b)(4)] turns/inch) were tested.

ii. Results

At [(b)(4)] inch radius,
Median = [(b)(4)] cycles

No specification exists for electrode coils, see Appendix 2.

2) Lead Joint Tensile Strengths

[B4] of the various lead joints is conducted to ensure that the integrity of each joint meets the design specification and is therefore adequate for its intended application. The testing conducted consists of a composite pull test which evaluates the overall pull strength of the lead and crimp/weld testing that evaluates the crimped/welded connections of the leads to assure specification conformance.

a) Composite Pull Strength

Leads were soaked at [(b)(4)] and pull tested, while wet, utilizing a [B4] testing machine. [(b)(4)] proximal ends were soaked in normal saline solution while [(b)(4)] distal ends were soaked in [(b)(4)] Fluid). The samples were pulled until failure at a rate of [(b)(4)] inches per minute. The initial failures were then analyzed statistically for the confidence level in meeting the specification for the composite lead which is [(b)(4)] minimum for the distal end and [(b)(4)] minimum for the proximal end. The current

reliability goal is for the design and process to demonstrate that with 95% confidence, at least 95% of the leads will meet or exceed the specification. The actual test results (mean and standard deviation) and the confidence intervals/levels generated by statistical analysis of the composite joint strength results are provided as follows:

Distal	Proximal
(b)(4)	(b)(4)

Distal lower limit is (b)(4)
Proximal lower limit is (b)(4)

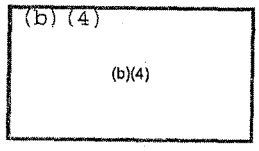
(With 95% confidence and 95% probability, since the specification is one-sided, only the lower limit is of relevance.)

The above data demonstrate that with a 99% confidence, at least 99.9% of the leads will meet or exceed the specification.

b) Crimp/Weld Pull Strengths

Lead crimps and welds were tested for joint pull strength by gripping the opposite ends of each connection in a tensile testing machine and pulling until failure at a rate of (b)(4) inches per minute. The test results (mean and standard deviation) and the confidence intervals/levels generated by statistical analysis of the individual crimp and weld strengths are provided as follows:

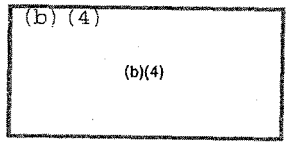
The helix electrode to inner conductor coil crimp testing consisted of pulling (b)(4) samples. All samples tested met the specification of (b)(4)



Lower limit is (b)(4) with 95% confidence and 95% probability.

The above data demonstrate that with a 99% confidence, at least 99.9% of the leads will meet or exceed the specification.

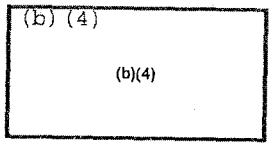
The electrode ring to middle conductor coil crimp testing consisted of pulling (b)(4) samples. All samples tested met the specification of (b)(4)



Lower limit is (b)(4) with 95% confidence and 95% probability.

The above data demonstrate that with a 99% confidence, at least 99.9% of the leads will meet or exceed the specification.

The transition sleeve to electrode coil weld testing consisted of pulling (b)(4) samples. All samples tested met the specification of (b)(4)



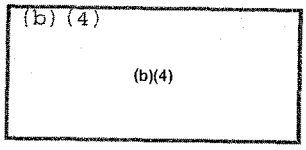
Lower limit is (b)(4) with 95% confidence and 95% probability.

The above data demonstrate that with a 99% confidence, at least 99% of the leads will meet or exceed the specification.

The <u>transition sleeve to outer conductor coil</u> crimp testing consisted of pulling (b)(4) samples. All samples tested met the specification of (b)(4)

(b)(4)

(b)(4)



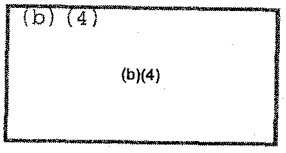
Lower limit is (b)(4) with 95% confidence and 95% probability.

The above data demonstrate that with a 99% confidence, at least 95% of the leads will meet or exceed the specification.

The <u>fixed connector pin to outer conductor coil</u> crimp testing consisted of pulling (b)(4) samples. All samples tested met the specification of (b)(4)

(b)(4)

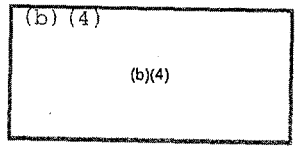
(b)(4)



Lower limit is (b)(4) with 95% confidence and 95% probability.

The above data demonstrate that with a 99% confidence, at least 95% of the leads will meet or exceed the specification.

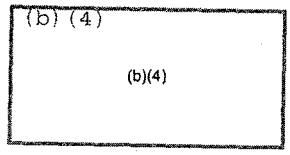
The connector ring to middle conductor coil crimp testing consisted of pulling (b)(4) samples. All samples tested met the specification of (b)(4)



Lower limit is (b)(4) with 95% confidence and 95% probability.

The above data demonstrate that with a 99% confidence, at least 98% of the leads will meet or exceed the specification.

The rotating connector pin to inner conductor coil crimp testing consisted of pulling (b)(4) samples. All samples tested met the specification of (b)(4)

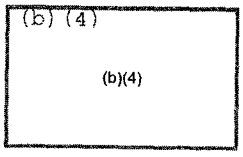


Lower limit is (b)(4) with 95% confidence and 95% probability.

The above data demonstrate that with a 99% confidence, at least 99.7% of the leads will meet or exceed the specification.

3) Lead Stiffness

Stiffness of the Model 6966 is measured to determine tip pressure exerted by the lead without a stylet. The specification is (b)(4) maximum.



The lead tip stiffness is less than the maximum and therefore meets the specified requirement.

4) Anchoring Sleeve Testing

(b)(4) Model 6966 lead segments with silicone rubber/(b) (4) (b)(4) anchoring sleeves were evaluated as to the effects of suture force on the lead body and sliding force (lubricity) on the lead body.

Sliding Force

Anchoring sleeves were sutured on lead bodies with a force of (b)(4) using (b)(4) suture. The force to slide the anchoring sleeve on the lead body was measured
after injecting canine blood into the lead body/anchoring sleeve interface. All samples met the specification.

Suture Force

Anchoring sleeves were sutured on the lead bodies with a force of (b)(4) using (b)(4) suture. After suturing, lead bodies were visually examined, grossly and microscopically, for insulation and conductor coil damage or deformation. No lead bodies evaluated at (b)(4) lbs. suture force demonstrated any insulation or conductor coil damage/deformation.

Silicone rubber/ (b) (4) (b)(4) anchoring sleeves are used in a variety of commercially available Medtronic cardiac pacing leads.

5) Leak Test--Lead Body

a) Test Method

Complete leads are immersed in water and pressurized to (b) (4) (b)(4) for a period of (b) (4) (b)(4) minutes. A visual examination is then done at 6X magnification for any evidence of water leakage into the space between the inner, middle and outer tubing. No visible leakage is permitted.

b) Rationale

Leak testing of the lead body is done to assure leak resistance to fluid entering the space between the inner, middle and outer tubing. Fluid leakage could result in an electrical leakage path between the inner, middle and outer conductors.

c) Test Equipment

Pressure chamber, pressure gage, stop watch, microscope and water.

d) Samples Tested

(b) (4) (b)(4) insulated coil assemblies were tested. Each assembly includes the middle and outer conductors which are sealed between the inner, middle and outer tubings. This test is performed on [B4] of production devices.

e) Results

No leakage was observed in any of the thirty samples tested.

6) Leak Test--Sleeve Head

a) Test Method

Complete leads are immersed in water. An air pressure of [(b)(4)] is applied to the distal end of the sleeve head for [(b)(4)] minutes minimum. The lead body and connector pin end are observed for signs of air bubbles.

b) Rationale

Leak testing of the sleeve head seal is done to assure the leak resistance is sufficient to prevent the excessive ingress of blood into the lead during implant. Excessive blood could impair the operation of the helix electrode mechanism during initial fixation or repositioning.

c) Test Equipment

Air pressure regulator and a container of water.

d) Samples Tested

[(b)(4)] complete Model 6966 lead assemblies were tested. This test is performed on [5 %] of production devices.

e) Results

No leakage was observed in any of the [(b)(4)] samples tested.

d. Model 6966 Biostability Testing

1) Background

Medtronic has developed an accelerated bench test to reproduce in-vitro a condition seen in-vivo, relative to (b)(4) leads. This [B4 ...is test, which serves as a predictor of (b)(4) lead performance with respect [B4 known as [B4 has been presented to FDA in several submissions to support biostability of (b)(4) leads, (e.g., reference Model 4004/4504 leads, Document Control Number P830061/S6, FDA approved on February 10, 1989, a copy of this document is provided in Appendix 3).

[B4 is a (b)(4) solution to which (b)(4) is added to make it (b)(4) saline.

2) Test Method/Rationale

Test samples were placed in [B4 [B4 was changed th[B4 During the first [B4 s of testing, test samples were removed [B4 and subjected to a total of (b)(4) defibrillation pulses at (b)(4) pulse width each in fresh [B4 Samples were pulsed from the defibrillation coil to an [B4 Samples were subjected to [B4 testing [B4 This afforded electrical evaluation of the inner and outer insulations. In addition, microscopic evaluations were conducted on the outer insulation at (b)(4) and (b)(4) days (at (b)(4)

3) Test Equipment

[(b) (4)] test set-up, Medtronic Model 2376 External Cardioverter/ Defibrillator and a [B4]

4) Samples Tested

[(b)(4)] Model 6966 distal lead subassemblies.

5) Results

No failures (insulation breaches) or visual evidence (cracks) of MIO degradation were observed on the subassembly bodies. All samples were still functional after [(b)(4)] days in [B4] exceeding the impedance specification of [(b) (4)] between the circuits.

6) Conclusion

Model 6966 subassemblies satisfied lead integrity requirements relative to [B4] testing. Therefore, the Model 6966 lead is acceptable for its intended use relative to biostability.

ATTACHMENT C

Copy from PMA Application
dated March 31, 1992, Volume 4, pp. 446-463.

Design Assurance Testing
Model 6881/6963

A. Laboratory (Bench) Testing of the Non-Thoracotomy Lead System

1. Model 6963

The Model 6963 Unipolar Coronary Sinus/Superior Vena Cava Lead is a permanent lead whose design is based on the Model 10285 Temporary Lead (Document Control Number G850153/S9). The Model 6963 is comprised of silicone insulation, a silver-cored inner conductor and an external coil electrode of platinum-iridium. See the figure on the following page for an illustration of the Model 6963.

Parameter	Model 6963
Lead length:	110 cm
Lead diameter:	7 French (2.26 mm)
Body diameter:	.072 inch
Insulation material:	(b) (4)
thickness:	
Conductor material:	
wire diameter:	
External coil electrode:	(b)(4)
External coil length:	
wire diameter:	
Conductive surface area:	
Connector:	

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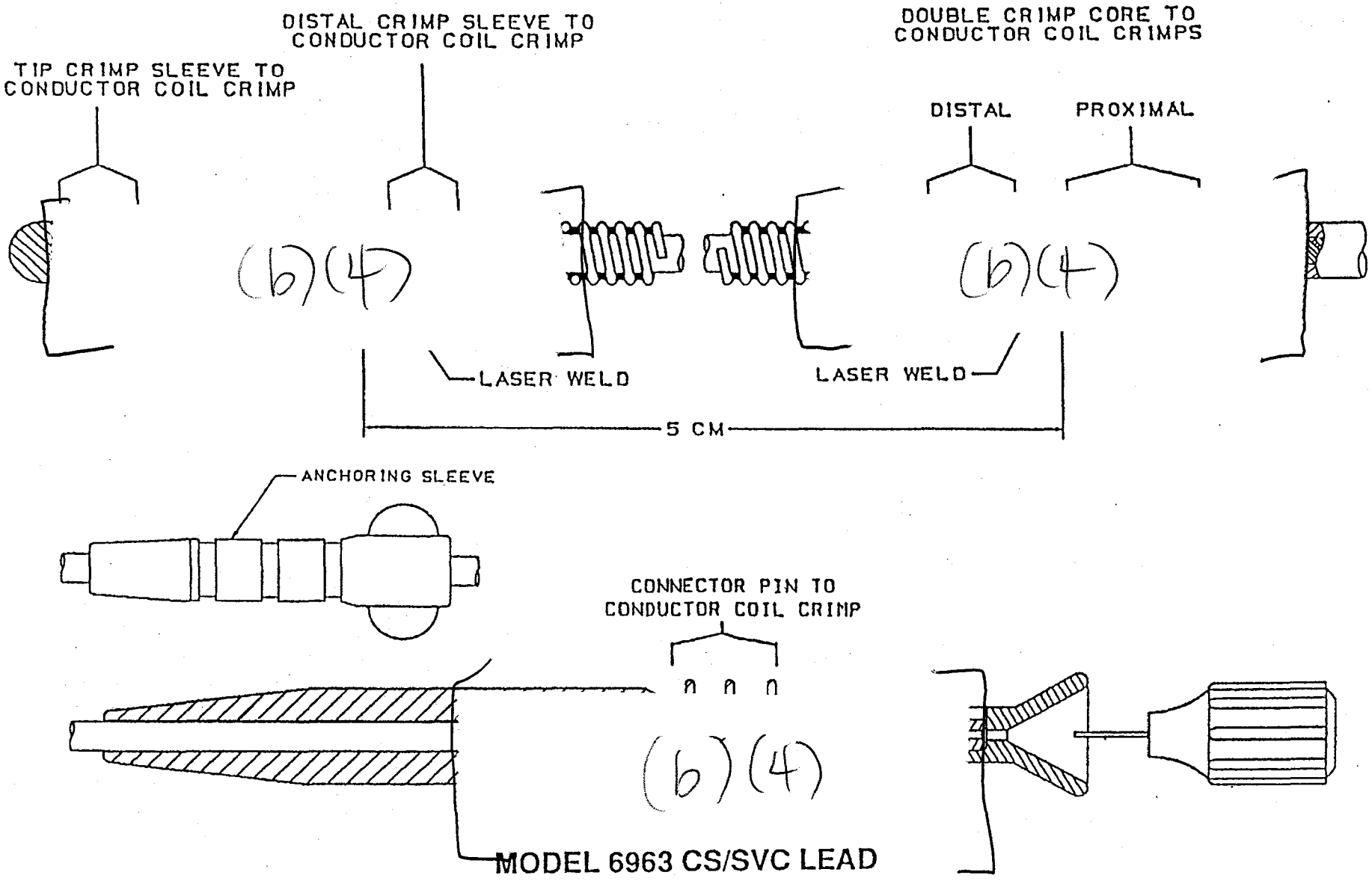


MEDTRONIC CONFIDENTIAL

a. Model 6963 Electrical Testing

Electrical Testing

1) D.C. Resistance

a) Test Method

Electrical resistance is measured between the connector pin and distal end of the defibrillation coil.

b) Rationale

Electrical D.C. resistance is measured to ensure proper functioning of the Model 6963 lead.

c) Test Equipment

(b) (4)

(b)(4)

d) Samples Tested

(b) (4) complete leads were measured for electrical resistance.

e) Results

Distal End of Defibrillation Coil to Connector Pin

Specification: (b) (4) maximum

(b) (4)

(b)(4)

The results are within the specified limits and therefore are considered acceptable.

b. Environmental Testing

1) Thermal Shock

a) Test Method

Leads were subjected to (b)(4) cycles from (b)(4) with a soak time of (b)(4) minutes at each extreme and a maximum transfer time of one minute.

b) Rationale

Thermal shocking is used to determine the resistance of the lead system to alternate exposure extremes of high and low temperatures as when transported from extremes of climate.

c) Test Equipment

(b)(4)

d) Samples Tested

(b)(4) complete Model 6963 leads were subjected to thermal shock.

e) Results

There were no visual defects. The electrical D.C. resistances were tested and all samples met specification.

c. Mechanical Testing

The purpose of the mechanical testing was to determine the mechanical integrity of the Model 6963 to ensure that the devices are suitable for their intended use and conform to design specifications.

1) Flex Testing of Insulated Conductor Coils and Non-insulated Electrode Coils*

a) Test Method

Samples are mounted in lead flex fixtures, then flexed under ambient room conditions at [redacted] over specified radii at the rate of [redacted] Samples are flexed until failure.

b) Rationale

Insulated conductor coils and non-insulated electrode coils are flex tested to assess longevity under accelerated use conditions.

c) Test Equipment

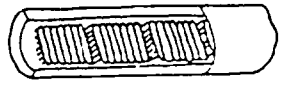
Medtronic Lead Flex Test Fixture.

d) Insulated Conductor Coil

i. Samples Tested

[redacted] samples of lead bodies (insulation/conductor coil subassemblies) were tested. See figure below.

Model 6963
Insulated Lead Body



* See Appendix 2 for additional information regarding development of the Medtronic flex test and information relative to the Transvene lead system.

ii. Results

At (b)(4) inch radius,
Median = (b)(4)(b)(4) cycles
(no failures)
Spec = (b)(4)(b)(4) cycles

Flex life measurements exceed specification and therefore are considered to be satisfactory.

e) Electrode Coil

i. Samples Tested

(b)(4)(b)(4) samples of the electrode coil (b)(4) turns/inch) were tested.

ii. Results

At (b)(4) inch radius,
Median = (b)(4)(b)(4) cycles
(no failures)

No specification exists for electrode coils, see Appendix 2.

2) Lead Joint Tensile Strengths

Pull testing of the various lead joints is conducted to ensure that the integrity of each joint meets the design specification and is therefore adequate for its intended application. The testing conducted consists of a composite pull test which evaluates the overall pull strength of the lead and the crimp/weld testing that evaluates the crimped/welded connections of the leads to assure specification conformance.

a) Composite Pull Strength

(b)(4)(b)(4) leads were soaked and pull tested, while wet, utilizing a [B4]

Part 1 - Page 1066

[(b)(4)] The proximal ends were soaked in normal saline solution (at [(b)(4)] while the distal ends were boiled in [(b)(4)] solution. The samples were pulled until failure at a rate of [(b)(4)] inches per minute. The initial failures were then analyzed statistically for the confidence level in meeting the specification for the composite lead which is [(b)(4)] minimum for the distal end and [(b)(4)] minimum for the proximal end. The current reliability goal is for the design and process to demonstrate that with 95% confidence, at least 95% of the leads will meet or exceed the specification. The actual test results (mean and standard deviation) and the confidence intervals/levels generated by statistical analysis of the composite joint strength results are provided as follows.

Distal	Proximal
(b)(4)	(b)(4)

Distal lower limit is [(b)(4)]
Proximal lower limit is [(b)(4)]

(With 95% confidence and 95% probability, since the specification is one-sided, only the lower limit is of relevance.)

The above data demonstrates that with a 95% confidence, at least 97% (distal) and 99.9% (proximal) of the leads will meet or exceed the specification.

b) Crimp/Weld Pull Strengths

Lead crimps and welds were tested for joint pull strength by gripping the opposite ends of each connection in a tensile testing machine and pulling until failure at a rate of (b)(4) inches per minute. The test results (mean and standard deviation) and the confidence intervals/levels generated by statistical analysis of the individual crimp and weld strengths are provided as follows:

The distal crimp sleeve to conductor coil crimp testing consisted of pulling (b)(4) samples. All samples tested met the specification of (b)(4)

(b)(4)

(b)(4)

Lower limit is (b)(4) with 95% confidence and 95% probability.

The above data demonstrates that with a 99% confidence, at least 99.9% of the leads will meet or exceed the specification.

The distal side of double crimp core to conductor coil crimp testing consisted of pulling (b)(4) samples. All samples tested met the specification of (b)(4)

(b)(4)

(b)(4)

Lower limit is (b)(4) with 95% confidence and 95% probability.

The above data demonstrates that with a 95% confidence, at least 99.3% of the leads will meet or exceed the specification.

The electrode coil to distal side of double crimp core weld testing consisted of pulling (b)(4) samples. All samples tested met the specification of (b)(4)

(b)(4)

Lower limit is (b)(4) with 95% confidence and 95% probability.

The above data demonstrates that with a 95% confidence, at least 95% of the leads will meet or exceed the specification.

The electrode coil to distal crimp sleeve weld testing consisted of pulling (b)(4) samples. All samples tested met specification of (b)(4)

(b)(4)

Lower limit is (b)(4) with 95% confidence and (b)(4) probability.

The above data demonstrates that with a 99% confidence, at least 99.5% of the leads will meet or exceed the specification.

The proximal side of double crimp core to conductor coil crimp testing consisted of pulling (b)(4) samples. All samples tested met the specification of (b)(4)

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(b) (4)

(b)(4)

Lower limit is (b) (4) with (b)(4) confidence and 95% probability.

The above data demonstrates that with a 99% confidence, at least 99.9% of the leads will meet or exceed the specification.

The tip crimp sleeve to conductor coil crimp testing consisted of pulling (b)(4) samples. All samples tested met the specification of (b)(4) push force.

(b) (4)

(b)(4)

Lower limit is (b)(4) with 95% confidence and 95% probability.

The above data demonstrates that with a 95% confidence, at least 97% of the leads will meet or exceed the specification.

The connector pin to conductor coil crimp testing consisted of pulling (b)(4) samples. All samples tested met the specification of (b)(4)

(b) (4)

(b)(4)

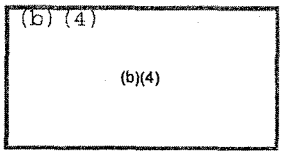
Lower limit is (b) (4) with 95% confidence and 95% probability.

The above data demonstrates that with a 99% confidence, at least 99.9% of the leads will meet or exceed specification.

3) Lead Stiffness

Stiffness of the Model 6963 is measured to determine tip pressure exerted by the lead without a stylet. The specification is (b)(4) maximum.

Results



The lead tip stiffness is less than the maximum and therefore meets the specified requirement.

4) Anchoring Sleeve Testing

(b) (4) Model 6963 lead segments with silicone rubber (b) (4) anchoring sleeves were evaluated as to the effects of suture force on the lead body and sliding force (lubricity) on the lead body.

Sliding Force

Anchoring sleeves were sutured on lead bodies with a force of (b)(4), using (b)(4) suture. The force to slide the anchoring sleeve on the lead body was measured after injecting canine blood into the lead body/anchoring sleeve interface. All samples met specification.

Suture Force

Anchoring sleeves were sutured on the lead bodies with a force of [redacted] using [redacted] suture. After suturing, lead bodies were visually examined, grossly and microscopically, for insulation and conductor coil damage or deformation. No lead bodies evaluated at [redacted] suture force demonstrated any insulation or conductor coil damage/deformation.

Silicone rubber [redacted] anchoring sleeves are used in a variety of commercially available Medtronic cardiac pacing leads.

d. Biostability Testing

1) Historical Overview

Silicone rubber was first used in implantable devices in 1950. Implantable cardiac pacing leads insulated with silicone rubber were first implanted in 1960. This rubber was applied to the lead in liquid form, then cured in situ. The silicone rubber in use today is initially a [redacted] composed of [redacted] This [redacted] is either molded or extruded into useful shapes, then heated. Silicone was first used in Medtronic implantable cardiovascular leads in 1962 (Model 5814). Because of the excellent demonstrated biostability (and other properties) of this material in cardiac pacing leads, it is still in use throughout the industry today. Human actuarial data on newer Medtronic leads are available in product performance reports that are distributed three times a year. This report contains information on the clinical performance of Medtronic pacing leads. This information

consists of returned product analysis, telephone monitoring of lead performance as well as a retrospective/prospective study of Medtronic leads followed at [redacted] institutions (Chronic Lead Study). Based on the information presented in the Chronic Lead Study Section of the report, Models 6961 and 6962 leads (silicone rubber insulated) have 94.4% actuarial survival at 12.5 years. These data include all complications, i.e., the data include not only leads whose integrity has failed, but also leads which dislodge, perforate, or experience exit block or sensing problems that are not due to lead integrity failure. Similar statistics based on telephone monitoring (CardioCare study) of patients yields a 98.2% survival at 12 years. Analysis of returned products shows not one insulation failure, i.e., due to environmental stress cracking and/or chemical reaction in [redacted] silicone rubber insulated lead models representing about [redacted] implants. These [redacted] lead models have been in service from about 20+ years (Models 6907 and 6901) to seven years (Models 6961 and 6962). Thus, silicone rubber has an excellent history of long-term biostability in cardiac pacing leads.

2) Rationale for Using Silicone Rubber

The rationale for using silicone rubber is stated above. It is a known safe and reliable polymer for cardiac pacing leads with excellent biocompatibility, biostability and physical/electrical properties.

3) Biostability of Silicone Rubber Leads

a) Analysis of Canine Explants

i. Test Methods

Several unipolar and bipolar silicone rubber leads have been

implanted in canines over the years to evaluate electrical properties, i.e., pacing thresholds. Standard implant procedures were used. The studies generally were conducted for twelve weeks. At approximately the twelve week interval, the canine(s) was terminated and the lead(s) removed for analysis.

Explanted leads were examined by optical microscopy (up to 30X).

ii. Rationale

Even though canine implant times are relatively short compared to permanent human use, one would expect to see evidence of very severe degradation mechanisms, if present.

One possibility, for example, would be dehiscence (splitting along mold lines) due to lipid absorption.

iii. Test Equipment

- Surgical suite, instruments, anesthesia, etc.
- Binocular microscope (30X)

iv. Samples Tested

Several models were examined (at least (b)(4) leads of each type) such as the Models 6917A, 6917, 6961, and 6962.

v. Results

No evidence of degradation was observed.

vi. Conclusion

Molded and extruded parts made from silicone rubber show no evidence of lack of biostability based upon examination of explanted leads.

b) Analysis of Human Explants

i. Test Methods

Human explants are typically received dry in envelopes. The returned leads are then examined by optical microscopy (up to 30X).

ii. Rationale

Routine analysis of explanted pacing leads is conducted as standard operating procedure.

iii. Test Equipment

- Binocular microscope (30X)

iv. Samples Tested

Several silicone pacing leads and/or segments, totaling approximately [(b)(4)] leads or portions thereof, have been examined, e.g., lead models such as 6917A, 6961, 6962, 6901, 6917, 6901R, 6907, and 6901R.

v. Results

No evidence of degradation, i.e., environmental stress cracking, chemical reaction, dehiscence, was observed.

vi. Conclusion

Molded and extruded parts made from silicone rubber show no evidence of lack of biostability based upon examination of explanted leads.

4) Biostability of Silicone Rubber Under Strain

a) Test Methods

(b) (4) wire was bent into figure (b)(4) shaped (b)(4) long mandrels. Tubing samples were then strained over the mandrels to various percent elongations. Strain was firmly fixed using (b) (4) Specimens were tied together in strings, color coded with beads, cleaned, sterilized and implanted subcutaneously in rabbits under general anesthesia.

Fixed strains included (b) (4) and (b)(4) elongations. (b)(4) specimens at each elongation were explanted weekly for twelve weeks. Specimens were examined by optical microscopy (30X) to find changes in surface morphology or defects.

b) Rationale

Certain early implanted medical devices (heart valve poppets) made from silicone rubber were found to be susceptible to a

stress cracking phenomenon-dehiscence. This has never been seen on Medtronic silicone rubber insulated leads. Standard silicone rubber was used as controls in tests to evaluate the stress cracking resistance of other polymers. Stress cracking was accelerated in these tests by using excessive strains.

Stress cracking phenomena require some combination of material strained beyond, a critical value, in contact with an active surface or plasticizing agent (in this scene, the biologic environment). The application of high fixed strains and sequential explants helps to determine what critical strain and induction times exist in polymers susceptible to stress cracking. If the material or part is not susceptible <u>in vivo</u> stress cracking, of course, it will not crack at any practical strain or implant time.

c) <u>Test Equipment</u>

- Specimens as described above
- Surgical suite, instruments, anesthesia, etc.
- Binocular microscope

d) <u>Samples Tested</u>

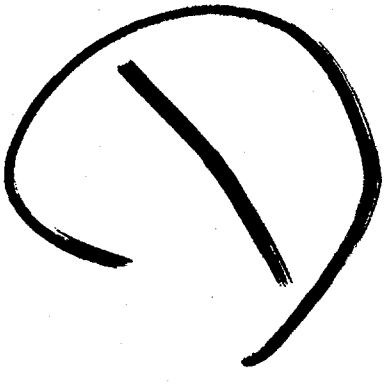
Silicone rubber tubing. This tubing is the same material as used in currently marketed leads. (b) (4) specimens approximately (b)(4) inches in length were tested.

e) Results

No stress cracking or other unexpected untoward results were observed. Some cases of ligature cut-through were discounted as a well known consequence of excessively tight ligation of silicone rubber insulation. Extruded silicone rubber tubing as used in cardiac pacing leads is not susceptible to stress cracking phenomena at static strains up to (b)(4) elongation.

f) Overall Conclusion

Based on literature, in vivo analysis of explants (animal and human), strain testing in rabbits, and 30 years of successful and widespread human clinical use, silicone rubber is an acceptable material for use in implantable cardiac pacing leads.



ATTACHMENT D

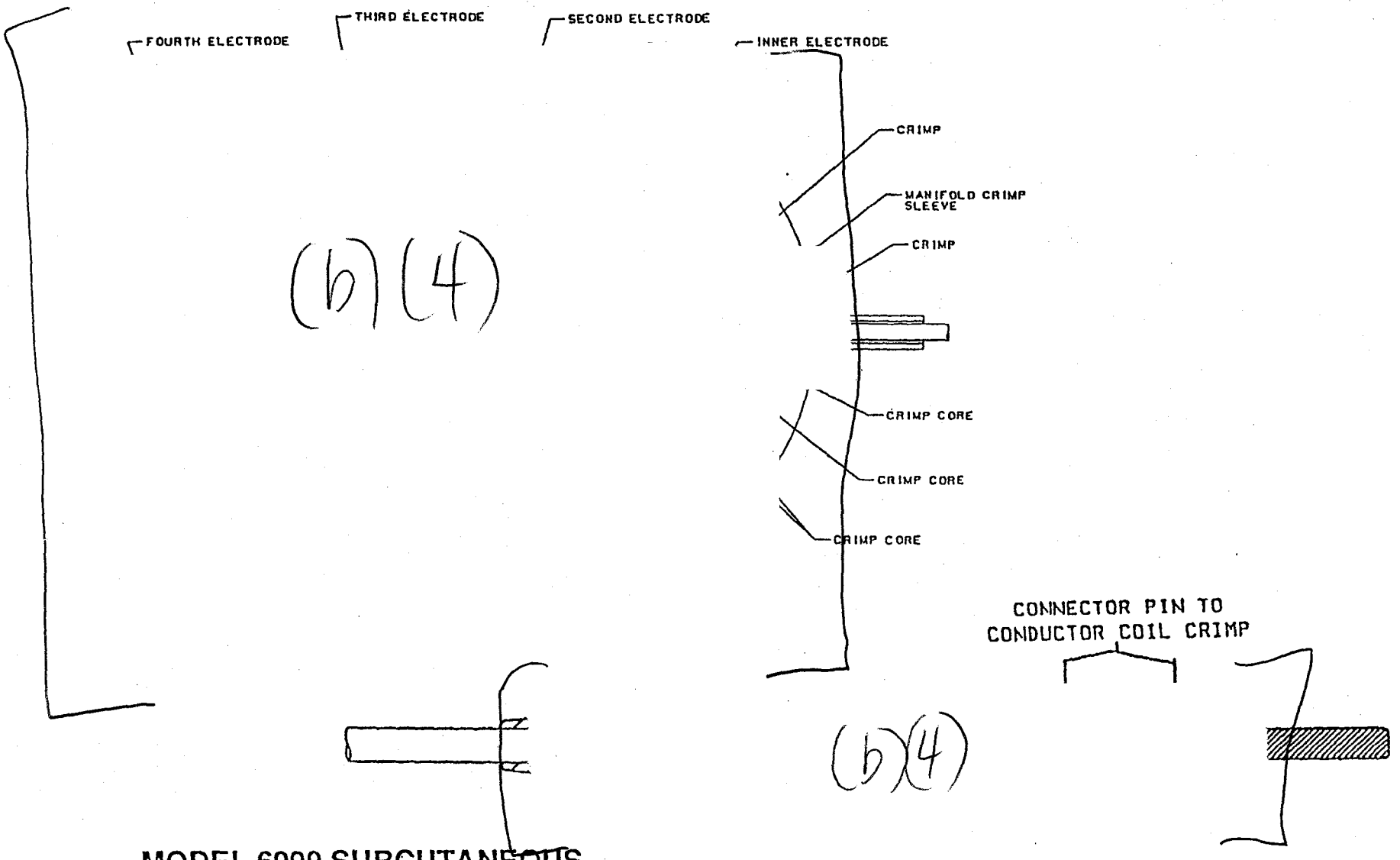
Copy from PMA Application
dated March 31, 1992, Volume 4, pp. 482-498

Design Assurance Testing
Model 6999

3. Model 6999

The Model 6999 unipolar, subcutaneous patch lead features an electrode for the delivery of cardioversion and defibrillation therapies. The lead is comprised of (b)(4) (b)(4) electrode coils partially embedded in a silicone patch body and covered with a (b)(4) The lead body is a silicone insulated (b)(4) conductor coil with a (b)(4) unipolar connector. See the figure on the following page for an illustration of the Model 6999.

Parameter	Model 6999
Lead length:	50 cm
Body diameter:	.098 inch (2.5 mm)
Insulation Material: Thickness:	(b)(4)
Conductor Material:	
Wire Diameter:	
External Coil Electrode:	
Patch dimensions:	
Conductive Surface Area:	
Fixation:	
Connector:	



MODEL 6999 SUBCUTANEOUS PATCH LEAD

Medtronic CONFIDENTIAL

a. Model 6999 Electrical Testing

Electrical Testing

1) D.C. Resistance

a) Test Method

Electrode resistance is measured between the distal end of each electrode coil and the manifold.

b) Rationale

Electrical D.C. resistance is measured to ensure proper functioning of the Model 6999 lead.

c) Test Equipment

(b) (4)

(b)(4)

d) Samples Tested

(b) (4) (b)(4) complete patch leads were measured for electrical resistance.

e) Results

Lead Body

Specification: (b) (4) (b)(4)

(b) (4)

(b)(4)

All samples tested met the specification. The results are within the specified limits and therefore are considered acceptable.

Distal End of Electrode Coils to Connector Pin

Inner Electrode

Specification: (b) (4) (b)(4) maximum

(b) (4)

(b)(4)

2nd Electrode

Specification: (b) (4) (b)(4) maximum

(b) (4)

(b)(4)

3rd Electrode

Specification: (b) (4) (b)(4) maximum

(b) (4)

(b)(4)

4th Electrode

Specification: (b) (4) (b)(4) maximum

(b) (4)

(b)(4)

All samples tested met specification. The results are within the specified limits and therefore are considered acceptable.

b. Environmental Testing

1) Thermal Shock

a) Test Method

Leads were subjected to (b)(4) cycles from (b)(4) with a soak time of (b)(4) minutes at each extreme and a maximum transfer time of one minute.

b) Rationale

Thermal shocking is used to determine the resistance of the lead system to alternate exposure extremes of high and low temperatures as when transported from extremes of climate.

c) Test Equipment

(b)(4)

d) Samples Tested

(b)(4) complete Model 6999 leads were subjected to thermal shock.

e) Results

There were no visual defects. The electrical D.C. resistance and intermittence were tested and all samples met specification.

c. Mechanical Testing

The purpose of the mechanical testing was to determine the mechanical integrity of the Model 6999 to ensure that the devices are suitable for their intended use and conform to design specifications.

1) Flex Testing of Insulated Conductor Coils and Non-insulated Electrode Coils*

a) Test Method

Samples are mounted in lead flex fixtures, then flexed under ambient room conditions at [redacted] over specified radii at the rate of [redacted] Samples are flexed until failure.

b) Rationale

Insulated conductor coils and non-insulated electrode coils are flex tested to assess longevity under accelerated use conditions.

c) Test Equipment

Medtronic Lead Flex Test Fixture.

d) Insulated Conductor Coils

i. Samples Tested

[redacted] samples of lead bodies (insulation/conductor coil subassemblies) were tested.

Model 6999
Insulated Lead Body

* See Appendix 2 for additional information regarding the development of the Medtronic flex test and information relative to the Transvene lead system.

ii. Results

At [redacted] inch radius,
Median = [redacted] cycles
Spec = [redacted] cycles

Individual failure times are:

1. [redacted]
2.
3.
4.
5.
6.
7.
8.
9-11. Test suspended at [redacted]

Flex life measurements exceed specification and therefore are considered satisfactory.

e) Electrode Coil

i. Samples Tested

[redacted] samples of the two electrode coils were tested. One coil is [redacted] turns per inch, the other is [redacted] turns per inch. Both electrode coils are used in the Model 6999 lead.

ii. Results

[redacted] turns/inch, at [redacted] inch radius
Median = [redacted]

Individual failure times are:

1. [redacted]
2.
3.
4.
5.
6.
7.
8.
9.
10.
11.

(b)(4) turns/inch, at (b)(4) inch radius
Median = (b) (4)(b)(4) cycles
(no failures)

No specification exists for electrode coils, see Appendix 2.

2) Lead Joint Tensile Strengths

Pull testing of the various lead joints is conducted to ensure that the integrity of each joint meets the design specification and is therefore adequate for its intended application. The testing conducted consists of a composite pull test which evaluates the overall pull strength of the lead and crimp testing that evaluates the crimped connections of the leads to assure specification conformance.

a) Composite Pull Strength

(b)(b)(4) leads were soaked and pull tested, while wet, utilizing a tensile testing machine. The proximal ends were soaked in normal saline solution (at (b)(b)(4) while the distal ends were boiled in (b)(b)(4) solution. The samples were pulled until failure at a rate of (b)(4) inches minute. The initial failures were then analyzed statistically for the confidence level in meeting the specification for the composite lead which is (b)(b)(4) minimum for the distal end and (b)(b)(4) minimum for the proximal end. The current reliability goal is for the design and process to demonstrate that with (b)(4) confidence, at least (b)(4) of the leads will meet or exceed the specification. The actual test results (mean and standard deviation) and the confidence intervals/levels generated by statistical analysis of the composite joint strength results are provided as follows:

Distal	Proximal
(b)(4)	

Distal lower limit is (b)(4)
Proximal lower limit is (b)(4)

(With 95% confidence and 95% probability, since the specification is one-sided, only the lower limit is of relevance.)

The above data demonstrate that with a 99% confidence, at least 99.9% of the leads will meet or exceed the specification.

b) Crimp Pull Strengths

Lead crimps were tested for joint pull strength by gripping the opposite ends of each connection in a tensile testing machine and pulling at a rate of (b)(4) inches per minute until failure. The test results (mean and standard deviation) and the confidence intervals/levels generated by statistical analysis of the individual crimp strengths are provided as follows:

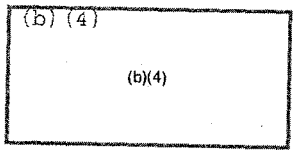
The connector pin to conductor coil crimp testing consisted of pulling (b)(4) samples. All samples tested met the specification of (b)(4)

(b)(4)

Lower limit is (b)(4) with 95% confidence and 95% probability.

The above data demonstrate that with a 99% confidence, at least 99.9% of the leads will meet or exceed the specification.

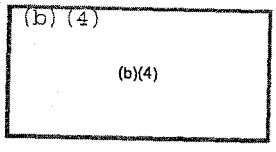
The manifold crimp sleeve to conductor coil crimp testing consisted of pulling (b)(4) samples. All samples tested met the specification of (b)(4)



Lower limit is (b)(4) with 95% confidence and 95% probability.

The above data demonstrate that with a 99% confidence, at least 99.9% of the leads will meet or exceed the specification.

Manifold crimp sleeve to electrode coil (b)(4) turns per inch) crimp testing consisted of pulling (b)(4) samples. All samples tested met the specification of (b)(4)

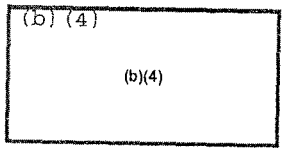


Lower limit is (b)(4) with 95% confidence and 95% probability.

The above data demonstrate that with a 99% confidence, at least 99% of the leads will meet or exceed the specification.

Manifold crimp sleeve to electrode coil ((b)(4) turns per inch) crimp testing consisted of pulling (b)(4) samples.

All samples tested met the specification of (b)(4)



Lower limit is (b)(4) with 95% confidence and 95% probability.

The above data demonstrate that with a 99% confidence, at least 99.9% of the leads will meet or exceed the specification.

d. Biostability Testing

1) Historical Overview

Silicone rubber was first used in implantable devices in 1950. Implantable cardiac pacing leads insulated with silicone rubber were first implanted in 1960. This rubber was applied to the lead in liquid form, then cured in situ. The silicone rubber in use today is initially a (b)(4) composed of (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4). This (b)(4) is either molded or extruded into useful shapes, then heated. Silicone was first used in Medtronic implantable cardiovascular leads in 1962 (Model 5814). Because of the excellent demonstrated biostability (and other properties) of this material in cardiac pacing leads, it is still in use throughout the industry today. Human actuarial data on newer Medtronic leads are available in product performance reports that are distributed three times a year. This report contains information on the clinical performance of Medtronic pacing leads. This information consists of returned product analysis, telephone monitoring of lead performance as well as a

retrospective/prospective study of Medtronic leads followed at [(b)(4)] institutions (Chronic Lead Study). Based on the information presented in the Chronic Lead Study Section of the report, Models 6961 and 6962 leads (silicone rubber insulated) have 94.4% actuarial survival at 12.5 years. These data include all complications, i.e., the data include not only leads whose integrity has failed, but also leads which dislodge, perforate, or experience exit block or sensing problems that are not due to lead integrity failure. Similar statistics based on telephone monitoring (CardioCare study) of patients yields a 98.2% survival at 12 years. Analysis of returned products shows not one insulation failure, i.e., due to environmental stress cracking and/or chemical reaction in [(b)(4)] silicone rubber insulated lead models representing about [(b)(4)] implants. These [(b)(4)] lead models have been in service from about 20+ years (Models 6907 and 6901) to seven years (Models 6961 and 6962). Thus, silicone rubber has an excellent history of long-term biostability in cardiac pacing leads.

2) Rationale for Using Silicone Rubber

The rationale for using silicone rubber is stated above. It is a known safe and reliable polymer for cardiac pacing leads with excellent biocompatibility, biostability and physical/electrical properties.

3) Biostability of Silicone Rubber Leads

a) Analysis of Canine Explants

i. Test Methods

Several unipolar and bipolar silicone rubber leads have been implanted in canines over the years to evaluate electrical

properties, i.e., pacing thresholds. Standard implant procedures were used. The studies generally were conducted for twelve weeks. At approximately the twelve week interval, the canine(s) was terminated and the lead(s) removed for analysis.

Explanted leads were examined by optical microscopy (up to 30X).

ii. Rationale

Even though canine implant times are relatively short compared to permanent human use, one would expect to see evidence of very severe degradation mechanisms, if present.

One possibility, for example, would be dehiscence (splitting along mold lines) due to lipid absorption.

iii. Test Equipment

- Surgical suite, instruments, anesthesia, etc.
- Binocular microscope (30X)

iv. Samples Tested

Several models were examined (at least [redacted] leads of each type) such as the Models 6917A, 6917, 6961, and 6962.

v. Results

No evidence of degradation was observed.

vi. Conclusion

Molded and extruded parts made from silicone rubber show no evidence of lack of biostability based upon examination of explanted leads.

b) Analysis of Human Explants

i. Test Methods

Human explants are typically received dry in envelopes. The returned leads are then examined by optical microscopy (up to 30X).

ii. Rationale

Routine analysis of explanted pacing leads is conducted as standard operating procedure.

iii. Test Equipment

- Binocular microscope (30X)

iv. Samples Tested

Several silicone pacing leads and/or segments, totaling approximately [(b)(4)] leads or portions thereof, have been examined, e.g., lead models such as 6917A, 6961, 6962, 6901, 6917, 6901R, 6907, and 6901R.

v. Results

No evidence of degradation, i.e., environmental stress cracking, chemical reaction, dehiscence, was observed.

vi. Conclusion

Molded and extruded parts made from silicone rubber show no evidence of lack of biostability based upon examination of explanted leads.

4) Biostability of Silicone Rubber Under Strain

a) Test Methods

(b) (4) wire was bent into figure (b)(4) shaped (b)(4) long mandrels. Tubing samples were then strained over the mandrels to various percent elongations. Strain was firmly fixed using (b) (4) (b)(4) Specimens were tied together in strings, color coded with beads, cleaned, sterilized and implanted subcutaneously in rabbits under general anesthesia.

Fixed strains included (b) (4) and (b)(4) elongations. (b)(4) specimens at each elongation were explanted weekly for twelve weeks. Specimens were examined by optical microscopy (30X) to find changes in surface morphology or defects.

b) Rationale

Certain early implanted medical devices (heart valve poppets) made from silicone rubber were found to be susceptible to a

stress cracking phenomenon-dehiscence. This has never been seen on Medtronic silicone rubber insulated leads. Standard silicone rubber was used as controls in tests to evaluate the stress cracking resistance of other polymers. Stress cracking was accelerated in these tests by using excessive strains.

Stress cracking phenomena require some combination of material strained beyond, a critical value, in contact with an active surface or plasticizing agent (in this scene, the biologic environment). The application of high fixed strains and sequential explants helps to determine what critical strain and induction times exist in polymers susceptible to stress cracking. If the material or part is not susceptible in vivo stress cracking, of course, it will not crack at any practical strain or implant time.

c) Test Equipment

- Specimens as described above
- Surgical suite, instruments, anesthesia, etc.
- Binocular microscope

d) Samples Tested

Silicone rubber tubing. This tubing is the same material as used in currently marketed leads. [redacted] specimens approximately [redacted] inches in length were tested.

e) Results

No stress cracking or other unexpected untoward results were observed. Some cases of ligature cut-through were discounted as a well known consequence of excessively tight ligation of silicone rubber insulation. Extruded silicone rubber tubing as used in cardiac pacing leads is not susceptible to stress cracking phenomena at static strains up to (b)(4) elongation.

f) Overall Conclusion

Based on literature, in vivo analysis of explants (animal and human), strain testing in rabbits, and 30 years of successful and widespread human clinical use, silicone rubber is an acceptable material for use in implantable cardiac pacing leads.

DCRND

P. J015/S000 21-Sep-1992

MPC

FROM:	LETTER DATE	LOGIN DATE	DUE DATE
MEDTRONIC INC. ATTN: JENNIFER M. MARRONE 7000 CENTRAL AVENUE, N.E. MINNEAPOLIS,, MN 554323576	09/18/92	09/21/92	/ /
	DOCUMENT: PMA	CONTROL # P920015/S000 AMENDMENT	

SUBJECT:
MEDTRONIC(R) TRANSVENE LEAD SYSTEM

	OFFICE	DATE REFERRED
13 COPIES OF VOLUME 1	~~CRH~~	9/21/92
13 COPIES OF VOLUME 2	DCRND	9/21/92
13 COPIES OF VOLUME 3		
13 COPIES OF VOLUME 4		
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2/16/93

MEMORANDUM

From: Doris Terry (HFZ-450)
To: File # P9110015
Subject: Medtronic Transvene Lead System
Date: December, 8, 1992
Office: DCRND/ODE

The sponsor has responded to our deficiency letter dated August 6, 1992.

Update of Patient Population

The update of the clinical experience of the Model 7217B and Transvene System is as of June 24, 1992. The Medtronic Models 7216A and 7217B PCD with epicardial leads underwent panel approval in February, 1992. The System presented for review in the referenced file is the Models 7216A and 7217B with non thoracotomy leads (Transvene™ System). The review will concentrate on the study of the Transvene leads in conjunction with the PCD models.

The patient population consists of 757 patients, three hundred and twenty-nine patients have implant durations greater than or equal to 6 months. Identical data pertaining to the spontaneous VT and VF efficacy, overall success rate, complications and observations and deaths were reviewed in the expansion request (b)(4) (b)(4) To reiterate there were 22 deaths (sudden cardiac - 3, non-sudden cardiac - 15 and noncardiac - 4).

A total of 854 patients were evaluated for the Transvene System. The patients were divided into the following groups: (1) patients who received a Transvene System (757) and (2) patients screened for a Transvene System and received an epicardial lead system (97). Of the 757 patients who received the Transvene System, 543 patients (71.1%) met the implant criteria and 214 patients (28.3%) did not. Of these 214 patients, 170 had an LED of less than or equal to 24 J and 194/214 had at least one successful termination of an induced ventricular tachyarrhythmia at 24 Joules or less. In 20 patients, their condition precluded further testing. Of the 97 patients who received the epicardial system, 81 patients met the implant criteria for the epicardial system and 16 patients did not. The overall survival for patients who met the implant criteria for the Transvene System was 94.9% and for the patients who did not was 97.4%. For the patients who received the epicardial system who met the criteria, the overall survival was 92.9% and for those who did not meet the implant criteria for the epicardial system was 80.7%.

It was stated that 737/757 (97.4%) received the Transvene System with at least a 10 Joule safety margin. The cardiovascular condition of 20 patients (2.6%) precluded an adequate definition of the safety margin. The investigators in these cases felt that the benefit of the Transvene System outweighed the risks of

2

further inductions and a thoracotomy. In most cases, the venous entry site for the placement of the Transvene Leads was the left subclavian vein. The majority of the investigators placed the SQ patch subcutaneously and laterally near the mid axillary line. The choice of the lead system was at the physician's discretion. The RV-SVC-SQ configuration was the selection in most cases.

A comparison between the PCD Transvene Study and the PCD Epicardial Lead System and Ventak P AICD studies was made. The comparison entailed looking at patient demographics, clinical performance (DFTs, incidence of spontaneous VT and VF episodes, incidence of complications) and one year survival. Overall there were no issues that rendered the groups significantly different and could be of concern in the evaluation of the data.

The pace/sense performance of the PCD Transvene versus the PCD Epicardial System was compared. In both systems sensing is performed in a standard bipolar configuration and pacing is performed in the integrated bipolar configuration. The pace/sense implant criteria are as follows: pacing threshold - less than or equal to 1.5V at 0.5 ms; R-wave amplitude - greater than or equal to 5 mv; slew rate - greater than or equal to 0.75 volt/sec; and resistance - 200-880 ohms. There was a statistically significant difference in all of the pace/sense parameters of the Transvene versus the epicardial lead system. This was anticipated due to reportedly better endocardial pace/sense parameters. However, it was stated that the difference had no impact on the pacing and sensing performance of the PCD Transvene System. The PCD Transvene System reported a higher mean implant DFT (14.8J versus 9.8J for the PCD Epicardial System). There was a statistically significant difference between the mean DFT obtained with the RV-CS-SQ System and the mean DFT obtained with the other lead systems (RV-CS-SVC and RV-SVC-SQ).

There was also a higher incidence of lead related complications in the PCD Transvene System (6.6% versus 2.8% in the epicardial population). Observations of interest included: inappropriate therapy - 8.2% for the Transvene - 10.6% for the Epicardial System; pace/sense related - 4.1% for the Transvene and 10.2% for the epicardial.

Statistical Analysis

The applicant provided a justification for pooling the U.S. and foreign data. The patient selection criteria, investigational protocol procedures and indications for implant of the Transvene System were identical in all of the studies. Even though there were statistically significant differences in the patient groups (U.S. and foreign), they were not considered to be clinically sitgnificant enough to require stratification of the U.S. and foreign populations. This issue will be left to the discretion of the reviewing statistician.

Patient Data

The applicant provided a list of the primary indications for use which are identical to those for the PCD Epicardial System. The patient demographics of the PCD Transvene Lead System were presented and discussed in detail. A description of the implant and follow-up procedures and a discussion of the data obtained at each interval were provided. The procedures performed at implant and follow-up were identical to those for the PCD Epicardial System.

Response to Deficiencies

The deficiencies relating to the leads were adequately addressed, as per the consulting review. I have the following concerns about the life testing. I have repeatedly questioned the sequence of testing flexing - soaking - high energy pulsing - soaking - electrical and visual inspection. The testing should have involved more than (b)(4) cycles per lead. (b)(4) leads (b)(4) Model 6963, (b)(4) Model 6966 and (b)(4) Model 6968 (b)(4) version of the Model 6966 which is not a subject of the PMA). I question the use of only (b)(4) Model 6966 leads during the life testing. How many Model 6966 leads were used during the course of bench testing and life testing? The data obtained from testing only (b)(4) leads during life testing appears to be inadequate. It was stated that the leads were placed back onto the test and flexed until failure, and that the data would be used only for improvement of the leads. It seems as if only the defibrillation segment of the leads were flexed to failure. Data from the defibrillation electrode segment of each lead model flexed at (b)(4) radius was reported as follows for the Model 6963 lead, the median was greater than (b)(4) cycles, for the Model 6966, the median was greater than (b)(4) cycles and for the Model 6999, median greater than (b)(4) cycles. A justification for the use of (b)(4) radius for flexing should be discussed. It is unclear how each segment (other than the defibrillation coil) of the Model 6966 lead was tested. The Model 6963 which has a (b)(4) (b)(4) lead body has the job of both pacing and sensing and defibrillation. In light of the recent failure of (b)(4) (b)(4) brady leads, alot of concentration should be placed on how each of the segments of the Model 6966 were tested. Some background about the failure and mechanism of the failure of the brady (b)(4) leads should be provided for our review.

An update of the animal studies which addressed the tumorigenesis issue was included. These findings were reviewed during the IDE study. There are no new findings to report.

The results of chronic animal studies which assessed chronic performance of the lead system were provided. Data, such as defibrillation thresholds, pacing thresholds, slew rates and R-wave amplitudes, the amount of energy delivered through the lead system for each shock delivered and the amount of current and

voltage across the lead system for each delivered shock were used in the chronic assessment of the Transvene Lead System. According to the manufacturer, the results of testing demonstrated the acceptable stability and performance for its intended use.

The manufacturer provided information regarding the improvement of perioperative and long term patient morbidity with use of the Transvene Lead System. The perioperative mortality of the patients implanted with the Transvene and the epicardial leads were compared and discussed. Undoubtedly, there is a decrease in perioperative mortality with use of the Transvene System. For as it was discussed, the majority of ICD patients are patients in which a thoracotomy poses an additional risk. The study has shown that the use of the Transvene Lead System which is implanted via a non-thoracotomy approach results in a decrease of perioperative death.

Treatment efficacy, complications and survival analysis on the patients followed for 6 months were provided for our review. There were 329 patients followed for 6 months. The primary indication for this group was recurrent sustained VT without an episode of sudden cardiac death. Sixty-six percent of the patients were implanted with the RV-SQ-SVC lead orientation. The mean LED was (b)(4) and the mean DFT was (b)(4) Percent success of VT spontaneous episodes was 99.0% and % success of spontaneous VF episodes was 98.7% The one year overall survival for patients followed for 6 months was 99.4% and the one year survival from sudden cardiac death was reported to be 100.0%.

There were 115 patients followed for one year. The primary indication was VT in 56 patients (48.7%). The mean LED and DFT were (b)(4) and (b)(4) respectively. The treatment efficacy was 98.9% for spontaneous VT and 98.8% for spontaneous VF episodes. The overall and sudden cardiac death at one year was reported as 100%. It was stated that one death which was classified as non-sudden occurred 22.5 months post implant. It was reported that 24 of the 115 patients followed for a year had as complication. Specific information will be requested regarding the patient deaths.

Complications and Observations

Complications were reported in 138 patients and 157 patients experienced clinical observations. The incidence of complications was 18.2% (18/757) and 20.8% (157/757) for the observations.

Complications included: increased defibrillation requirements - 0.8%; pace/sense performance related - 0.8%; infection related-explant required - 2.0%; infection related - 1.5%; lead related 12.4%; and device related - 0.5%. The observations were increased defibrillation requirements 0.5%, inappropriate

therapy delivery- 8.2%, pace/sense performance related- 4.1%, infection related - 4.9% and lead related 2.6%. Of the observations related to inappropriate therapy delivery, there were 49 observations which involved inappropriate VT therapy delivery
and 13 observations of inappropriate VF therapy delivery. The manufacturer made a comparison of the Transvene complications and observations to those reported for the PCD Epicardial System. Of interest, the comparison showed that the lead related complications for the Transvene were 6.6% versus 2.8% for the PCD epi and pace/sense related complication which were considerably less (0.9%) for the Transvene and 3.5% for the epi. there were more infection related observations with the Transvene (5.3%) versus 2.2% for the epi and more lead related observations with the Transvene (2.2%) than with the epi (1.2%).

Lead dislodgement which has been a problem in the study, has been addressed in earlier IDE supplements. IDE approval was granted for the use of new anchoring sleeves. It was requested that the results of the experience of at least 50 patients with the new sleeves implanted for 30 days be provided in the PMA for our review According to the manufacturer the lead dislodements have occurred within the first 30 days of implant. However, the frequency of dislodgement greater than 30 days is also of interest. The majority of the dislodgements were reported as complications since reoperation was necessary.Most of the dislodgements involved the Model 6881/6963 CS/SVC lead.

Patient Deaths

As of 6/24/92, there have been 22 deaths (15 U.S. and 7 foreign). Three of the deaths were sudden cardiac, non-sudden cardiac 16 and noncardiac 3. The PCD Transvene sudden cardiac death survival at one year is 99.8% which is comparable to that of the PCD Epicardial System (98.7%) and the commercially available AICD (98.6%). There were 5 perioperative deaths out of the total deaths with a resultant perioperative mortality of 0.7% (sudden cardiac 2, non-sudden 2 and non-cardiac 1). A Table which included the clinical characteristics of the patients who expired was submitted for our review. Death classifications were also provided by primary indication. There was no difference in patient survival based on the Transvene configuration or the indication for implant. The PCD Transvene one year actuarial survival is as follows: sudden cardiac 99.8%; non-sudden cardiac 96.8%; all cardiac 96.6%; noncardiac 99.4%; and overall 95.3% (includes perioperative deaths).

My concerns regarding the referenced will be relayed in the form of deficiencies which should be fully addressed and documented in a PMA Amendment for our review.

Questions and Concerns

1. For documentation and purposes of the PMA application, please reiterate and outline the following:

    a. the hypothesis and the objectives of the study;

    b. a discussion of the use of the AICD™ as a historical control, and how your study addressed the concept of a control which is pertinent in clinical trials, and the practicality, at this time, of the use of a concurrent control during an implantable defibrillator study (ICD);

    c. the endpoints of the study; and

    d. and how the data provided in the PMA application support the specified endpoints.

2. Based on data provided in your PMA application, please prepare Tables which will include a side-by-side comparison of the PCD™ Transvene™ and the PCD™ Epicardial System and the PCD™ Transvene™ and Ventak P AICD™ populations. The data should also include inclusion and exclusion criteria which were used in each study. A discussion of how these data may or not represent a valid comparison and other comments which justify, and support the use of these groups as controls should be included.

3. An update of the PMA population should be provided. The update should include the data as presented in the PMA application. Your update should also include the clinical experience in the use of the new anchoring sleeves which are aimed at decreasing the incidence of dislodgement, and a summary of the clinical experience (spontaneous treatment efficacy of VT and VF, observations and complications, number of patient deaths and overall survival) of the patients followed for a year or more.

4. For purposes of documentation in the PMA, please clarify and reiterate how you identified the "patient who did not meet the implant criteria." Please discuss your implant criteria and how implant testing attempted to satisfy protocol requirements.

5. Of the 214 patients who did not meet the implant criteria, 170 patients had successful defibrillation with 24 Joules (J). Please provide a updated summary of the clinical experience (as referenced in item # 2) on these patients.

6. There were 20 patients among the 214 who did not meet the implant criteria who were implanted without the 10 J safety margin. An update of the spontaneous episode experience in

the treatment of VT and VF in these patients and the overall survival should be provided.

7. Table IK-4, page 151, compares the patients meeting the implant criteria to those who did not met the criteria. However, many of the percentages were presented without numerical support. Please provide the appropriate numbers.

8. Please provide an update on the patients who are implanted with the Transvene™ System and were not counted in the PMA population. The update should include a summary of the clinical experience as referenced in item # 2.

9. Based on your study protocol, please differentiate between defibrillation threshold (DFT) testing and lowest energy to defibrillate (LED) testing. Based on the individual patient report forms, of the 757 patients, how many patients underwent what is described as DFT testing and how many had LED testing? Samples of the patient report forms showing the scheme of testing which was categorized as DFT and LED testing should be provided. Please discuss how the DFT and LED data were reported and presented in the PMA application.

10. There is a statistically significant difference between the mean DFT obtained with the RV-CS-SQ lead configuration and the mean DFT obtained with the other lead configurations. How do you account for this difference? Was the DFT as reported and discussed for all lead configurations obtained using an identical or similar scheme? Please discuss. It should be documented that there were no significant differences between the scheme for performing DFT and LED testing between the PCD Transvene™ and PCD Epicardial patient populations.

11. Please elaborate on how the comparison of DFTs obtained from the PCD™ Epicardial Lead study and the Transvene™ study can be considered as a valid comparison in that the majority of the patients (574 (75.3%)) in the Transvene™ study were programmed with the sequential pathway and 178 (23.4%) were programmed via the simultaneous pathway. The majority of the patients (496 (65.2%)) in the PCD™ Epicardial study were programmed with the single pathway. Based on your PCD™ Epicardial study, please discuss the DFTs or energy requirements obtained with the use of the single defibrillation pathway versus the sequential and simultaneous pathways.

12. Please discuss the time between detection and delivery of therapy of the Transvene™ PCD™ System versus the PCD™ Epicardial System.

13. On page 125 of the application, please explain and/or discuss what is meant by (b)(4) VF sensing margin", how it

is determined and if the patients met the criteria.

14. Of the 329 patients who were followed for 6 months, 130 patients had spontaneous episodes, what was the average number of VT and VF episodes per patient? Of the patients followed for a year, how many had spontaneous episodes of VT and VF and what was the mean number of episodes per patient in this group?

15. On page 130, Table IF-4, it was reported that there were 5362 episodes of VT successfully terminated. On page 131, paragraph 2, it was stated that 25 patients experienced 45 (0.8%) episodes of sinus tachycardia or atrial fibrillation. Are these patients included in the success or failure category? Nine hundred and sixty-four episodes of VF were reported, however, 75 episodes were not actual VF. It should be clarified how the successful and ineffective therapies and failures are discerned and categorized. Please prepare a Table which includes a category of ineffective therapies with actual patient numbers and percentages.

16. Table IM-6, page 173 should be modified to include a column on inappropriate therapy or therapies delivered as device was programmed so that the percentage can add up to 100%.

17. On page 162, Table IL-2 lists a category "Fail to Cardiovert/Defibrillate" as 0.8%, please clarify. If a patient survives an episode of an inappropriate therapy, is it categorized as a success? Please discuss. The Tables should include percentages with the representative numerical support.

18. There were 38 inactive patients reported in Table IH-1, however, 34 patients were reported to be no longer active. Please clarify.

19. Please discuss how the one year sudden cardiac death survival, as reported in Table IF-2 page 128, was calculated. The numbers and an explanation of patient classification should be included. Was every patient who had a prior cardiac arrest regardless of the arrhythmia included?

20. On page 177, the number of patients should be provided so that the percentages an calculated p-values can be confirmed.

21. Table IV-C shows a comparison of patient variables for the three lead systems. Please state the hypothesis of the study. The p-values obtained when reporting by primary indication should be discussed. The chi-square test of the data set and how it was computed should be discussed.

22. For purposes of justification of data pooling and data analysis of Table IV -C, please discuss why the multiple statistical significant difference was not adjusted at a (b)(4) significance level using a more widely accepted procedure such as the Hochberg procedure (Dunnett and Tarnhoue: A Step-up Multiple Test Procedure, Journal of the American Statistical Association, March, 1992, Vol 87: pp.162-170).

23. A comparison was made between the mortality between the PCD™ and AICD™ populations. What was the confidence interval?

24. Please clarify and/or discuss the following regarding Table XB-1, page 378, Volume 2:
    a. the total number of patients in the Ventak P population (292) versus those reported by primary indication (291); and

    b. a chi-square test of primary indication, using the (b)(4) yields a p-value of nearly (b)(4) This is statistically significant, indicating the PCD™ and Ventak P populations are significantly different.

25. Please discuss the incidence of inappropriate therapies reported as observations in the Transvene™ study. It appears as if there has only been a slight improvement over the PCD™ Epicardial study as it relates to programming and patient management (drug therapy). Please discuss the experience of both studies and how the labeling supports effective programming of the device parameters and the use of the Onset and Stability algorithms. How many patients in the Transvene™ study have the Onset and Stability algorithms programmed ON? At what interval during the study were the majority of patients programmed with the algorithms? Your experience in the treatment induced and spontaneous episodes with use the algorithms should be discussed.

26. Please discuses the "device related" complications reported for the Transvene™ and the PCD™ epicardial System.

27. Please describe in detail the complications reported in the patients followed for a year.

28. There was a substantial increase in the number of infections reported in the Transvene™ study. Even though you discussed why there was an increase, based on your experience, how will your labeling address the reduction in the number of infections?

29. A discussion of your experience in the use of the different entry sites for the placement of the Transvene™ leads and how your labeling assist in the selection of an entry site should be provided.

30. Of the 22 deaths, 15 systems were explanted and returned for analysis. The results of the analyses (PCD™ and Transvene™ leads should be provided. What did device interrogation reveal? How many of the 41 Transvene™ lead systems which were explanted were returned and analyzed? How long were the leads implanted? A description of the protocol for analysis and the results of the analyses on all leads and devices should be provided. The PMA application should document how your study has addressed the need for the return and analysis of all Transvene™ leads and the PCD™.

31. Please discuss the circumstances surrounding the death in the patient who died 22.5 months post implant. What did interrogation of the device reveal?

32. Of the perioperative deaths, how many devices were programmed OFF. Please discuss the circumstances surrounding each death. The number of perioperative deaths should be reported in a Table. The deaths should also be reported as sudden cardiac, non-sudden cardiac and cardiac non-cardiac. Were there other deaths when the device was programmed OFF?

33. It was stated that there have been no reported patient deaths in the group with a one year sudden cardiac death survival and overall actuarial survival of 100%. Does this include the patients who have been followed out for a year and the perioperative deaths?

34. An engineering drawing of each Transvene™ lead model which identifies the segments of the lead and a description of the tests that each segment and the full lead body underwent should be provided.

35. Since flex testing exerts a considerable amount of stress on the lead, and is essential to life testing, why was it considered that (b)(4) cycles at a bend radius of (b)(4) per lead model over a 12 month period would be sufficient. Describe how the lead and different segments were flexed.

36. In light of the failure of your (b)(4) (b)(4) bradycardia pacing leads, and since the Transvene™ lead Model 6966 is also a (b)(4) (b)(4) lead, please provide documentation regarding the failure mechanism of the pacing leads and all relevant information pertaining to these cases. How can we be assured that the failure may be restricted to the bradycardia pacing leads. Based on your testing to date regarding the pacing leads and the testing of the Model 6966 lead, discuss the potential and the probability of failure of the Model 6966 lead. A side by side comparison of the Model 6966 and the 4,000 series bradycardia pacing leads should be provided. The comparison should include material,

design, dimensions, function, tests performed and a schematic drawing.

The deficiencies also include the concerns as per the consulting reviews. See memos.

2/16/93

Memorandum

January 25, 1993

To: Doris Terry, Reviewer, DCRND

From: Jeffrey D. Jones, M.D., F.A.C.C., Medical Officer

RE: Medtronic PCD Transvene, Clinical Review

At your request I have reviewed the clinical data found in the PMA Amendment to the Medtronic PCD Transvene System. I will first answer your specific questions but will then expand to a more general evaluation with specific comments.

In response to your questions regarding the data presented by the company concerning the patients that did not met the recommended defibrillation implant criteria but who received a device anyway. Apparently each individual investigator who implanted such a device was given the latitude to make such a decision if he/she felt it was clinically appropriate. Reportedly, when the implant criteria could not be met but the patient was felt to be at increased risk for an arrhythmic death the device was subsequently implanted. Medtronic claims that regardless of the implant criteria that almost all of the patients had a 10 j safety margin. This "safety margin" has not been established in the literature by a well controlled prospective study. The reference sited by Medtronic on page 145 of the PMA does not discuss safety margins at all. It was however discussed in a subsequent reference of theirs. In addition, 20 patients had no DFT trial performed because they were judged to be in "poor condition". One could argue that if their general medical status was so poor that they could not undergo testing of the device then perhaps their short term survival was such that they should not have received the device at all. However, with such a high risk group of patients with a high likelihood of cardiac death perhaps it is acceptable to proceed in this fashion. It does unfortunately give the impression that Medtronic has little control over its investigators. Regardless, the reported overall survival in this group is 97.4% This is presented on pg. 153. We are not informed as to the average time of follow-up and maximum time of follow-up in these patients.

Therefore, my recommendations are as follows. We insist that Medtronic restrain investigators from implanting devices in patients that do not meet the implant criteria. This is not only bad science but it will decrease the actual patient population cohort that will be available and potentially prolong their study and subsequent approval. If Medtronic wishes to change their implant criteria they should provide data to support their position. I spoke to James D. Maloney, M.D. who was recently appointed Chief of Cardiovascular Electrophysiology at Baylor College of Medicine in Houston. He claims that no standard for defibrillation threshold exists but that the recommendations that he

recently presented at the NASPE Board Review Course in Cardiac Electrophysiology are based on his experience in electrophysiology. We need a more scientific approach. This burden should be placed on the manufacturer. I would also like to see up to date data on the overall survival between those meeting implant criteria and those patients not meeting implant criteria along with statistical analysis of those data. They should include the average and total time of follow-up.

Medtronic uses three historical control study populations in evaluating the safety and effectiveness of the PCD Transvene. They utilize the Ventak-P data, obtained through the freedom of information act, for comparison of patient characterists, clinical performance, and survival analysis (to include perioperative death).

The comparison is acceptable and favors the PCD Transvene in several ways. 92% of VT's were successfully treated with anti-tachycardia pacing and did not require further therapy. This represents an advantage with translates into better tolerance by the patient. My concern as explained below is that this figure may be artificially inflated. It requires that we assume that the attending physician is correct 100% of the time when he reports the device functioned properly after treatment. All that is available to the physician is the R-R interval and it would be relatively easy to misinterpret SVT as VT. For this reason we should refrain Medtronic from boldly proclaiming 99+% success rate (also see #4 and #5 below).

Perioperative mortality was lower in the PCD Transvene population at 0.7% compared to 2.7% with (b) (4)(b)(4). DFT's were reported as similar although we are not told how Ventex-P determined the DFT's, this is necessary to make an accurate comparison.

In addition to the specific questions you asked I would like to take this opportunity to comment in general on the presentation of the clinical data. A recurring difficulty I encountered was the presentation in table form of percentages when comparing two or more variables. It is very frequently unclear how these percentages are calculated. For example, in the table on pg. 128 it is unclear how the "One Year SCD Survival" percentages presented are calculated. They repeatedly place the burden on us to manipulate the numbers to achieve their percentages. In addition, an accompanying P value is often presented and again, it is unclear how this number is calculated. Frequently the number of patients is very small and representing this information as a percentage is misleading (eg; the number of patients in several categories followed for one year). In future submissions, all data presented as percentages should be accompanied by the number of patients so that the numbers can be easily verified and all P values can be easily confirmed by our statisticians. This would also allow us to easily add up all patients at a glance to confirm that all patients are accounted for and appropriately classified.

The general presentation of the data is also disorganized and very often redundant. I would suggest that for future submissions we insist on a clinical study mainframe for presentation of their data. For example, all the clinical data is presented in a section called "Clinical Data" in

table form where all the information can be easily review and compared and all calculations confirmed. They should save their comments and conclusions for those specific sections. This would greatly reduce our review time. There were also several occasions in which I came upon a term that had not yet been defined and I had to "stumble" through the data until I eventually came upon a definition (eg: DFT and LED). A section entitled, "Definitions" would have been helpful. We should insist on the same standards that a peer review journal would insist upon prior to publishing a manuscript.

In addition, when a manufacturer sites a specific reference and/or author to support their position they should not only provide a copy of the reference but also highlight the pertinent portion of the document. This would greatly reduce our reviewing time and speed up the review process in general. I spent approximately 6 hours looking up references cited by the authors in this current clinical section. The librarian had to call several other libraries to find one particular reference which was subsequently faxxed to me.

To continue, I have several additional recommendations to make and specific questions to pose.

1) Pg. 125, #2 near the bottom of the page. It is unclear to me what "a (b)(4) VF sensing safety margin" is. This is not defined. How is it determined and did the patients meet the criteria.

2) Pg. 128, at the bottom of the table. How was "One year SCD Survival" calculated ? We need the specific numbers and an explanation of patient classification. Was every patient that had a prior cardiac arrest regardless of the arrhythmia included ?

3) Pg. 129, end of paragraph 2. Do we know what the manufactures recommendations are that they reportedly give to institutions "that prefer to obtain DFT,s during the implant procedure ?"

4) Pg. 130, table. The manufacturer claims that there were 5362 successful episodes of VT termination. On pg. 131, paragraph 2, they claim that 25 patients experienced 45 (0.8%) episodes of sinus tachycardia or atrial fibrillation. Are these patients included in the success or failure category. They should not only clarify this but restructure the table to include a category of ineffective therapy with actual patient numbers and percentages.

5) As in #4 above, 964 successful episodes of VF are reported but on pg. 131 at the bottom they claim that 75 episodes were not VF. It appears to me that they count these episodes as successes when they should place them in the category of ineffective therapy. I would also like to know how they definitively confirm that an episode of VT or VF was definitely an episode. Is there a blinded third party interpreter of the interrogated retrieved events or is this based solely on the opinion of the attending physician ?

6) Pg. 136, Table H. There are a total of 38 patients who are inactive according to the chart but this does not correlate with the 34

patients as listed in the paragraph above the table.

7) There should be a similar table for periopeative deaths as the one shown on pg. 138. Perioperative deaths should be classified in chart form with numbers and percentages into sudden cardiac, non-sudden cardiac and non-cardiac deaths. I realize this is done in sentence form on page 451 but it would lend itself to more efficient review and comparison if it was present with the rest of the clinical data.

8) Pg. 139, The table at the top of the page relates a value for overall one year actuarial survival and again it is unclear how many patients actually were followed for a year. As I mentioned previously, every percentage should have an associated number of patients so we may verify the calculations immediately and not spend unnecessary time trying to confirm their calculations. 13

9) Pg. 151, The table compares the patients meeting and those not meeting implant criteria but again many percentages are presented without numerical support.

10) Pg. 156, They claim that there have been no reported patients deaths in the patient group with a resultant one year sudden cardiac death survival and overall actuarial survival of 100%. The real important data is the number of patients followed out this far. Does this also include perioperative deaths ?

11) Pg. 160, The DFT of the Ventak-P is compared to the DFT of the Transvene but we are never told how the DFT of the Ventak-P is determined. This is a worthless comparison without that knowledge. This mistake is repeated when the PCD-Transvene is compared to the PCD Epicardial device in chart form on pg. 171.

12) Pg. 162, The chart lists a "Fail to Cardiovert/Defibrillate" as 0.8% but for the reasons I provided above this is a gross misrepresentation. If a patient survives an episode of inappropriate therapy it should not be classified as a success. Again, tables of percentages are not acceptable without the numbers of patients in an adjacent column.

13) Pg. 173, The chart lists efficacy of termination of spontaneous episodes of VT and VF. The chart should be modified to include the total number of episodes out of the total and a column on inappropriate therapy so that the percentages all add up to 100% in each column.

14) Pg 177, Again, the number of patients should be provided so that the percentages and calculated P-Value can be confirmed. Stat

In general, the comparison of the Transvene clinical data to data collected from three different historical sources gives the impression of manipulation to selectively compare in a manner aimed at maximizing the advantage of the Transvene. In the future, a single historical source should be used unless the manufacturer can convincingly argue to the contrary. Lastly, I would suggest that you obtain statistical input from our statistician in those areas that I have suggested above.

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date DEC 9 1992

From Engineer, DCRND, ICDB

Subject Platinum-Iridium Mesh Leads

To Doris Terry, DCRND, PEDB

This memorandum is a formal response to your question regarding the possibility that (b)(4) could be a contributing factor in the observation of tumor growth in canines in which epicardial patch defibrillation leads were implanted. It should be noted that my comments are purely speculative and are not based upon a review of the leads in question or any data associated with such.

The toxicity of elements contained in alloys is related to the solubility of their corrosion products and the levels of the element present. Tumors can result because of one or several of the following factors:

1. Presence of a chemical carcinogen.
2. Generation of a carcinogenic chemical(s) through degradation of the material or through a chemical reaction of an ingredient in the material.
3. Cancer through physical effects (referred to as a solid state cancer).

With the defibrillation patch leads, solid-state carcinogenicity is a definite possibility. The use of (b)(4) in the lead (versus another material) could influence this phenomenon since the mechanical/physical properties of the patch will be influenced by the materials of construction, i.e., stiffness, thickness, etc.

With respect to the presence of a chemical carcinogen in the (b)(4) it is doubtful that the metal itself would produce a toxic effect. However, the use of (b)(4) in defibrillation leads could present new safety concerns. One obvious problem would be the fatigue resistance of the (b)(4). This material is not used as a coil material in permanent pacing leads so I am unsure of its fatigue properties for this application. Given the large amount of current used in defibrillation leads, filar breakage could be the cause of the burning/degradation observed in some studies. Also if a filar were to break (without complete fracture of the coil and subsequent loss of current delivery) the metal is subject to accelerated corrosive attack. Products of corrosion will diffuse out and local tissues can suffer from both metallic toxicity and electrochemical changes at the implant surface.

The issue of electrochemical reaction at the stimulation electrode-physiological saline interface is significant and the possibility of dangerous electrochemical reactions should be eliminated. A conservative requirement

for any "safe" electrical stimulation is the absence of chemical changes adjacent to the stimulating electrode. In electrochemical terms, this means that charge transfer processes producing dissolved species or gaseous products must be avoided. Possible dissolved species resulting from reactions at the Pt/saline interface include chloride oxidation products (ClO^-, ClO_3^-, etc.) H^+ or OH^- ions and Pt ions. Little information is available about the body's tolerance for the species produced at the Pt/saline interface and I cannot provide any estimate of a "safe level". Possible damage resulting from the flow of electric current through the physiologic solution produced at the interface presents another layer of complexity which may need to be considered.

In summary then, it may be advisable to have the manufacturers of these devices explore these areas in more detail to ensure safety and effectiveness, particularly long-term. If you have any questions please let me know.

Tara A. Ryan

cc: Nancy Teague
Christopher B. Sloan

2/16/93

MEMO

To: Doris Terry
From: Quynh Hoang
Date: 1/27/93

Regarding: Review of the Medtronic PCD Transvene System - P920015 amendment dated 9/18/92

SUMMARY

This amendment contains the response to the deficiencies of the original PMA. It also contains a clinical update on the PCD Transvene System.

Response to Deficiencies

The amendment have fully addressed a majority of the deficiencies. There remain, however, a few items which were not fully answered. Please refer to the Questions section below.

Clinical update

The clinical update covers 757 Transvene patients (447 US) in 78 investigational centers (35 US), as of 6/24/92. For the 757 patients, 762 Transvene systems were used since 5 systems were explanted and replaced due to infection. The 762 lead systems included 762 RV leads, 801 CS/SVC leads, and 723 SQ patches.

By indication: 37.1% of the implants were due to SCD (281/757), 49.8 % for VT (377/757), and 13.1% for SCD/VT (99/757). Coronary artery disease existed in 74.1% (561/757). The mean ejection fraction was 35.6% (688/757). Only 1.5% were of NYHA class IV (11/757). The patients were primarily male (80.6%, 610/757) with a mean age of 59.4 years.

At implant: 71.7% (543/757) met criteria, 97.4% (737/757) had at least a 10 J margin safety, and 2.6% (20/757) failed to finish the implant evaluation due to poor conditions. The most chosen Transvene configuration included: left subclavian as the entry site, RV-SVC-SQ as the lead system (65.6%, 500/762), and sequential as the shock pathway (75.3%, 574/762). The RV always served as the common (-) defibrillation electrode. The mean DFT at implant was 14.8J (316/757), and mean LED was 16.0J (702/757). Sixteen patients also have each a concomitant pacemaker.

Follow-up at one year have been performed on 113 patients, and six month follow-up on 329. Spontaneous VT occurred in 226 patients for a total of 5430 episodes. There were 68 episodes (1.3%, 68/5430) in 30 patients where all four VT therapies were unsuccessful

in terminating the problem; none resulted in a patient death. Spontaneous VF occurred in 198 patients for a total of 973 episodes. Nine episodes (0.9%, 9/973) in 2 patients could not be terminated by the four VF therapies; no patient died. At 3 month, the mean DFT was 15.9 J (54 patients), and mean LED was 19.3 J (88 patients).

There were 138 complications occurred in 138 patients (18.2%, 138/757) and 157 observations occurred in 157 patients (20.8%, 157/757). The majority of the complications were because of lead dislodgement (77 cases) and pocket related (26 cases). Most of the observations were due to inappropriate therapies (62 cases), pocket related (37 cases), and pace/sense related (31 cases). Of the 295 complications and observations, 48.1% (142/295) occurred during the perioperative period. There were 22 patient deaths with 5 in the perioperative period. Thirty-eight patients are no longer active in the study (22 deaths, 11 explants due to infection, and 5 heart transplants). Forty-one systems were explanted.

As of 6/24/92, there are also 548 patients who received the Transvene after the cutoff for the study population. These patients and the 43 who received non-standard lead systems were not included in this clinical update.

Please refer to the Questions section below, for the clarifications required of this update.

QUESTIONS

1. Please describe the similarities and differences between the 6966 and 6968 to justify the use of the 6968 lifetest results in supporting the reliability of the 6966.

2. Given their respective defibrillation thresholds, discuss the differences in battery or energy requirement of the Transvene and Epicardial systems.

3. Clearly identify the objectives, endpoints, and indicators which show that the endpoints have been met. Also, discuss the control in this study.

4. Provide data to show that the new anchoring sleeve does reduce the number of lead dislodgement.

5. Please give the time between Detection and Delivery of therapy. Compare the data from the Transvene and the patch leads.

6. Please provide a breakdown of the electrodes' polarities (cathode or anode) and pathways.

7. Provide the number of patients who died when their devices were turned off. Please breakdown the number by follow-up period.

8. Provide an update analysis of the explanted devices.

9. Provide a profile of the explanted system: how long were the leads implanted; what was found with the leads; and, explanting due to lead or device failure.

10. Document the comparability of the PCD Transvene and the PCD epicardial systems.

12. Provide the status (complications, observations, and death rate) of the "Other" patients who were not in the study population, and of the patients with the non-standard lead systems.

PHONE MEMO

On 1/26/93, Medtronic is contacted. Jennifer Marrone and colleagues responded.

1. Please explain the discoloration of the 6999 lead which occurred during lifetesting. Was it also observed in the explanted leads from human implants?

   Response: The discoloration was an anomaly induced by the lifetest procedure, because the lead was in and out of the saline solution for flexing. They attempted to dry the lead before flexing, but were not entirely successful. Analysis showed that the discoloration was not due to corrosion and there were no electrical problem. It is not expected that the lead would discolor while implanted, since the lead would not be moved in and out of the liquid environment.

2. Please identify the sections on the leads where flex testing was performed. Describe the comparability of the Transvene lead and the 6907 lead, such that the flexing criterion derived from the 6907 data may be applied to the Transvene.

   Response: A section of the defibrillation coil and a section of the cable body were flexed. The whole lead was not flexed since the flex equipment can handle a small section at a time. It is assumed that the cable body is homogeneous so that one section is identical to another. No testing on the distal tip of any of the lead was performed because that part is stiff and not expected to flex.

   There does not exist a model to predict the reliability of a lead; thus, data on the Model 6907 pacing lead were used because the lead has the worst performance of any Medtronic leads. The only determining factor for the choice is the fact that the

Model 6907 is an endocardial lead, and so are the Transvene. The Model 6907 is a silicone lead; however, this should not be a factor where the functional specification is concerned.

During benchtesting, the minimum of flex cycle to failure was [redacted] for 6966 where [redacted] leads were tested. Only [redacted] 6966 underwent lifetesting because the 6968 is considered equivalent to the 6966 lead, and [redacted] 6968 were used in the lifetest.

3. In this study, is the RV coil always serves as the common electrode.

   Response: No.

4. Please verify these tables:

   a. Tables E-2 and E-3, the number of patients followed at [redacted] does not match.

      Resp: [redacted] is the correct number.

   b. Table E-7, switch the numbers under the "attempts" and "successes" headings.

      Resp: will modify accordingly.

   c. Explain why the numbers in Table F-2 do not add up to the 18.2% rate of complications and 20.7% rate of observations.

      Resp: some data are not included. Will be more complete in the next summary

   d. Include <u>all</u> lead-related complications in Table F-3 (and not just those beyond the perioperative period), since it is intended to be a <u>summary</u> of clinical experience.

      Resp: will modify accordingly.

5. Discuss how the screening requirements (Transvene leads or epicardial patches) are different from the implant requirements. If they are the same, explain the Transvene subset that did not meet implant criteria.

   Resp: All study subjects undergo the Transvene implant evaluation (3 out of 4 at 18 J or less). Those who didn't have a 10J safety margin were screened out to receive

the epicardial patches. Of the remaining, they were divided into two groups: one which meets the implant criteria and one which didn't meet the implant criteria. The ones designated to have the epicardial patches would then undergo the patch lead implant evaluation.

6. In the cases where inappropriate VT therapy was delivered, was ONSET programmed On? If so, please explain why this algorithm fails to detect.

   Resp: Refer to page 417 of the 9/18/92 submission. Out of 49 instances of inappropriate VT therapy, 21 was resolved by reprogramming, 26 by drugs, 1 with no action, and 1 by AV node ablation. In 2 patients with sinus tachycardia, the ONSET algorithm was enabled and was successful in resolving the problem. In 3 patients with atrial fib, the STABILITY algorithm was enabled and resolved the problem.

7. How are those dropped from the study (due to infection or heart transplant) classified in the survival analysis?

   Those patients who were alive when they received heart transplants, a new PCD system, etc. were included in the analysis up to the day where the changes took place. After which, they were censored out of the data. Those receiving the new PCD system will be considered as new patients in the survival curve.

1992 for the use of new anchoring sleeves which will aid in eliminating lead dislodgement. In the last expansion request, we requested one month follow-up experience on at least 50 patients implanted with the new anchoring sleeves to be reported in the PMA application.

Recommendation: Approval to add 150 patients to the study. At this time, no specific plan of expansion which will allow a certain number of patients per month to be added to the study is being approved.

2/16/93

MEMORANDUM

From: Doris Terry (HFZ-450)
To: File # G870102/S87
Subject: Medtronic Transvene System
Date: December 7, 1992
Office: DCRND/ODE

The sponsor is requesting expansion of the Transvene study to include an additional 150 patients.

The following is an overview of the clinical data as of June 24, 1992:

- Patient population of 757, 329 patients have implant durations equal to or greater than 6 months

- 744 PCD implants and 18 7216A implants, of these 444 Model 7217B in U.S. and 300 Model 7217B implants internationally)

- Mean implant duration - 5.6 months

- Defibrillation pathway: sequential - 574 (75.3%); simultaneous - 178 (23.4%); and single - 10 (1.3%)

- Mean DFT - (b)(4) (b)(4)

- Mean LED (b)(4) (b)(4)

- Spontaneous VT: 226 patients, 5430 episodes % success = 98.7%

- Spontaneous VF: 198 patients, 973 episodes, % success = 99.1%

- One year survival 99.8%

Of the 757 patients who received the PCD Transvene System, 443 patients (58.5%- 443/757) have either experienced a spontaneous VT or VF episode or had VT or VF induced during a post implant EP study.

There have been 138 complications identified in 138 patients (77 U.S.) and 157 observations identified in 157 patients (68 U.S.) in the Transvene patient population. None of the complications and observations resulted in patient death. Included among the complications were 33 lead dislodgements reported in 33 patients at greater than 30 days. The dislodgements were identified through fluoroscopic examinations during EP evaluation and chest x-rays and pacing/sensing threshold evaluations during routine follow-up. In all cases reoperation was performed and the leads were repositioned. Approval was obtained under IDE in September,

MEMO

To: Doris Terry
From: Quynh Hoang, ODE/DCRND/PEDB
Date: 1/7/93

Regarding: Descriptions of the Transvene leads from Medtronic - P920015

Parameter	Model 6963	Model 6966	Model 6999
Intended Use	cardioversion defibrillation	cardioversion defibrillation pacing sensing	cardioversion defibrillation
Location of use	coronary sinus, or superior vena cava	right ventricle	subcutaneous/ left pectoral
Polarity	unipolar	tripolar	unipolar
Lead length	110 cm	110 cm	50 cm
Lead diameter	7 French	11 French	2.5 mm cable, and 11cm x 8cm patch
Distal end			
electrodes	5cm coil	distal 2mm helix middle ring proximal 5cm coil	4 concentric coils embedded in a silicone/ (b)(4) (b)(4)
cardioversion/ defibrillation	coil	coil	coil
pacing		helix - coil	
sensing		helix - ring	

electrode material	[redacted] turns per inch	[redacted] coil is [redacted] turns per inch	[redacted] inner coils are [redacted] turns per inch, [redacted] outer coils are [redacted] turns per inch
fixation method	passive	active/screw tip	sutured to site
Cable body			
conductor material	[redacted] of [redacted] inch wire diameter; wire is [redacted] shell	inner: [redacted] of [redacted] inch wire diameter; middle: [redacted] of [redacted] inch wire diameter; outer: [redacted] of [redacted] inch wire diameter; wire is [redacted] shell, [redacted] coated	[redacted] of [redacted] inch wire diameter; wire is [redacted] shell
insulation material	silicone rubber [redacted] inch thick	inner: [redacted] polyurethan [redacted] inch thick middle: [redacted] polyurethane [redacted] inch thick outer: [redacted] polyurethane [redacted] inch thick	silicone rubber [redacted] inch thick
Proximal end			
connector	unipolar 6.5 mm	bipolar 3.2 mm unipolar 6.5 mm	unipolar 6.5 mm

connector material	stainless steel connector pin; silicone rubber sleeve	bipolar: stainless (b)(4) ring and rotatable pin; unipolar: stainless (b)(4) pin; silicone rubber sleeve	stainless steel connector pin; silicone rubber sleeve
anchoring sleeve material	silicone rubber/ (b)(4)	silicone rubber/ (b)(4)	
Electrical testing	check the DC resistance between the connector pin and electrode coil (b)(4)	check the DC resistance between the connector pins and each electrode (ohms) (inner helix: (b)(4) (mid ring: (b)(4) (outer coil: (b)(4)	check the DC resistance between each coil and the manifold (ohms) (lead body: (b)(4) (b)(4) (inner coil: (b)(4) (2nd coil: (3rd coil: (outer coil:

Environmental testing leads were subjected to (b)(4) cycles from (b)(4) degree C with a soak time of (b)(4) minutes at each extreme and a maximum transfer time of (b)(4) minute. Post temperature cycling, visual and electrical tests were given.

Mechanical tests' passing criteria

flexing insulated cable body and noninsulated electrode coil were flexed under ambient room temperature at (b)(4) degree over a (b)(4) inch radius at the rate (b)(4) cpm; samples were flexed until failure. Passing criteria was that the median failure cycle should be at least (b)(4) based on Medtronic experience with the Model 6907 pacing lead which has been in the market for about 20 years and has a failure rate of 0.05%.

flexing 2 subassemblies
flexing 2 lead leads

median flexing failure cycle	cable: [redacted] coil: [redacted] cable: [redacted] [redacted] turns/inch coil: = [redacted] [redacted] turns/inch coil:
composite pull test	proximal end was soaked in normal saline solution (at [redacted] and distal end was boiled in [redacted] samples were pulled until failure at a rate of [redacted] inches per minute; a lead must exceed the [redacted] minimum for the distal end and [redacted] minimum for the proximal end.
crimp/weld pull test	crimp and weld were pulled at [redacted] inches per minute; the lb force specs varied from [redacted] to [redacted] for each crimp or weld.
anchoring sleeve test (Models 6963 and 6966)	anchoring sleeves were evaluated for tolerance of a [redacted] suture force using [redacted] suture, and of the force necessary to slide the anchoring sleeve on the lead body (no minimum slide force was given).
leak test (Model 6966)	model 6966 leads were immersed in pressurized water at [redacted] psi for [redacted] minutes, and examined at 6X magnification for evidence of water between the inner, middle, and outer tubing. Also while immersed in water, air pressure of [redacted] is applied to the distal end of the sleeve head for [redacted] minutes. The lead body and connector pin were observed for signs of air bubbles.
connector test	dried leads were inserted to dried connector modules to determine maximum the insertion and withdrawal forces. The insertion force should be at most [redacted] and withdrawal force at most [redacted]

Biocompatibility testing	except for the [redacted] which is embedded in the silicone and wasn't tested for mutagenicity, all of the other materials have been tested in accordance with the tripartite requirements.
Biostability testing	
Models 6963 and 6999	evidence of degradation such as dehiscence (splitting along mold lines due to lipid absorption) was verified by implanting silicone rubber leads for 12 weeks in canines and explanting them to examine at 30X magnification. Human explants, approximately [redacted] leads or portions, were examined at 30X magnification. Silicone rubber tubings at [redacted] and [redacted] elongation were stretched over figure [redacted] shaped mandrels of [redacted] long and implanted subcutaneously in rabbits to check for evidence of stress cracking; weekly explants over the 12 weeks were examined at 30X magnification. All of the human and animal explants did not show any evidence of degradation.
Model 6966	accelerated benchtest, to emulate in-vivo metal induced oxidation of polyurethane, was performed by placing the leads in a [redacted] and [redacted] saline solution (Solution A). During the first 6 weeks, each lead was removed weekly and placed in a fresh Solution A where it was subjected to [redacted] defibrillation pulses at [redacted] and [redacted] pulse width. Insulation breach or cracks were visually checked at the [redacted] and [redacted] days at a 30-64X magnification. At the [redacted] day, impedance between the lead circuits were exceeding the specification of [redacted] Twenty-four week implants of stretched tubings in rabbits resulted in only cosmetic environmental stress cracking.
Life testing	Cables, electrode coils, and patches were subjected to [redacted] cycles of flexing [redacted] times/cycle), soaking in [redacted] ([redacted] days/cycle), high energy pulsing [redacted] shocks at [redacted] shocks/cycle), soaking in [redacted] ([redacted] days) and electrical/visual inspection. Discoloration was observed on the connector pin and the electrode coil of some Model 6999 leads. All the leads passed the impedance requirements. The electrode section of the leads were then flexed

until failure; the median failure cycle for each lead was > 1 million.

Crush testing (Models 6963 and 6966)

To simulate the crushing load encountered in the area of the first rib and clavicle, a Model 6963 and a Model 6966 were clamped together in a cross configuration between [redacted] After soaking in [redacted] solution for [redacted] hours, the leads were compressed at either a [redacted] or [redacted] force; thus, respectively reducing the combined diameters by either [redacted], or [redacted]. Each lead was then given [redacted] shocks at each incremental voltage level of [redacted] and [redacted] Impedance between the leads was checked after each series of [redacted] shocks. Subsequently, a hipot test at [redacted] No failure was observed.

Animal Studies

Four canine studies (32 dogs) were performed. Temporary, prototype, and the present leads were used in the studies. Induced VTs and VFs were successfully terminated during implant, post-implant, and/or EP evaluation. Gross and histopathologic examination revealed shock-induced necroses which were described as small and negligible in its effects on the function of the myocardium. Stability of the lead system was verified by x-ray or fluoroscopy, sensing amplitudes, defibrillation and pacing thresholds. Problems experienced during the studies include mast cell tumors on thigh and shoulder, oversensing, T-wave sensing following a pacing pulse of maximum programmable output and pulse width, patch lead fracture, helix electrode backing out of the tissue, CS lead dislodgement, and shorting of the RV and CS leads. Five dogs are still being studied; their average time on study is 60 weeks.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

MEMORANDUM

DATE: JAN 8 1993

FROM: Bioresearch Monitoring Branch, HFZ-324

SUBJECT: Classification of EIR: Compliance Program 7348.811
Clinical Investigator

TO: Supervisory Investigator: Bruce W. Williamson
SEA-DO, HFR-PA350

Firm Inspected: Gust H. Brady, M.D.
University of Washington Medical Center
Seattle, Washington 98195

Sponsor: Medtronic, Inc.; PMA # P920015

Device: Transvene Transvenous Lead system

Date Inspected: November 16, 17 and 19, 1992

Assignment Date: July 14, 1992

We have reviewed the report for this inspection and are hereby sending you its classification status.

Status Summary

District conclusion	In compliance
Final CDRH Classification	NAI
Follow-up planned	None

Broden Staples Jr.
Broden Staples Jr.
Consumer Safety Officer
Bioresearch Monitoring Branch, CDRH

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cc:

HFZ-324 (JYGrayson, ESantiago, LBowlding, BStaples, Reading file)
HFZ-450 (DJTerry)
HFC-132 (JPrego)
HFC-230 (PLepore)
HFZ-300 (RJohnson)
HFZ-320 (WFHooten)
HFR-PA300 (RLowell)
HFR-PA350 (WGZuber)
HFA-224

Drafted:BStaples:12/15/92
Reviewed:ESantiago:12/16/92
t/f:cmbraxton:12/23/92

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date *December 16, 1992

From Mathematical Statistician (T. C. Lu) HFZ-162
Statistical Branch, Division of Biometric Sciences, OST

Subject Statistical Review of PMA P920015 Amendment, Medtronic Multiprogrammable Tachyarrhythmia Control System with Non-thoracotomy Cardvioversion and Defibrillation Electrodes, Medtronic, Inc.

To

Doris Terry - HFZ-450
Division of Cardiovascular, Respiratory, and Neurological Devices
Through: Director, Division of Biometric Sciences, OST MKB for RPC
Through: Chief, Statistics Branch, DBS, OST CSL for HFB

1. Background

Per our telephone conversation on December 7, 1992, you requested a statistical review of this PMA amendment. This amendment was received at FDA on September 21, 1992. I wasn't notified of any action until December 7. This amendment was sent to me on December 8, 1992. You indicate that you would like to receive my comments before December 18, 1992. With the limited time frame, I can only concentrate on the sponsor's response to the deficiency letter dated August 6 from FDA to the sponsor.

2. Reviewer's Comments

2.1. Item 21. Sponsor provided the p-values for Tables IV-B and IV-C of the original PMA. This reviewer recomputed the p-values and found them identical to those of the sponsor's. However, there is a problem, sample sizes are 18 for 7216A and 739 for 7217B. With such a large difference in sample size, this will cause very low statistical power, then the small difference is very difficult to detect.

2.2. Table IV-C shows comparisons of patient variables for the three lead systems. All the p-values computed by this reviewer is identical to those of the sponsor's. The total numbers of patients of primary indication are 329 for RV/SVC/SQ (of which 187 for SCD, 114 for VT, and 28 for SCDlVT), which are not in agreement with a total sample size of 496 (403 males and 93 females). The sponsor provided p-values for variables tested in Table IV-C. The hypothesis was not clearly stated. After recomputing the p-values listed in the table, all are in agreement except primary indication. The chi-square test of this data set, computed using (b)(4) (b)(4) yield a p-value of nearly (b)(4) which is also different from that of sponsor's computed p-value of 0.984.

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2.3. The sponsor, for the purpose of justification of data pooling and data analysis of Table IV-C, adjust the multiple statistical significant difference at 0.05 significance level using Hochberg procedure (Dunnett & Tarnhoue: A Step-up Multiple Test Procedure, Journal of the American Statistical Association, March 1992, 87:162-170). Although this is a published, peer reviewed article, the sponsor's multiple test adjustment procedure is not widely accepted by the biostatistical and clinical community.

2.4. Comparison of Mortality Between One PCD and the AICD

Item 25. The sponsor compared the end points of the two devices. Sponsor claimed that confidence interval analysis was performed but that confidence interval was not given. Confidence interval should be computed by the sponsor to support this claim.

Sponsor provided a table for the comparison of patient characteristics, PCD versus ventak-P. I have two questions about Table XB-1, Page 378, Vol. 2:

(i) The total numbers of patients of primary indication, 291 for Ventak-P (49 for SCD, 169 for VT, and 73 for SCD/VT) are not equal to the total number of patients of Ventak-P of 292.

(ii) A chi-square test of primary indication, using (b)(4) (b)(4) yield a p-value of nearly (b)(4) This is statistically significant, indicating that PCD and Ventak-P are significantly different.

The inclusion and exclusion criteria for patients of PCD and AICD studies are not discussed by the sponsor.

Conclusion

The sponsor needs to adequately address the issues raised in Section 2 above before the safety and effectiveness of the PCD transvene system can be evaluated from a statistical perspective.

T. C. Lu

T. C. Lu

cc: Abhijit Acharya, Ph.D. - HFZ-450
Donald F. Dahms - HFZ-450
Lynne A. Reamer - HFZ-450
PMS Group - HFZ-402
DCC - HFZ-401
Medical Device File
Board File

Medtronic

227-84-1 T.C. Lee

Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576
Telephone: (612) 574-4000
Cable: Medtronic Telex: 29-0598
FAX: (612) 574-4879

September 18, 1992

Office of Device Evaluation
PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

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FDA/CDRH/ODE/DMC

Re: P920015 PMA Amendment to the Medtronic® PCD™ Transvene™ System Lead Models 6963, 6966 and 6999

The purpose of this submission is to amend the aforementioned PMA application as specified in FDA's letter dated August 6, 1992.

This includes responses to all deficiencies noted in FDA's letter, an updated Summary of Safety and Effectiveness, and an updated clinical experience report, inclusive of 757 patients followed for an average of 6 months.

Clinical data continues to demonstrate the PCD Transvene system performs as specified and is therefore safe and effective for its intended use.

The existence of this PMA Amendment and the data and other information it contains are confidential, and the protection afforded to such confidential information by 18 USC 1905 and other applicable laws is hereby claimed.

Twelve copies of this PMA Amendment are provided. Should additional information be required by the Agency, please contact the undersigned.

Sincerely yours,

MEDTRONIC, INC.

Jennifer M. Marrone
Cardiac Pacing Business
Manager, Regulatory Affairs
(612) 574-4688
(612) 574-6424 FAX

Attachment

:hr

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For later

Food and Drug Administration
1390 Piccard Drive
Rockville MD 20850

Ms. Jennifer Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

AUG - 6 1992

Re: P920015
Transvene™ Lead System
Filed: April 1, 1992

Dear Ms. Marrone:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial scientific review of the above referenced premarket approval application (PMA). We regret to inform you that on the basis of this review, we have concluded that the PMA lacks information needed to complete the review and determine whether there is reasonable assurance that the device is safe and effective for its intended use.

Because of this lack of information, review of the PMA cannot continue and, accordingly, we have listed the following significant deficiencies which require the responses as indicated:

1. Discuss how the use of a silicone adhesive prevents tissue in-growth in the Model 6963 lead. Where is the adhesive placed? From experience, discuss the use of polyurethane and silicone in leads to prevent tissue in-growth.

2. Please provide the results of mutagenicity testing for the (b)(4) mesh and the silicone rubber (b)(4) (anchor sleeve). If the tests have not been done please provide a justification for not doing so.

3. Provide a description of the helix electrode fixation tool and of the tests to verify the torsional force for implanting the helix electrode.

4. Based on your experience, identify the minimum number of flex cycles that a lead should withstand. Also, give the stress level exerted on the Model 6907 lead (from which the median failure time of (b)(4) cycles was observed), and on the Transvene™ leads.

5. Since the electrode coil is flexed separately from the insulated conductor, discuss the reliability of the section where the electrode is coaxial to the conductor. Is there friction between the electrode and the conductor when the section is flexed?

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AUG 10 1992

Part 1 - Page 1137

6. The Model 6999's (b)(4) turns/inch electrode coil fails at a much lower flex cycle than the (b)(4) turns/inch electrode coil. Discuss the reliability of the (b)(4) turns/inch electrode coil, and the effects of its failure on the performance of the lead.

7. Please discuss how patient treatment is affected if one or two of the electrode coils of the Model 6999 patch lead becomes damaged.

8. Please specify the section of each lead assembly that was flexed during life testing. Does this section include the electrode coil? The results of the tests should be included.

9. Provide an update of the 12 month life test.

10. The data indicate that a new lead is used for each (temperature tolerance, crush load, or life) test. Correlate the results from those tests to the worst case condition where the same lead has to face temperature differences, crushing, and flexing. Why was sequential testing not performed?

11. Discuss the differences in battery life or energy requirements between the epi-lead system and the Transvene™ system.

12. An update of the chronic animal studies should be provided.

13. An update of the clinical experience of the Transvene™ Lead System should be provided. The update should include all additional patients and the clinical experience to date. The data should be presented as done in your original PMA application, and should include, e.g., implant and follow-up data, lead orientations including patch location, spontaneous episode experience, analyses by different groups, complications/observations, and survival analysis. All remaining deficiencies listed below which pertain to your patient population should be addressed using the updated patient group.

14. Please discuss your clinical data which support the claim which states that the Transvene™ Lead System improves both perioperative and long term patient morbidity.

15. Based on your experience and on the data as reported in the literature, what is the percentage of patients who have been found unable to withstand a thoracotomy?

16. Data such as treatment efficacy, complications and survival analysis on the patients followed for 6 months should be provided.

17. Please discuss your clinical experience (treatment efficacy, lead orientation, complications and survival rates) of the patients who have been followed for 1 year and more.

18. Provide a detailed discussion of the clinical experience (implant duration, lead orientations, spontaneous episodes, treatment efficacy, survival analysis, complications, etc.) of the patients who did not meet the implant criteria and were implanted with the Transvene™ System. Also discuss the experience of the patients who were implanted without the 10 Joule safety margin.

19. A breakdown of the different lead orientations within the patient population, and the treatment efficacy reported for each configuration should be included.

20. Based upon your clinical experience, the Physician's Manual should recommend the sequence of testing with the different lead orientations during implant.

21. Please provide the P-values as listed in Table IV B and IV C of the original PMA application for the new patient population.

22. Please discuss the reasons why some patients dropped out of the study, either withdrawn alive or lost to follow-up. There were 224 patients at 1 month and only 154 patients at 3 months. Please explain the difference of 70 patients during this 2 month period.

23. For the comparison of complications/observations rates for the PCD™ versus the AICD™, please provide the following:

    a. the number of complications and patients for the PCD™ and AICD™ populations;

    b. the clinical success/failure criteria used for "Failure to Cardiovert/Defibrillate and Inappropriate Problematic VT/VF Therapy Delivery"; and

    c. a discussion of the pocket infection rate of the PCD™ and the AICD™ and the lead related complications of the PCD™ Transvene™ System versus the PCD™ Epicardial System.

24. Some Transvene™ patients were also evaluated with the Model 10388 hollow can electrode. Please compare the infection rate of these patients to those who did not undergo the hollow can evaluation.

25. Please discuss and/or provide the following regarding the 1 year actuarial survival comparison of mortality between the PCD™ and the AICD™:

    a. the statistical test that was used to compare survival; and

    b. the two survival or life tables by year of follow-up.

26. Please discuss the statistical techniques used to derive the P-values in Table XI G-2, page 862, Vol. 5 and Table J-2, page 54, Vol. 1.

The following additional deficiencies were noted in this initial scientific review and the indicated responses should be provided:

1. Discuss the properties of polyurethane which make it the ideal insulation material for the 6966 lead. Why was silicone not chosen?

2. Discuss the biostability tests (stress cracking, metal induced oxidation, etc.) performed on the (b)(4) types of polyurethane. Why was a different polyurethane chosen for the inner coil?

3. Based on the results of the life test, what is the life expectancy of the leads? Please include your assumptions.

4. Provide a side-by-side comparison between the Model 6999 and the epicardial patch lead.

5. Discuss the possible interactions between implanted pacemaker leads and the Transvene™ leads. Also, discuss the effects of the leads on the tricuspid valve and the host vein.

6. The Transvene™ leads seem to tolerate crush testing better than the pacing leads. Please discuss the properties of the Transvene™ leads which support this capability.

7. Are there patients currently implanted with the Model 6895 and 10317 patch leads? If so, please provide a breakdown of the clinical data, e.g., complications, survival, etc. for each lead.

8. Please list the reasons for not performing pre-hospital discharge testing.

9. The number of spontaneous episodes of the patients followed for 6 months and beyond should be provided.

10. A copy of the Summary of Safety and Effectiveness with the updated clinical data should be submitted.

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period up to 180 days. As provided by 21 CFR 814.37(c), you may decline to submit a major amendment requested by FDA in which case the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

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As provided under 21 CFR 814.44(g), FDA will consider this PMA to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA amendment. You may, however, amend the PMA within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180-day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA and will be assigned a new number.

You may amend the PMA to provide the above requested information 12 copies, voluntarily withdraw the PMA (3 copies), direct CDRH to complete processing the PMA without the submission of additional information (3 copies) or request an extension. The required copies of the amended PMA should include the FDA reference number for this PMA and should be submitted to the following address:

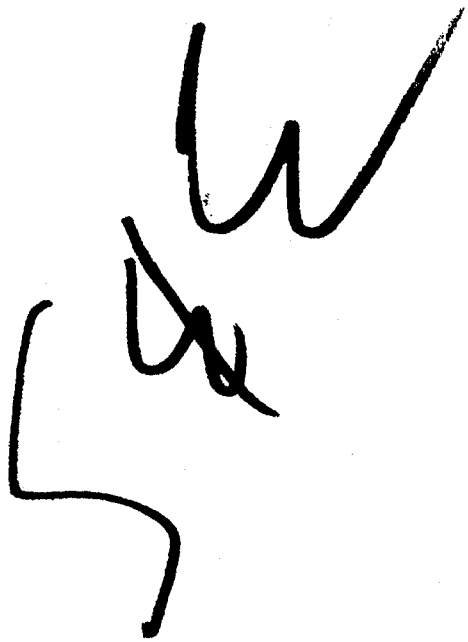
PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

Upon receipt of an amendment adequately addressing the above requests or a written response declining to submit the requested amendment, CDRH may schedule an advisory panel meeting at which your PMA will be reviewed. You will be notified of the location and date of this meeting should one be necessary. In order to provide adequate time for CDRH and advisory panel review, information received by FDA less than 8 weeks in advance of any scheduled advisory committee meeting will not be considered or reviewed at the meeting and may delay consideration of your PMA until a subsequent advisory committee meeting.

If you have questions concerning this deficiency letter, please contact Doris Terry at (301) 427-1018 or Arnold Alpert, Ph.D., at (301) 427-1186.

Sincerely yours,

for F. Alan Andersen, Ph.D.
Acting Director
Office of Device Evaluation
Center for Devices and
Radiological Health



Summary of Safety and Effectiveness (September 18, 1992)

A. Indications For Use

The Medtronic PCD Model 7217B Multiprogrammable Tachyarrhythmia Control System with Nonthoracotomy Cardioversion and Defibrillation Electrodes (hereafter referred to as the PCD Transvene System) is intended to treat patients at risk of sudden cardiac death due to ventricular tachyarrhythmias. Indications for use include:

- Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or
- Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.
- Patients undergoing replacement of a previously implanted implantable cardioverter defibrillator.

The patients who meet the above patient selection criteria should have also undergone a complete cardiological evaluation that includes electrophysiological testing. Electrophysiologic evaluation and testing of the safety and efficacy of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the PCD Transvene System.

The PCD Transvene System components, except for the defibrillation lead system, are identical to the PCD Epicardial System which was unanimously recommended for approval by the FDA Advisory Panel on February 3, 1992.

Market approval **is not** being sought for use of the PCD Device with other manufacturers transvenous defibrillation lead systems. In addition, market approval **is not** being sought for the use of the PCD Transvene lead system with other manufacturers implantable cardioverter defibrillators.

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B. Description of the Transvene Lead/PCD System

The Medtronic Tachyarrhythmia Control System consists of two fundamental configurations: (1) the implantable configuration and (2) the external configuration. Both configurations use the Transvene lead system. See Figure III B-1

The implantable configuration is composed of a Pacer-Cardioverter-Defibrillator (PCD) device, implantable leads, and a programmer. The PCD device is an implantable, multiprogrammable, automatic tachyarrhythmia control device.

The external configuration is composed of an External Tachyarrhythmia Control Device (ETCD), a patient cable, implantable leads, and a programmer. The ETCD is an externally-operated, multiprogrammable, tachyarrhythmia control device.

Intended Uses - Transvene Leads

Model 6963 Lead

The Medtronic Transvene Model 6963 Unipolar, Coronary Sinus or Superior Vena Cava, Transvenous Lead features an electrode for the delivery of cardioversion and defibrillation therapies. It is intended for long-term use in the coronary sinus or superior vena cava and is designed to be used with an implantable tachyarrhythmia control device along with at least one other lead, such as the Model 6966 Tripolar, Right Ventricular, Transvenous Lead.

The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

Model 6966 Lead

The Medtronic Transvene Model 6966 Tripolar, Endocardial, Screw-In Lead is designed for pacing, sensing, and delivering cardioversion and defibrillation pulses in the ventricle. The lead has application where implantable tachyarrhythmia control systems are indicated.

The Model 6966 lead has a helical electrode made of platinum alloy that can be actively fixed in the endocardium. The helix can be extended or retracted by rotating the lead connector pin with a special fixation tool.

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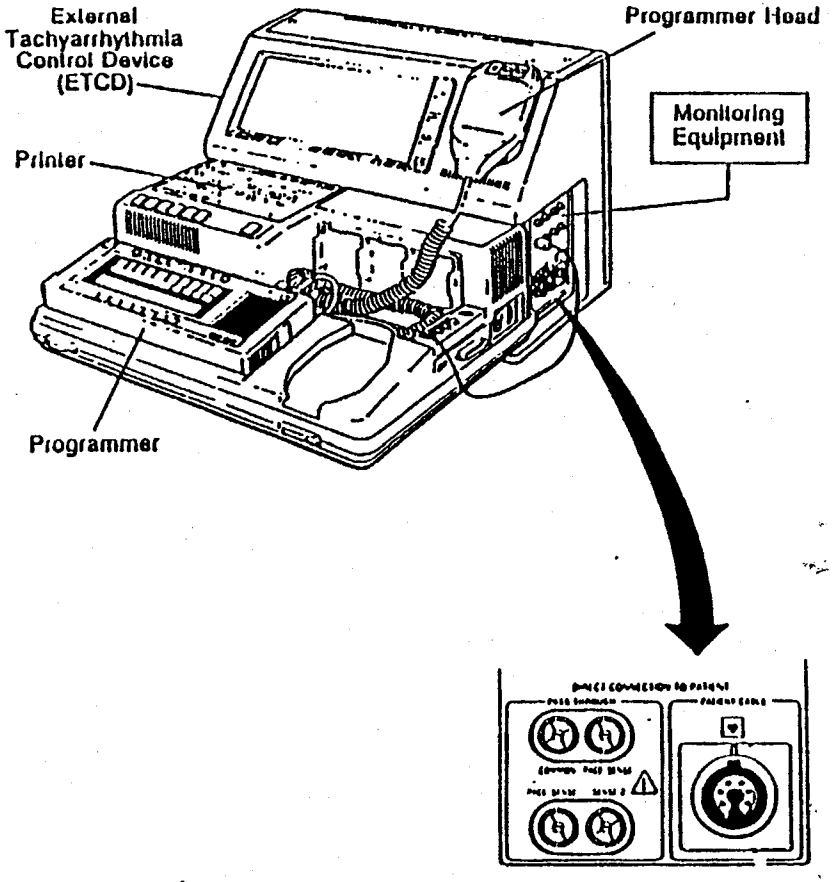

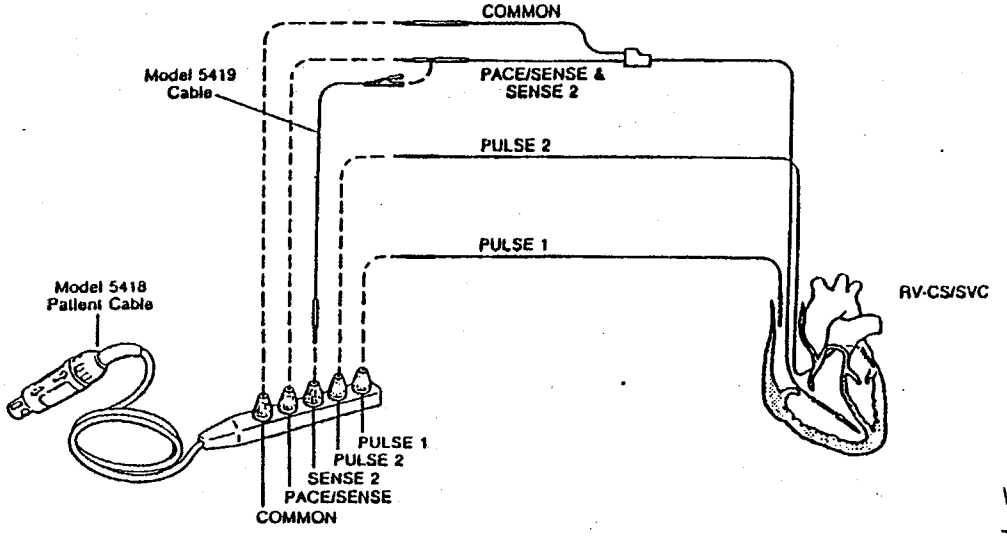

Connections to Model 5418 Patient Cable for
Typical Simultaneous or Sequential Pathway (RV-CS/SVC).

FIGURE III B-1

Active fixation leads are particularly beneficial for patients who have smooth or hypertrophic hearts where lead dislodgement may be potential a problem.

The three electrodes of this lead are the coil, ring, and helix:

The defibrillating **coil electrode** is most proximal to the pulse generator and connects electrically to the connector pin of the unipolar leg of the bifurcation. This unipolar leg will not accept a stylet.

The **ring electrode** is proximal to the helix and connects electrically to the connector ring of the bipolar leg of the bifurcation.

The **helix tip electrode** is most distal to the pulse generator and provides active fixation in the endocardium. It can be extended or retracted by rotating the lead connector pin with a special fixation tool. The helix electrode connects electrically to the connector PIN of the bipolar leg of the bifurcation. This bipolar leg is the only one that will accept a stylet.

The helix tip electrode and the ring electrode may be used for bipolar pacing and sensing; the coil electrode is intended to be used for delivery of cardioversion and defibrillation pulses.

The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

Model 6999 Lead

The Medtronic Model 6999 Unipolar, Subcutaneous, Oval, Patch Lead features an electrode for the delivery of cardioversion and defibrillation therapies. It is intended for long-term use and is designed to be used with an implantable tachyarrhythmia control device along with at least one complementary defibrillating electrode and a pacing/sensing lead; a third defibrillating electrode may also be used.

The lead has application for patients in whom implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

Intended Uses - PCD Device

The Model 7217B PCD device is intended for use in patients who are at high risk of sudden death due to ventricular tachyarrhythmia.

Current medical research indicates that such patients should:

- have survived at least one episode of a cardiac arrest, presumably due to a ventricular tachyarrhythmia as evidenced by resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; or

- in the absence of a prior cardiac arrest, have recurrent, sustained ventricular tachycardia that occur spontaneously or can be induced, despite the most efficacious antiarrhythmic drug therapy that can be tolerated chronically.

Extensive electrophysiologic evaluation and testing of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the Model 7217B PCD device. Before permanently programming the PCD device to the automatic detection and delivery of the VT and/or VF therapies, the patient should have demonstrated a satisfactory response to the proposed therapy.

Intended Uses - ETCD

The Model 5355 External Tachyarrhythmia Control Device is intended for use in conjunction with an antitachycardia/defibrillation lead system during diagnostic studies for implanting the Model 7217B PCD device.

Indications for use of the ETCD include:

- Patients experiencing recurrent episodes of ventricular tachyarrhythmia,

- Patients who survived a cardiac arrest due to a ventricular tachyarrhythmia and are at risk for repeated episodes,

- Patients who are undergoing an assessment of the efficacy of antitachycardia pacing, cardioversion, or defibrillation therapies in anticipation of an implantable cardioverter-defibrillator.

Components of the System

A list of components used in the system is given below. It is separated into a listing of those components for which market approval is sought and those components that are now commercially available. Market approval is not being sought for use of the PCD Device with other manufacturers transvenous defibrillation lead systems or for the use of the PCD Transvene lead system with other manufacturers implantable cardioverter defibrillators.

Seeking Approval:

Transvene Leads
- Model 6963
- Model 6966
- Model 6999

Pacer-Cardioverter-Defibrillator (PCD) Device*
- Model 7217B

External Tachyarrhythmia Control Device (ETCD)*
- Model 5355 ETCD
- Model 5418 Patient Cable
- Model 5419 Patient Cable
- Model 5414 Test Load
- Model 5417 EGM Cable

Programmer Software Cartridge*
- Model 9788 - Memory Module for 7217B PCD Device and 5355 ETCD Devices

Lead Accessories*
- Model 6701 Lead End Cap

Commercially Available:

Programmers Model 9710 and accessories

Printers Model 9751/9712

* Indicates devices pending FDA approval, P900061

Components Used in the Implantable Configuration

The implantable configuration is composed of a PCD Device, lead system, and a 9710 Programmer with applicable software cartridge. The implantable device is a Model 7217B PCD Device. The PCD device requires an appropriate lead system consisting of up to three cardioversion/defibrillation electrodes. See Figure III B-2. The Transvene leads used with the Model 7217B PCD Device are the Models 6963, 6966, and 6999.

The Model 9710 Programmer is commercially available. Two printers are also commercially available. When higher printing speeds are desired, it is recommended that the programmer be used with the faster printer, the Model 9751. If slower printing speeds are acceptable, as may be the case in some follow-up situations, the Model 9710 Programmer can be used with the battery-powered Model 9712 Printer.

Components used in the External Configuration

The external tachyarrhythmia control system is composed of the Model 5355 ETCD, a Model 5418 Patient Cable, a Model 5419 cable, lead system, and a Model 9710 Programmer with applicable software cartridge, see Figures IV-A-3, 4. The ETCD uses replaceable batteries as its power source. The Model 5418 Patient Cable and Model 5419 Cable are designed to connect the Transvene leads to the ETCD. Like the implantable system, the ETCD uses the same Transvene leads (Models 6963, 6966, and 6999).

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FIGURE III B--2
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Non-Thoracotomy Lead System for PCD

Model 6963 Coronary Sinus or Superior Vena Cava

Model 6966 Right Ventricle

Subcutaneous Patch

Model 6999

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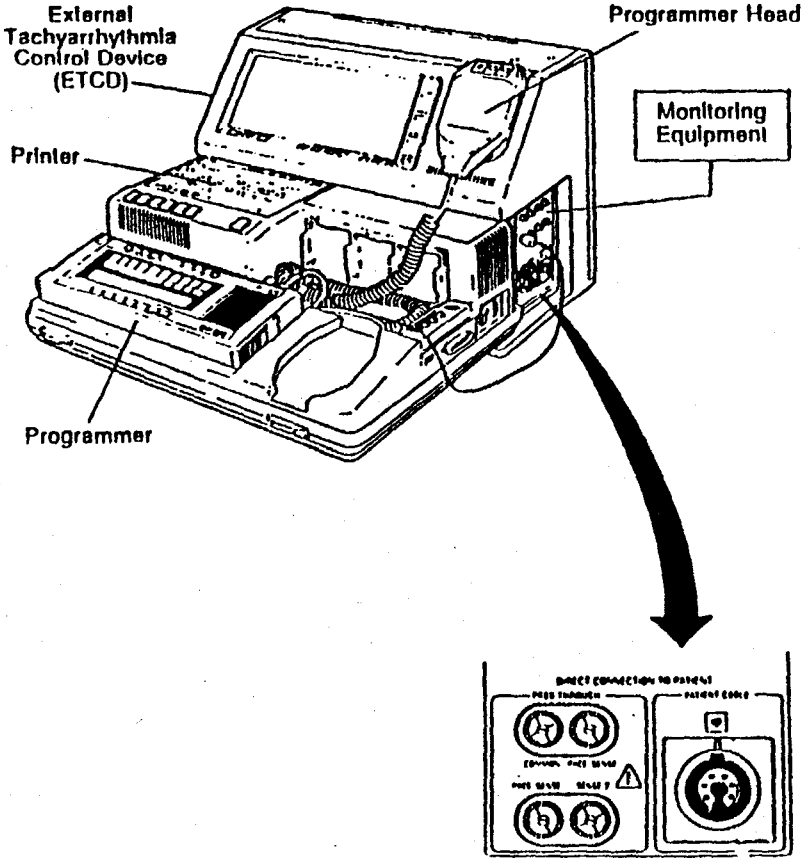

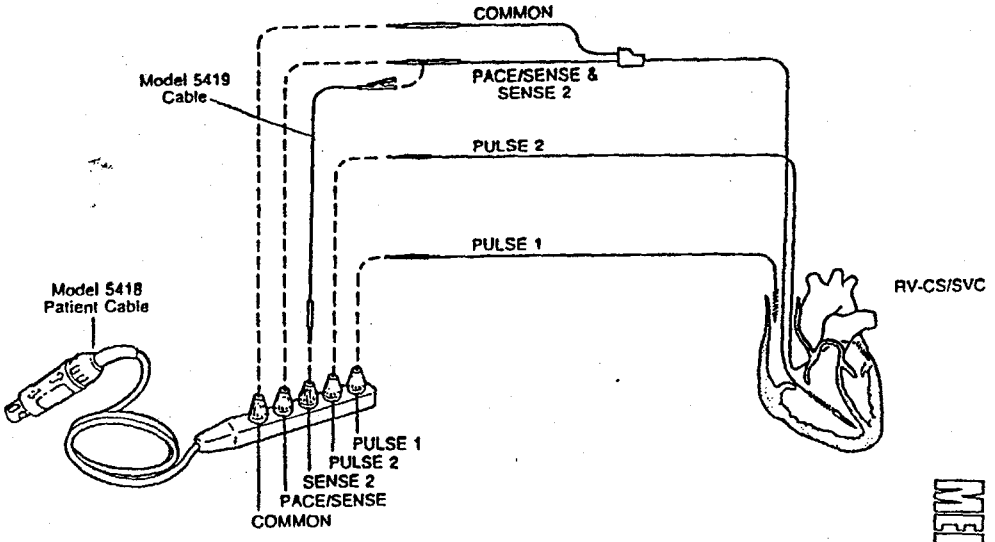

Connections to Model 5418 Patient Cable for
Typical Simultaneous or Sequential Pathway (RV-CS/SVC).

Figure IV-A-3

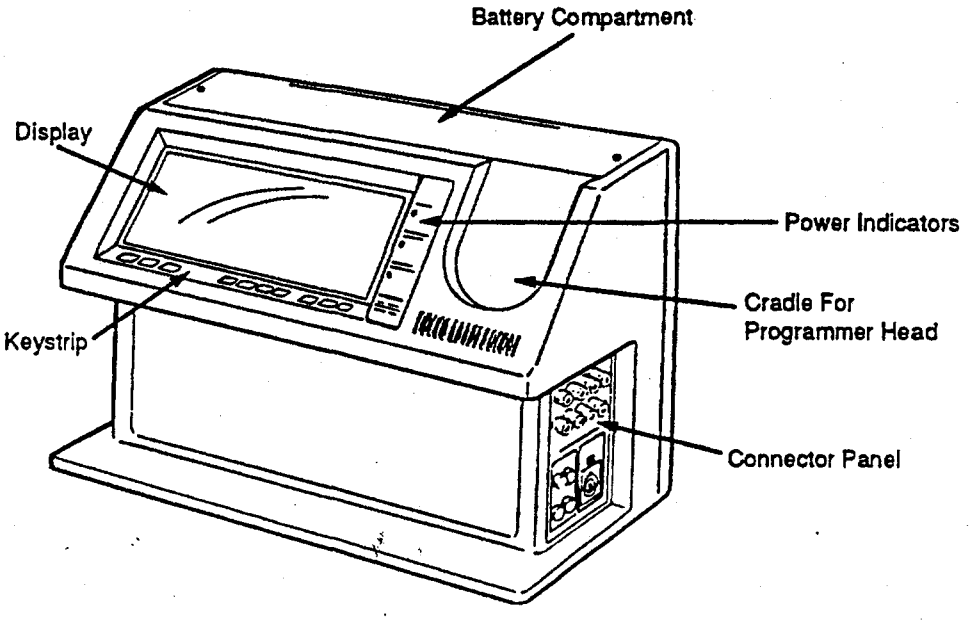

Figure IV-A-4. Model 5355 External Tachyarrhythmia Control Device

Purpose of the System

PCD System Configuration

The PCD Device is an implantable device designed to detect episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF), and upon detection, automatically deliver the appropriate therapy or a progression of therapies programmed by the physician for each patient. The available therapy types that can be programmed are overdrive pacing, cardioversion, and defibrillation. The PCD Device also has bradycardia pacing capability. The Transvene leads allow the PCD device to deliver these therapies to the heart.

ETCD System Configuration

The ETCD is an external tachyarrhythmia control device designed to deliver overdrive pacing, cardioversion, defibrillation, and bradycardia therapies in the same fashion as the PCD device. The ETCD can be programmed to automatically deliver overdrive pacing therapy upon detection of VT. When used as a component of a system that includes the appropriate Medtronic programmer and applicable software cartridge, the ETCD can deliver manually-initiated VT pacing, cardioversion, and defibrillation therapies. The ETCD allows the assessment of the Transvene lead system characteristics and aids in the assessment of lead system pacing and sensing characteristics.

Overview of System Features

General

The PCD device is designed to automatically detect episodes of VT or VF and, upon detection, deliver the appropriate programmed pacing, cardioversion, or defibrillation therapies. The device has two independently programmable detection and therapy procedures, one for VT and a second for VF.

When used as a component of a system that includes the appropriate Medtronic programmer and dedicated software, the ETCD is designed to deliver manually initiated cardioversion and defibrillation therapies. The ETCD is also designed to detect episodes of VT and VF. It can automatically deliver VT overdrive therapies (burst and ramp) upon detection of a VT.

VT Detection and Therapy

Both the PCD device and ETCD use a VT detection algorithm which can use up to three separately programmable criteria as it monitors the cardiac cycle length to identify the presence of a tachycardia. Upon detection, the devices deliver their first programmed VT therapy. If the VT episode persists and is again detected, up to three additional independently programmable VT therapies may be delivered to restore the patient's normal cardiac rhythm. This progression of four VT therapies can be tailored to each patient's need. For the PCD device the therapies may be selected from two methods of overdrive pacing (burst and ramp) and synchronized cardioversion.

For the ETCD the same overdrive pacing therapies can be automatically delivered, with cardioversion therapy being available as a manual therapy.

VF Detection and Therapy

The VF Detection algorithm monitors the cardiac cycle length to identify a VF episode. Upon detection, the PCD device provides a programmable high energy defibrillation pulse for VF therapy. Up to a maximum of four VF therapies may be delivered for ongoing detected VF episodes. Each defibrillation therapy consists of one (single pulse) or two (simultaneous or sequential) high voltage pulses designed to restore the normal cardiac rhythm.

For the ETCD, each cardioversion or defibrillation therapy, which must be initiated manually via the programmer, also consists of one high-voltage pulse or two (simultaneous or sequential) high-voltage pulses in the same fashion as the PCD devices.

Bradycardia Therapy

For both the ETCD and PCD devices, bradycardia pacing is delivered in the VVI mode. Asynchronous, (VOO), pacing is not available, and is avoided even with magnet application since this type of pacing has increased potential to initiate ventricular arrhythmias in patients receiving this system.

Lead Systems

The PCD Device and the ETCD perform pacing, sensing, cardioversion, and defibrillation through multiple electrodes in the lead system. Listed below are the electrodes and their function:

- The PACE/SENSE electrodes are incorporated in the right ventricular defibrillation lead. These electrodes function as the sensing circuit and deliver pacing pulses. The PACE/SENSE electrodes are used for sensing in conjunction with the SENSE2 electrode.
- The COMMON electrode is an electrode coil that serves as the cathode for cardioversion, defibrillation, and pacing.
- The PULSE2 electrode is an electrode coil that serves as the anode for cardioversion and defibrillation.
- The PULSE1 electrode is an optional electrode coil that serves as an additional anode for sequential and simultaneous cardioversion and defibrillation.

Cardioversion and defibrillation current pathways are between the PULSE2 and COMMON electrode coils and, if the additional lead is implanted, between the PULSE1 and COMMON electrode coils.

Other Capabilities

The physician may use the ETCD or the PCD devices to conduct noninvasive electrophysiologic studies (EPS) via the programmer with the appropriate software cartridge. The physician can also manually deliver various therapies via the programmer to manage an induced or spontaneous tachyarrhythmia.

The PCD device will provide the physician with information, via the Programmer, about its present programmed status and data on its operation accumulated between office visits. This information may be printed and retained in the patient's file.

The PCD Device and ETCD can also transmit an electrogram to the programmer. The electrogram is the electrical signal sensed on the leads.

A programmer-generated set of symbols, termed Marker Channel™, allows real-time visualization of sensing, pacing, detection, and therapy events occurring within the device.

In addition, the ETCD provides a display of measurements and other information related to delivered cardioversion and defibrillation pulses. With this information and other features, the ETCD can be used to assess the suitability of the lead system and its placement for individual patients.

PCD Battery Longevity Expectations

The longevity of the Model 7217B PCD Device depends upon several factors, including programmed bradycardia pacing parameters, the percentage of paced to sensed events, the pacing load, and on the frequency of high voltage capacitor charging. The longevity projections found in Table IV-A-1 apply under the following conditions:

- 65 ppm pacing rate,
- 5.4 V pacing pulse amplitude,
- 0.49 ms pacing pulse width, and
- 500 ohm pacing lead.

Projected Longevity[1]
Table IV-A-1

Pacing/Sensing	34 Joule Charging Frequency	Average Longevity Model 7217B
100% Sensing	Quarterly	5.0 years
15% Pacing	Monthly	4.2 years
100% Pacing	Monthly	3.4 years

The longevity of the device decreases with the following:

- An increase in pacing rate,
- An increase in pacing amplitude,
- A decrease in pacing impedance,
- An increase in pacing pulse width,
- An increase in the percentage of bradycardia paced to sensed events, or
- An increase in the charging frequency.

Each 34 Joule charging cycle will typically decrease the longevity of the device by approximately four to six days.

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[1] These preliminary longevity projections are based upon accelerated battery data and device modeling. With the stated condition, 100% pacing and monthly 34 Joule charging cycles, the minimum longevity of the device will be 2.5 years (7217B). Average refers to the projected mean longevity of the modeled run of PCD devices at the stated conditions. Minimum longevity means that virtually all (i.e., 99.9%) of all modeled production run of PCD devices will attain the value given.

C. Alternative Practices and Procedures

The use of implantable defibrillators in patients with drug refractory ventricular tachycardia/ fibrillation (VT/VF) and in survivors of sudden cardiac death has reduced the arrhythmic mortality in these patients. Other treatments available to treat ventricular tachyarrhythmias include antiarrhythmic drug therapy, ventricular tachycardia surgery, transthoracic defibrillation and other market released implantable defibrillators with epicardial defibrillation lead systems.

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D. Marketing History

All of the Medtronic Tachyarrhythmia Control System device components which have been implanted in the U.S. to date have been part of the IDE clinical study and have followed the FDA approved investigational protocol. In November 1991, the Medtronic PCD Transvene System, and respective components described in this submission, were market released in Europe. In March 1991, the Medtronic PCD Epicardial System, and respective components, were market released in Europe. And in February 1992, the FDA Advisory Panel recommended the approval of the Medtronic PCD Epicardial System.

E. Adverse Effects

Potential adverse effects which may be associated with the use of the PCD Device include but are not limited to: failure to detect ventricular tachycardia or ventricular fibrillation; failure to terminate ventricular tachycardia or ventricular fibrillation; delivery of pacing or shock therapy when no ventricular tachyarrhythmia is present, which would precipitate an episode of ventricular tachycardia or ventricular fibrillation; acceleration of a ventricular arrhythmia; failure to capture after a shock delivery; discomfort or pain during or following the delivery of electrical shock; or infection.

The following additional, potential adverse effects associated with all pacemaker systems include loss of normal pacemaker function due to battery failure or other component failure, inability to program a pacemaker pulse generator because of programmer failure, infection, erosion, undesired muscle or nerve stimulation, and inadequate sensing or pacing. Any demand pulse generator can be affected by magnetic, electrical and electromagnetic signals of sufficient strength or with characteristics which mimic cardiac function. Possible effects of electrical interference on pulse generator operation include reversion to asynchronous pacing, inhibition of output pulses and rapid synchronous pacing. Certain environmental sources can couple sufficient energy into a cardiac pacing system to damage the pulse generator or cardiac tissue adjacent to the electrodes.

Failure of the pulse generator system to function properly may result in the patient experiencing the symptoms for which the pulse generator was originally indicated.

The potential complications related to the use of the PCD Transvene Lead System include, but are not limited to, the following patient-related conditions: fibrillation, air embolism, cardiac perforation, heart wall rupture, cardiac tamponade, pericardial rub, infection, myocarditis, constrictive pericarditis, pneumothorax and hemothorax. Other potential complications related to the lead system include, but are not limited to, the following: lead dislodgement, lead conductor fracture, and insulation failure.

The above referenced information is provided in the labelling of the PCD Transvene System.

F. Summary of Studies

To validate the performance of the Medtronic Tachyarrhythmia Control System nonclinical laboratory (bench) testing, animal studies and human clinical trials were performed. All of the nonclinical bench and animal testing demonstrated that the devices are safe and performed according to design intent.

The nonclinical laboratory (bench) testing provides information relative to the Model 6966, Model 6963 and Model 6999 Transvene Leads, Model 7217B PCD, Model 5355 ETCD, and Model 9788 Memory Module.

The animal studies were performed to evaluate acute and chronic performance PCD Transvene System and to validate that the PCD and ETCD System are safe for human use.

Finally, human clinical trials were performed to evaluate the safety and effectiveness of the PCD Transvene System in treating patients with life-threatening ventricular arrhythmias.

All of the studies have demonstrated that the PCD Transvene System functions safely and is appropriate for human use.

The following summaries are provided in this section.

1. Model 6966, Model 6963 and Model 6999 Nonclinical Testing

2. Non-clinical Testing of the Related Components of the Transvene Lead system: Models 7217B PCD, Model 5355 ETCD and Model 9788 MemoryMod Model 7217B PCD Nonclinical Testing

3. Animal Testing

4. Clinical Study of the PCD Transvene System

1. Model 6966, Model 6963 and Model 6999 Defibrillation Leads: Summary of Nonclinical Testing

To validate the performance of the Medtronic Tachyarrhythmia Control System nonclinical laboratory (bench) testing, animal studies and human clinical trials were performed. All of the nonclinical bench and animal testing demonstrated that the devices are safe and performed according to design intent.

The nonclinical laboratory (bench) testing provides information relative to the Model 6963 CS/SVC lead, Model 6966 RV lead, Model 6999 SQ patch lead, and related system components.

a. Electrical Testing

Electrical D.C. resistance testing was performed to ensure proper functioning of the Model 6963, 6966 and 6999 leads.

Seventeen Model 6963, thirty-five Model 6966 and eighteen Model 6999 leads were submitted for testing. Electrical resistance was measured utilizing a milliammeter under ambient room conditions. All samples measured were within the individual design specifications.

b. Environmental Analysis Testing

The purpose of the testing was to subject the lead to temperature extremes to determine the lead's resistance to the thermal stresses when transported from extremes of climate.

Thermal Shock

Fifteen Model 6963 and thirty-five Model 6966 leads were subjected to five cycles from -45°C to 70°C with a soak time of thirty minutes at each temperature extreme with a transfer time of one minute. Thirty-five Model 6999 leads were subjected to five cycles from -40°C to 66°C with a soak time of thirty minutes at each temperature extreme with a transfer time of one minute.

After the thermal shock testing was completed visual inspection and electrical resistance measurements were performed. There were no visual defects and the electrical D.C. resistance of all the samples met the design specification.

c. Mechanical Testing

The purpose of the mechanical testing was to determine the mechanical integrity of the leads to ensure that the devices are safe, reliable, and suitable for their intended use and conform to design specifications. The leads and/or assemblies were subjected to the following:

- flex testing
- composite pull strength testing
- crimp/weld pull strength testing
- insertion/withdrawal force testing
- A.C. impedance/leakage testing

Flex Testing

The flex testing consisted of mounting the insulated conductor coils and uninsulated electrode coils of the Models 6963, 6966 and 6999 in a lead flex test fixture. The insulated conductor coils and uninsulated electrode coils were flexed under ambient room conditions at a specified radius. Eleven samples were used in each test. Samples exceeded specifications and therefore are considered to be satisfactory for their intended use.

Lead Joint Tensile Strengths

Pull testing of the various lead joints is conducted to ensure that the integrity of the joint meets the design specification and is, therefore, adequate for its intended application. The testing conducted consists of a composite pull test which evaluates the overall pull strength of the lead and crimp pull testing that evaluates the crimped connections of the leads to assure specification conformance.

Composite Pull Strength

Leads were boiled in Ringer's solution or soaked in normal saline and pull tested, while wet (the lead is usually cut in half to facilitate fixturing limitations) utilizing a tensile testing machine. The samples were pulled until failure at a rate of five inches per minute. The initial failures were then analyzed statistically for the confidence level in meeting the specification for the composite lead which is 1.0 lb. minimum.

Model 6963 data demonstrates that with a 95% confidence at least 97% (distal) and 99.9% (proximal) of the leads will meet or exceed the specification.

Model 6966 data demonstrate that with a 99% confidence at least 99.9% of the leads will meet or exceed the specification.

Model 6999 data demonstrate that with a 99% confidence at least 99.9% of the leads will meet or exceed the specification.

Therefore, Models 6963, 6966 and 6999 leads, with respect to composite pull strength, are adequate for their intended use.

Crimp/Weld Pull Strengths

Crimp and weld pull strength tests were conducted to evaluate the strength of the connections to ensure that they meet the design specification and are, therefore, adequate for their intended application. The connections tested are:

- Distal crimp sleeve to conductor coil crimp (6963)
- Double crimp core to conductor coil crimp (6963)
- Electrode coil to double crimp core weld (6963)
- Electrode coil to distal crimp sleeve weld (6963)
- Tip crimp sleeve to conductor coil crimp (6963)
- Connector pin to conductor coil crimp (6963 and 6999)
- Helix electrode to inner conductor coil crimp (6966)
- Electrode ring to middle conductor coil crimp (6966)
- Transition sleeve to electrode coil weld (6966)
- Transition sleeve to outer conductor coil crimp (6966)
- Fixed connector pin to outer conductor coil crimp (6966)
- Connector ring to middle conductor coil crimp (6966)
- Rotating connector pin to inner conductor coil crimp (6966)
- Manifold crimp sleeve to conductor coil crimp (6999)
- Manifold crimp sleeve to electrode coil (24 turns per inch) crimp (6999)
- Manifold crimp sleeve to electrode coil (48 turns per inch) crimp (6999)

Subassemblies were submitted for testing and pull tested by using a tensile testing machine. The samples were pulled until failure at a rate of four inches per minute.

Pull strength testing consisted of a minimum of 15 subassemblies of each crimp connection and a minimum of 7 subassemblies of each weld connection All samples tested exceeded the individual specification. The test results indicated that with a 95% confidence, at least 95% of the leads will have crimp and weld strengths that exceed the specification.

Therefore, the Model 6963, 6966 and 6999 leads, with respect to crimp and weld connection pull strengths, are adequate for their intended use.

Insertion/Withdrawal Forces

Insertion/withdrawal forces are measured to ensure compatibility with the implantable device without causing damage to the lead. Twenty five each of the lead Models 6963, 6966 and 6999 were tested with the Model 7217B PCD Device connector modules. There were no physical changes and all measurements met the design specification.

A.C Impedance/Leakage Testing

Fluid leakage tests are conducted on the lead assemblies/implantable device connector to determine leakage. Ten of each lead model Models 6963, 6966 and 6999 were tested with the Model 7217B connector modules. A.C. impedance was measured from the PCD device case to the lead connections while immersed in fluid. All samples met the design specification.

d. Biocompatibility Testing

The materials used in the Models 6963, 6966 and 6999 that are directly exposed to body tissue are:

- Polyurethane
- Silicone rubber (methylvinylpolysiloxane)
- Silicone rubber/titanium dioxide
- Platinum/Iridium

These materials have been shown to be biocompatible through many years of use in Medtronic permanent implantable endocardial/myocardial permanent pacing leads. In addition to extensive implant experience with these materials, standard biocompatibility tests have been performed to verify the biocompatibility of the above-listed materials. Testing has demonstrated that all materials are nonhemolytic, nonpyrogenic, nontoxic, nonmutagenic and biocompatible. Therefore, the materials passed the tests and are considered suitable for human implant. The materials used in the Models 6963, 6966 and 6999 are identical to those used in other commercially available Medtronic pacing leads.

e. Lead System (Life) Testing

In addition to the aforementioned tests, the Transvene leads were subjected to system, or life, testing. Further testing also evaluated the leads with respect to crush resistance. Testing included subjecting the leads to soaking, flexing and high-voltage pulsing. A separate test evaluated crush performance. The purpose of these tests was to subject the leads to severe conditions and assess the overall integrity of the system.

D.C. resistance values and intermittance data measured before and after being subjected to soaking, multiple flexing and high voltage pulsing, as well as crushing, demonstrated the non-thoracotomy leads satisfied requirements and are therefore acceptable for their intended use.

2. Non-clinical Testing of the Related Components of the Transvene Lead system: Models 7217B PCD, Model 5355 ETCD and Model 9788 MemoryMod

Non-clinical testing of these components was provided Volume 4 of the original PMA application (P900061) dated September 27, 1990, Volume 3 of the amendment dated March 8, 1991, and Volume 2 of the amendment dated August 30, 1991. A summary of the test results for each of the components is provided.

Model 7217B PCD: Summary of Nonclinical Testing

Testing of the Model 7217B pulse generators and the peripheral devices that comprise the system, i.e., the Pacing System Analyzers, the Model 9710 Programmer utilizing the Model 9788 MemoryMod and the Model 9751 Printer have been tested and found to be acceptable. All aspects of system interaction and operation are in accordance with the Model 7217B PCD Device and Model 9788 technical manuals and system specifications. Therefore, the Medtronic Tachyarrhythmia Control System, in its entirety, is acceptable for its intended use.

Model 9788 Memory Module: Summary of Nonclinical Testing

The Medtronic Model 9788 MemoryMod Cartridge was designed for insertion into the commercially available Model 9710 Programmer. When inserted, it becomes an integral part of the non-invasive programming system for the implantable PCD devices to establish pacing, ventricular tachycardia (VT) detection and therapy, ventricular fibrillation (VF) detection and therapy, and electrophysiological study (EPS) capabilities of an implanted pacemaker/ cardioverter/defibrillator (PCD). Both the Model 7217B PCD device and the Model 5355 ETCD are programmed with the Model 9788 MemoryMod cartridge when used with the Model 9710 Programmer.

Testing of the Model 9788 MemoryMod cartridge has demonstrated conformance to specification requirements. Therefore, the Model 9788 MemoryMod is acceptable for its intended use with the Model 7217B PCD Devices and the Model 5355 ETCD Device.

Model 5355 ETCD: Summary of Nonclinical Testing

Testing of the Model 5355 ETCD and respective accessories has shown conformance to specification requirements. Therefore, the Model 5355 ETCD Device/accessories are acceptable for their intended use.

3. Animal Testing

The information presented in this section is an accumulation of several studies, some of which FDA has previously reviewed in IDE submissions (G870102). These studies demonstrate the safety of the Transvene lead Models 6963, 6966 and 6999.

A variety of non-thoracotomy leads were evaluated in a series of four canine studies. Descriptions of the leads, as well as the study number(s) (1, 2, 3 or 4) in which they were evaluated, are presented below.

Description: Non-thoracotomy Leads

CORONARY SINUS/SUPERIOR VENA CAVA LEADS

Model 6963, evaluated in Study No. 4, is a silicone, unipolar, coronary sinus or superior vena cava lead with a 6.5 mm connector and platinum alloy electrode for delivery of cardioversion and defibrillation therapies.

Model 6881, evaluated in Study Nos. 2, 3 and 4 is functionally equivalent to the Model 6963 except the 6881 has a 3.2 mm connector.

Model 10285, evaluated in Study No. 1, is the temporary version of the Model 6963/6881.

RIGHT VENTRICULAR LEADS

Model 6966, evaluated in Study No. 4, is a polyurethane, tripolar, extendable/retractable, screw-in lead with a 6.5 mm connector and platinum alloy electrode for delivery of cardioversion and defibrillation therapies. Additionally, the 6966 has a 3.2 mm connector for pacing and sensing.

Model 6884, evaluated in Study Nos. 2 and 3, is functionally equivalent to the Model 6966 except the 6884 has a 3.2 mm connector in place of the 6.5 mm connector for the cardioversion-defibrillation electrode.

Model 10284, evaluated in Study No. 1, is the temporary version of the Model 6966/6884.

SUBCUTANEOUS PATCH LEADS

Model 6999, evaluated in Study No. 4, is a silicone, unipolar, oval, subcutaneous patch with a 6.5 mm connector and platinum alloy electrode coils that are partially embedded in the silicone patch for delivery of cardioversion and defibrillation therapies. Additionally, the patch is embedded with polyester/dacron mesh.

Model 6895, evaluated in Study Nos. 2 and 3, is functionally equivalent to the Model 6999 except the 6895 has a 3.2 mm connector and is covered with polyester/dacron mesh.

Model 10317, evaluated in Study No. 3, is functionally equivalent to the 6895 except it is embedded on the outer edge with polyester/dacron mesh.

Although model numbers differ, all leads in each of the three groups are functionally equivalent. The various model numbers reflect an evolution of temporary to transvenous lead development, as well as minor changes, such as the connector pin modification from 3.2 mm to 6.5 mm.

Additional devices were used to evaluate the non-thoracotomy lead studies in canines. These are described below.

External Devices for Implant Support

Model 5355 External Tachyarrhythmia Control Device (ETCD)

The Model 5355 ETCD provides the same detection capabilities as the implantable Model 7217B PCD Device. Therapies are identical except that the maximum output energy is 40 joules (J) and automatic defibrillation and cardioversion are not available in the Model 5355. The Model 5355 ETCD provides measurement and display of output waveform parameters and ETCD status, an isolated electrogram signal, and passthrough connections of pacing and sensing electrodes to external instrumentation.

Model 2394 External Cardioverter/Defibrillator (ECVD)

The Model 2394 ECVD instrument can deliver: (1) a single stimulation pulse on one output channel, or (2) a pair of pulses, delivered individually on the two different output channels.

Monophasic and biphasic pulses are provided, output capacitance can be varied between 10 and 150 microFarads (mf) depending on which external capacitor modules are used, and pulse width can be specified as a fixed duration (0.1-19.9 ms) or "tilt" (10-90%). Pulse output voltages can range between 50 and 1090 volts and may be delivered asynchronously (upon manual command) or synchronized with an intrinsic sensed event.

Model 2376 External Cardioverter/Defibrillator (ECVD)

The output stimulation parameters of the Model 2376 are very similar to those of the Model 2394 except for the following modifications:

- All pulses are monophasic, truncated, exponential waveforms.
- Output capacitance is fixed at 50 microFarads and pulse width is determined by a fixed pulse duration only.
- Pulse output voltages can range between 50 and 1090 volts and may be delivered asynchronously (upon manual command) or synchronized with an intrinsic sensed event.

Study Methods

All canine studies were conducted according to the 1966 and 1970 Animal Welfare Acts, 1985 NIH Laboratory Animal Use and Care Guidelines and GLP regulations. Adult mongrel canines were used for all studies. The dogs weighed 20 kg or more.

Specific details of each study are presented in the following "Animal Studies/Results" section.

Each study is briefly described below. Both acute and chronic studies were performed to assess the toxicity of the non-thoracotomy lead system as well as its stability over time.

Study #1: Acute Toxicity Testing of Non-thoracotomy Leads

The objective of this study was to quantify the amount and nature of shock-induced damage to the myocardial tissue resulting from multiple, high energy defibrillation shocks delivered through transvenous defibrillation leads and a subcutaneous patch. This information has previously been submitted to the agency in the Non-

Thoracotomy IDE, reference Document Control Number G870102/S23; FDA Approved October 4, 1990. Lead models evaluated in this study are functionally equivalent to the Models 6963, 6966 and 6999. Results of these studies revealed only minimal shock-induced necrosis (<0.1-0.5 percent by weight), which did not result in functional impairment of the cardiac tissue. Therefore, the use of the Model 6963, 6966 and 6999 leads did not result in significant myocardial damage in canines and could be safely implanted in humans.

Study #2: Model 6881, 6884 and 6895 Chronic Lead Evaluation

The objective of this study was to evaluate the suitability of the lead system for human clinical use. Lead models evaluated in this study are functionally equivalent to the Models 6963, 6966 and 6999. Study results demonstrate that the performance of the non-thoracotomy lead system when used with the PCD and ETCD devices is in conformance with system design and expected operation.

One canine in this study has presented with two mastocytomas; a common type of skin tumor in middle-aged canines. This observation is not related to the PCD system, nor is it relevant to the clinical application of the PCD system. The tumors were excised and the animal remains in good health.

Study #3: Model 6881, 6884 and 6895 Chronic Lead Defibrillation Study

This study is an evaluation of the chronic stability of the non-thoracotomy lead system via the monitoring of defibrillation and pacing thresholds. In addition, histopathological examinations have been performed to assess the amount and nature of shock-induced damage to the myocardial tissue resulting from defibrillation shocks. Lead models evaluated in this study are functionally equivalent to the Models 6963, 6966 and 6999. Results demonstrate stable pacing, sensing and defibrillation thresholds over time. Additionally, histopathology analysis shows no cardiac tissue damage due to delivery of defibrillation shocks.

Study #4: Model 6963, 6966 and 6999 Chronic Lead Defibrillation Study

This study is an ongoing evaluation of the non-thoracotomy lead system to assess chronic defibrillation threshold stability, pacing thresholds, intracardiac sensing capabilities and tissue damage. Results indicate the lead system performs as intended; DFTs and pacing thresholds have remained stable throughout the study (60 weeks) and intracardiac sensing is appropriate. Additionally, pathology data, to date, indicates minimal localized trauma to the cardiac tissue (<0.05 percent by weight).

Conclusion

All of these canine studies have demonstrated that the non-thoracotomy lead system, which includes the Model 6963 CS/SVC lead, 6966 RV lead and 6999 SQ patch lead, functions safely and is therefore appropriate for human use.

4. Summary of Clinical Experience

A. Introduction

The efficacy and safety of implantable cardioverter defibrillator (ICD) therapy for recurrent ventricular tachycardia (VT) and ventricular fibrillation (VF) has been well established. The current market released device provides defibrillation therapy for VF or hemodynamically unstable VT, however, this type of therapy may not be optimal for patients with stable, well tolerated VT that is amenable to antitachycardia pacing. It is necessary to perform a significantly more invasive procedure, a thoracotomy, in order to implant the epicardial leads. Thus, the need to incorporate programmability, multiple detection and therapeutic options, and a less invasive lead system has lead to the development of a tiered therapy device, the PCD™ Transvene™ System.

This report represents a full report of Medtronic's clinical experience with the Medtronic PCD™ Model 7217B Multiprogrammable Tachyarrhythmia Control System with Transvene™ Cardioversion and Defibrillation Electrodes (Reference IDE G870102). The data included in this analysis is all data that was received by Medtronic and entered onto the clinical database as of June 24, 1992.

The PCD™ Model 7217B Multiprogrammable Tachyarrhythmia Control System described in this submission is identical to the system which was recommended for approval by the FDA advisory panel on February 3, 1992, with the addition of Transvene™ leads.

The data analysis is organized in functional rather than chronological categories in order to present a complete picture of each of the PCD™ Device's various functions. The sections included in this summary are:

- Indicated Patient Population/Therapeutic Options
- PCD Therapy Applications
- Indicated Patient Population
- Study Objectives and Protocol Summary
- Overview of Clinical Experience
  - Implant Data
  - Spontaneous VT/VF Episode Experience
  - Overall Success Rate
- Complications and Observations
- Inactive Patients
- Patient Deaths

- Clinical Experience by Primary Indication
- Patients not Meeting Implant Criteria
- Comparison to AICD Clinical Experience
- Comparison to PCD™ Epicardial Clinical Experience
- PCD™ Transvene™ System Performance

This summary provides an overview of the clinical experience which verifies that the PCD™ Transvene™ System is safe and effective in the indicated patient population.

B. Indicated Patient Population

B.1 Patient Population

The PCD™ Transvene™ System is intended to treat patients at risk of sudden cardiac death due to ventricular tachyarrhythmias which have been shown to be reliably terminated, and in the case of VF, terminated at an energy level below the maximum output of the PCD™ Device.

Results provided in this application will support Medtronic's request for market release of the PCD™ System for use in the following patient population:

- Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or

- Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

Malignant ventricular tachyarrhythmias remain a major unsolved problem in the management and prevention of coronary artery disease. It is estimated that 450,000 people experience sudden cardiac death annually, and 80%-90% of these events are caused by ventricular fibrillation. (Gillum RF. Sudden coronary death in the United States. Circulation 1989; 79:756-765.)

Survivors of out-of-hospital cardiac arrest not associated with acute myocardial infarction are at risk for recurrent cardiac arrest as reported by Wilber, et al.(Wilber, et al. Out-of-Hospital Cardiac Arrest - Use of Electrophysiologic Testing in the Prediction of Long-Term Outcome. NEJM 1988;

Vol.318:19-24.). In this study group of 166 survivors of out-of-hospital cardiac arrest, ventricular arrhythmias were inducible in 131 patients (79%) and were suppressed by antiarrhythmic drug therapy or surgery (or both) in 91 patients (72%). During a median follow-up of 21 months, cardiac arrest recurred in 29 patients: 11 in whom inducible arrhythmias had been suppressed, 12 in whom inducible arrhythmias persisted and 6 in whom arrhythmias could not be induced at initial electrophysiologic study.

C. PCD™ Transvene System Therapy Applications

The PCD™ System is intended to treat patients at risk of sudden cardiac death due to ventricular tachyarrhythmias and/or recurrent ventricular tachycardia.

For this patient population, the primary benefits from the use of the PCD™ System center on the detection and termination of life-threatening ventricular arrhythmias. The use of the PCD™ Transvene™ system allows for the application of identical therapies as an epicardial system without requiring an open chest procedure for implantation of the lead system. This less invasive surgical approach allows the system to be applied in patients who may not be able to undergo an open chest procedure. The use of pacing therapies for the treatment of ventricular tachycardia reduces patient trauma associated with higher energy cardioversion pulses and extends the longevity of the PCD™ pulse generator.

The PCD™ System allows the titration of therapies for patients with ventricular tachycardia while providing critical defibrillation backup. Multiple detection algorithms are designed to allow the device to distinguish ventricular tachycardia from sinus tachycardia and atrial fibrillation. In addition, independent detection algorithms for VT and VF allow the delivery of different types of therapy for each of these two arrhythmias. The incorporation of antitachycardia pacing algorithms allows the use of pacing for the termination of well tolerated ventricular tachycardia. These algorithms, which are rate adaptive, can adapt to changes in the ventricular tachycardia and successfully terminate the episode. Defibrillation therapy is important in the event that an episode of VT accelerates to VF whether spontaneously or as a result of a delivered therapy. The incorporation of multiple cardioversion and defibrillation pathways (SINGLE, SEQUENTIAL and SIMULTANEOUS) allows the

physician to provide an adequate cardioversion/defibrillation efficacy safety margin for all patients. The capacity to provide programmable extrastimuli pacing allows noninvasive electrophysiologic studies to be performed. The potential benefits from permanent cardiac pacing provide support for chronic and transient episodes of bradycardia.

Finally, the benefits of programmability of tachyarrhythmia detection and therapy parameters, VVI parameters, and stored telemetry data on the delivery of therapy may avert the need for reoperation in the event of changing patient conditions or complications.

D. Study Objectives and Protocol Summary

The clinical study was designed to evaluate the operation, safety and effectiveness of the PCD™ System components in detecting and treating episodes of ventricular tachycardia and ventricular fibrillation.

The analysis focuses on data supporting the safety and effectiveness of the PCD™ system, including the implantable pulse generator and associated transvenous lead system and its therapy in this patient population. The analysis includes the clinical experience with the PCD™ system, pace/sense, detection and therapy functions in both the acute and chronic implant settings. In addition, data is provided on clinical observations, clinical complications and deaths in this patient population. The analysis will also provide data demonstrating the safety and effectiveness of the Model 5355 ETCD.

This summary presents safety and efficacy evaluation performed on 757 patients, 329 of which have implant durations equal to or greater than six months.

Clinical data was collected at the following study points to support the safety and efficacy of the PCD™ System:

Pre-implant Patient Assessment
Lead System Testing at Implant
Implantable Pulse Generator Testing at Implant
Pre-hospital Discharge Testing
Follow-up Evaluation 1 and 3 months post implant then at 3 month intervals

Patients were evaluated prior to hospital discharge and/or one (1) month post implant, three months post-implant and then at intervals of every three months. In some cases additional testing was performed at physician discretion to evaluate spontaneous events and/or potential clinical complications.

Medtronic collected all clinical data on the PCD™ System and its components under the clinical protocol outlined in the Investigational Plan. A common protocol was used on all study patients on a worldwide basis.

International centers were subject to the appropriate requirements (e.g., the Declaration of Helsinki) in order that the data met the statutory requirements of the FDA. All clinical data, U.S. and International, obtained with the PCD™ System with Transvene™ Leads is included in this report.

E. Overview of Clinical Experience

This report covers a total of 762 implants in 757 patients of the PCD™ Device with the Transvene™ Defibrillation Lead System. A total of 78 investigative centers participated in the clinical trial with 35 centers in the U.S. and 43 Internationally. The first implant occurred internationally on October 20, 1989, and the first implant in the U.S. occurred on October 16, 1990. Table E-1 shows the distribution of Model 7216A and Model 7217B patients between U.S. and International investigators.

PCD™ Transvene™ System Implant Distribution			
	Total	U.S.	Int'l
7216A	18 (2.4%)	3 (0.7%)	15 (4.8%)
7217B	744 (97.6%)	444 (99.3%)	300 (95.2%)

Table E-1: PCD™ Transvene™ System - Implant Distributions - 6/24/92

The mean documented implant duration for this patient population is 5.6 months and ranged from implant to 28.6 months. The cumulative implant duration is 4246.4 months. There are 329 patients with implant durations equal to or greater than six months. Table E-2 provides a data summary on these patients. Also included is the data summary of the patients with 6 months of follow-up.

PCD™ Transvene™ System Follow-Up Quantity by Data Form Type											
PHD	1 M	3 M	6 M	9 M	12 M	15 M	18 M	21 M	24 M	27 M	Other
753	631	496	322	182	113	63	39	14	8	4	548

Table E-2: PCD™ Transvene™ System - Follow-Up Quantity - 6/24/92

The patient population enrolled in the clinical trial was predominately male (80.6%) with a mean age of 59.4 years. In half of the patients (49.8%), the primary indication for implant was recurrent, sustained ventricular tachycardia without an episode of sudden cardiac death. Sudden Cardiac Death was the primary indication for 37.1% of the patients and SCD in combination with recurrent, sustained VT was the primary indication in 13.1%. Coronary artery disease was the primary heart disease in 74.1% of the patient population with a mean reported ejection fraction of 35.6% Table E-3 provides a data summary on these patients. Also included is the data summary of the patients with 6 months of follow-up.

PCD™ Transvene™ System Data Summary		
	All Patients (3 Electrode Systems)	Patients with 6 months of Follow-up
Number of Patients	757	329
Device Months Follow-up	4246.4	3367.8
Mean Follow-up Time	5.6 mo	10.2 mo
Maximum Follow-up Time	28.6 mo	28.6 mo
Number, % Male Number, % Female	610 80.6% 147 19.4%	264 80.2% 65 19.8%
Mean Age	59.4 yrs	58.0 yrs
Primary Indication: SCD VT SCD/VT	 281 37.1% 377 49.8% 99 13.1%	 130 39.5% 152 46.2% 47 14.3%
Coronary Artery Disease	561 74.1%	228 69.3%
Mean Ejection Fraction	688 35.6%	301 38.0%
Defibrillation Pathway: Sequential Simultaneous Single	 574 75.3% 178 23.4% 10 1.3%	 247 74.6% 77 23.3% 7 2.1%
Mean LED	16.0J (N=702)	15.4J (N=306)
Mean DFT	14.8J (N=316)	13.9J (N=155)
Spontaneous VT: Number of Patients Number of Episodes % Success	 226 5430 98.7%	 130 3752 99.0%
Spontaneous VF: Number of Patients Number of Episodes % Success	 198 973 99.1%	 120 667 98.7%
One Year SCD Survival	99.8%	100.0%

Table E-3: PCD™ System Data Summary - All Transvene™ Patients versus Transvene™ Patients with 6 mo Follow-up - 6/24/92

E.1 Implant Data

Implants of the PCD™ Device may use two or three Transvene™ leads. The physician has the flexibility to use whichever lead system best meets the patient's needs.

Table E-4 illustrates the lowest energy of defibrillation (LED) and defibrillation threshold (DFT) for the implanted lead systems. The implant criteria for the PCD™ Device was 3 of 4 episodes of VF successfully terminated at 18 Joules or less with a given lead configuration. Some patients did not have a LED at implant. The LED is only identified if the investigator reported the induced rhythm as VF. Conversion of VT or V Flutter (as defined by the physician) to sinus rhythm was not included in the determination of the LED. In addition, it is not a protocol requirement to obtain a DFT at implant. However, recommendations have been provided to those institutions that prefer to obtain DFT's during the implant procedure.

PCD™ Transvene™ System
Mean LED and DFT Values

Lead System	Implant Frequency	Mean LED	Implant Frequency	Mean DFT
All Systems	702	16.0J	316	14.8J
RV-SVC-SQ	455	16.7J	187	15.8J
RV-CS-SQ	210	14.6J	110	12.8J
RV-CS-SVC	37	15.2J	19	16.0J

Table E-4: PCD™ Transvene™ System - LED and DFT Values - 6/24/92

The mean implant Lowest Energy of Defibrillation (LED) for all lead systems was 16.0J and mean implant Defibrillation threshold (DFT) for all lead systems was 14.8J. As the mean DFT's and LED's indicate, VF was reliably terminated at an energy value below the maximum output (34 Joules) of the PCD™ Device.

E.2 Spontaneous VT and VF Episode Experience

A total of 311 patients (41.1%) have experienced a spontaneous ventricular tachyarrhythmia episode that has been detected and treated by the PCD™ Device. One hundred and thirteen patients (14.9%) experienced VT only, 85 patients (11.2%) experienced VF only and 113 patients (14.9%) experienced both an episode of VT and VF.

There have been a total of 6403 episodes of spontaneous VT or VF as detected by the PCD™. The overall PCD™ Device success rate in terminating spontaneous VT/VF episodes as detected by the PCD™ is presented in Table E-5.

PCD™ Transvene™ System Success Rate in Terminating Spontaneous VT/VF Episodes			
	Number of Episodes Successful	Total Number of Episodes	Efficacy Rate
VT	5362	5430	98.7%
VF	964	973	99.1%
Total	6326	6403	98.8%

Table E-5: PCD™ Transvene™ System - Success Rate for Spontaneous VT/VF Episodes - 6/24/92

E.2.1 Spontaneous VT

For the purposes of this clinical trial, spontaneous VT was defined as those episodes that satisfied the programmed VT detection criteria. Specifically, all programmed VT detection criteria must be fulfilled to detect a VT episode. Successful termination of the episode was defined as satisfying the VT episode termination criteria.

To date, 5430 spontaneous episodes of VT have been detected by the PCD™ Device in 226 patients. The mean number of episodes per patient with VT was 24 and ranged from 1 - 413 episodes.

Most spontaneous VT episodes (91.0%) were successfully treated with VT Therapy #1 and 98.7% were successfully treated with one of the four programmable VT therapies.

Of the 5362 successfully terminated spontaneous VT episodes, 92.4% were treated with one of the programmed antitachycardia pacing therapies incorporated in the PCD™ Transvene™ System. The clinical benefit of tiered therapy is the reduction of delivery of high energy shocks for the treatment of stable recurrent ventricular tachycardia. This greatly enhances the patient acceptance of ICD therapy since antitachycardia pacing is usually not perceived by the patient.

Thirty patients experienced 68 (1.3%) episodes in which the PCD™ Device was ineffective in terminating a spontaneous episode of VT despite delivery of all four programmed VT therapies. Twenty five patients experienced 45 (0.8%) episodes that were due to sinus tachycardia or atrial fibrillation/flutter (SVT) with a rapid ventricular response that had been detected as VT. These episodes were resolved with either modification of programmed parameters or of antiarrhythmic drug therapy. It should be noted that the PCD™ Device responded appropriately based on the programmed detection parameters.

The remaining 23 episodes occurred in five patients in which the programmed VT therapies were ineffective in terminating a spontaneous VT episode. **No patient deaths occurred as a result of ineffective VT therapy**. The patient's antiarrhythmic drug regimen was modified to improve efficacy.

E.2.2 Spontaneous VT Episode Experience By Primary Indication

The primary indications for implant of the PCD Transvene System were sudden cardiac death (**SCD**), recurrent sustained ventricular tachycardia (**VT**) and sudden cardiac death associated with recurrent

sustained ventricular tachycardia (SCD/VT). Spontaneous VT episode efficacy by primary indication is provided in Table E-6. The overall efficacy for spontaneous VT episodes is greater than 98% for each of the patient groups. There is no difference in therapy efficacy among the patient's indications. Table E-6 contains the spontaneous VT episode therapeutic efficacy.

PCD™ Transvene™ System Spontaneous VT Episode Therapeutic Efficacy By Primary Indication			
Indication	**# Episodes Successful**	**# Total Episodes**	**% Success**
SCD	762	765	99.6%
VT	3681	3735	98.6%
SCD/VT	919	930	98.9%
TOTAL	5362	5430	98.7%

Table E-6: PCD™ Transvene™ System - Spontaneous VT Episode Efficacy by Primary Indication -6/24/92

E.2.3 Spontaneous VT Episode Experience By Therapy Type

The PCD™ Device incorporates three programmable VT therapy types, RAMP, BURST and CARDIOVERSION, for the treatment of recurrent ventricular tachycardia. Spontaneous VT episode efficacy by programmed therapy type is provided in Table E-7.

PCD™ Transvene™ System Spontaneous VT Episode Efficacy By Programmed Therapy Type			
VT Therapy Type	**# Success**	**# Attempts**	**% Efficacy**
Ramp	2913	2661	91.3%
Burst	2539	2293	90.3%
Cardioversion	463	408	88.1%

Table E-7: Spontaneous VT Episode Efficacy by Therapy Type - 6/24/92

E.2.4 Spontaneous VF

For purposes of this clinical trial, VF is defined as those episodes that satisfy the programmed VF detection criteria. Specifically, all programmed VF detection criteria must be fulfilled to detect a VF episode. Successful termination of the episode is defined as satisfying the VF detection criterion for episode termination.

To date, 973 spontaneous episodes of VF have been detected by the PCD™ Device in 198 patients. The mean number of episodes per patient was 4.9 and ranged from 1 - 77 episodes. A review of the chart per investigator for this patient that experienced the 77 episodes of VF revealed that 75 were most likely due to atrial fibrillation. VF detection parameters were modified in this patient.

Most (87.3%) spontaneous VF episodes were successfully treated with VF Therapy #1 and 99.1% were successfully treated with one of the four programmable VF therapies.

Five patients experienced 9 episodes (0.9%) in which the PCD™ Device was ineffective in terminating a spontaneous episode of VF despite delivery of all four programmed VF therapies. Four patients had eight reported ineffective VF spontaneous episodes that were due to sinus tachycardia or atrial fibrillation with rapid ventricular response rather than VF. Reprogramming and pharmacologic intervention resolved these problems. The other patient (96223) required external defibrillation to convert the VF episode. This patient's antiarrhythmic drug regimen was modified to improve defibrillation efficacy. All of these patients have subsequently done well with no more reported ineffective VF therapies.

E.2.5 Spontaneous VF Episode Experience By Primary Indication

The primary indications for implant of the PCD™ Transvene™ System were sudden cardiac death (**SCD**), recurrent sustained ventricular tachycardia (**VT**) and sudden cardiac death associated with recurrent sustained ventricular tachycardia (**SCD/VT**). Spontaneous VF episode efficacy by primary indication is provided in Table E-8. There is no difference in therapy efficacy among the patient's indications. The overall efficacy for spontaneous VF episodes is greater than 98% for each of the patient groups.

PCD™ Transvene™ System Spontaneous VF Episode Therapeutic Efficacy By Primary Indication			
Indication	# Episodes Successful	# Total Episodes	% Success
SCD	289	296	97.6%
VT	420	421	99.8%
SCD/VT	255	256	99.6%
TOTAL	964	973	99.1%

Table E-8: PCD™ Transvene™ System - Spontaneous VF Episode Efficacy by Primary Indication -6/24/92

E.2.6 Spontaneous VF Episode Experience By Therapy Type

The PCD™ Device incorporates three programmable defibrillation pathways, SEQUENTIAL, SINGLE and SIMULTANEOUS, for the treatment of ventricular fibrillation. Spontaneous VF episode efficacy by programmed defibrillation pathway is provided in Table E-9.

PCD™ Transvene™ System Spontaneous VF Episode Efficacy By Programmed Therapy Type			
VF Therapy Type	# Success	# Attempts	% Efficacy
Sequential	781	789	99.0%
Simultaneous	183	184	99.5%

Table E-9: PCD™ Transvene™ System - Spontaneous VF Episode Efficacy by Therapy Type - 6/24/92

E.3 Overall Success Rate

Of the 757 patients who received a PCD™ Transvene™ System, 443 patients (58.5% - 443/757) have either experienced a spontaneous VT/VF episode or had VT/VF induced during a post implant electrophysiology study. The performance of the PCD™ Transvene™ System therapies have

been thoroughly evaluated and been shown to be effective in detecting and terminating episodes of ventricular tachyarrhythmia.

There have been no reports of a patient death due to the PCD™ Transvene™ System not detecting a spontaneous episode of VT or VF.

The overall success rate of the PCD™ Transvene™ System in terminating spontaneous episodes of either VT or VF was 98.8% with a VT success rate of 98.7% and VF success rate of 99.1%. The incidence of unsuccessful termination of an apparent "true" episode of ventricular tachycardia despite delivery of all four therapies was 0.4% (23/5430).

The incidence of unsuccessful termination of an apparent "true" episode of ventricular fibrillation despite delivery of all four therapies was 0.1% (1/973).

The evaluation of spontaneous episode experience indicates that the PCD™ Transvene™ System's VT and VF detection and therapy functions have performed safely and effectively in the indicated patient population.

F. Complications and Observations

The use of a multiprogrammable implantable cardioverter defibrillator (ICD) device allows the physician to resolve most relevant medical events by noninvasively changing programmed parameters thus, avoiding invasive procedures. However, there will continue to be certain relevant medical events which will require invasive procedures for resolution.

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following definitions:

COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

As of June 24, 1992, there have been a total of 138 complications identified in 138 patients and 157 observations identified in 157 patients in the PCD™ Transvene™ System patient population. Thus, 18.2% (138/757) of the patients have experienced a clinical event which was defined as a complication and 20.7% (157/757) of the patients have experienced a clinical event which was defined as an observation. Table F-1 summarizes how these events were reported with U.S versus International.

PCD™ Transvene™ System
Reported Complications/Observations
U.S versus International

	Complications	Observations
	# of Patients	# of Patients
U.S.	77	68
International	61	89
Total	138	157

Table F-1: PCD™ Transvene™ System Complications/Observations U.S. versus International - 6/24/92

Table F-2 summarizes the reported PCD™ Transvene™ System complications and observations by category. The category "Ineffective Therapies" included patients in whom increased defibrillation requirements were documented; "Inappropriate Therapies" includes patients in whom VT/VF therapies were delivered for nonpathological rhythms; "Pacing or Pace/Sense Related" includes patients in whom undersensing, oversensing or loss of capture was documented; "Infection Related" includes reports of pocket infection, seroma, and hematoma was documented; and "Device Related" includes patients in whom the device was explanted for reasons other than patient death, infection, or transplant.

The reported complications and observations are recognized clinical events that may occur with any of the current ICD devices. These complications and observations are discussed in the PCD™ device and Transvene™ manual. **None of the reported complications or observations have resulted in a patient death.**

PCD™ Transvene™ System Reported Complications/Observations By Category		
Category	**Complications**	**Observations**
Ineffective Therapies	0.8%	0.5%
Inappropriate Therapies	-	8.2%
Pacing or Pace/Sense Related	0.8%	4.1%
Infection Related - Device Explanted	2.0%	-
Infection Related - Device not Explanted	1.5	4.9%
Device Related	0.5%	-

Table F-2: PCD™ Transvene™System - Complications/Observations - 6/24/92

The "Lead Related" complications/observations include perforation, lead fracture, subcutaneous patch crinkling, and lead dislodgement. Table F-3 contains a summary of the reported "Lead Related" complications/observations.

PCD™ Transvene™ System Lead Related Complications	
Category	**Complication**
Right Ventricular Perforation	5 (0.7%)
Subclavian Vein Thrombosis	1 (0.1%)
Lead Fracture	4 (0.5%)
Subcutaneous Patch Crinkling	7 (0.9%)
Lead Dislodgement	33 (4.4%)

Table F-3: PCD™ Transvene™ System - Lead Related Complications - 6/24/92

There have been a total of 33 lead dislodgements reported in 33 patients at greater than 30 days. None of the lead dislodgements resulted in an ineffective therapy for a spontaneous VT of VF episode or patient death. Lead dislodgements were documented by fluoroscopic examination during electrophysiologic evaluation, chest x-ray obtained during routine follow-up, or during pacing/sensing threshold evaluation during routine follow-up. In all 33 cases, reoperation was required to reposition the lead and reestablish an effective defibrillation lead system.

Lead dislodgements are not specific to the PCD™ Transvene™ System and have been reported with dual chamber pacemakers and the current market released implantable cardioverter defibrillator (ICD) system. The early history of dual chamber pacemakers witnessed a high lead dislodgement rate of at least 20% (Smyth, PND, et al. Permanent pervenous atrial sensing and pacing with a new J-shaped lead. J Thoracic Cardiovascular Surgery. 1976;72:565-570). Winkle, et al reported that the incidence of dislodgement of the superior vena cava spring leads with the current market release ICD system to be 6.3%. (Winkle, et al. Automatic Implantable Cardioverter-Defibrillator: Efficacy, Complications, and Survival in Patients with Malignant Ventricular Arrhythmias. JACC. June 1988; Vol.11, No.6:1278-86).

G. Inactive Patients

There are a total of 34 patients who had received a PCD™ System and are no longer active in the study as of 6/24/92. Table G-1 shows the distribution of inactive patients by reason for no longer being active in the PCD™ Transvene™ System clinical study.

PCD™ Transvene™ System Inactive Patients	
Inactive Patients	**All Patients**
Patient Deaths	22
Infection (Explant)	11
Heart Transplant	5
Total	38

Table G-1: PCD™ Transvene™ System - Inactive Patients - 6/24/92

H. Patient Deaths

The positive impact of implantable cardioverter defibrillator (ICD) therapy on sudden cardiac death mortality has been well documented in the medical literature. The use of device therapy for the treatment of recurrent ventricular arrhythmias has become an accepted and important clinical tool. An analysis of the sudden cardiac death survival in the PCD™ Transvene™ System patient population was performed.

For purposes of the clinical study, each of the patient deaths was categorized using the following definitions:

Non-Cardiac:	Deaths that occurred where the primary cause of death was determined to be non cardiac in nature, e.g. stroke, cancer, etc.
Cardiac:	Deaths that occurred where the primary cause of death was determined to be cardiac in nature.
Non-Sudden:	Deaths that occur greater than one hour after the onset of symptoms.
Sudden:	Deaths that occur within one hour of the onset of symptoms or where the death is unwitnessed. Sudden cardiac deaths were also categorized as being Witnessed or Unwitnessed.
Perioperative:	Deaths that occur within thirty days of implant.
System Related:	A death which results from a malfunction (operation not according to design specification) of a PCD™ System component, or as a result of a device induced arrhythmia, or an interaction between a PCD™ System component and the patient.
Procedure Related:	A death which occurs as a result of a procedure required to implant, follow or test a PCD™ System.

All deaths and significant complications have been and will continue to be reviewed by a committee comprised of PCD™ Transvene™ System investigators and other physicians. Two committees (Clinical Event Review Committees) have been formed, one to review North American deaths and complications, and the other to review European clinical events. The primary purpose of these reviews was to determine whether the PCD™ System was related to the deaths or significant complications that have occurred and, if so, what changes may be required to prevent such events in the future.

There have been a total of 22 patient deaths reported in the PCD™ Transvene™ System patient population. Table H-1 summarizes how these patient deaths have been classified.

PCD™ Transvene™ System Summary of Death Classifications (n = 757)	
Classifications	**Number of Deaths**
Sudden Cardiac	3
Non-Sudden Cardiac	15
Noncardiac	4
TOTAL	22

Table H-1: PCD™ Transvene™ System - Summary of Death Classifications - 6/24/92

None of the patient deaths were attributed to a malfunction of the PCD™ Transvene™ System.

Actuarial survival analysis on the PCD™ Transvene™ System was done on all patients who were either evaluated for implantation or in whom the device was implanted. Thus, the analysis is done from the perspective of **intention to treat**. Those patients in whom the PCD™ Device was OFF at the time of death or in whom no device was implanted are included in the survival analysis. Those patients that were screened for a PCD™ Transvene™ System but failed to receive a Transvene™ system are not included in this analysis.

Projected one year survival calculations for the various death classifications are provided in Table H-2. **The actuarial projections include perioperative deaths only in the calculation of one year survival from death due to all causes (shown in the row labelled Overall).** The perioperative death rate defined as deaths which occurred within thirty days of implant was 0.7% (5/757) which is considerably less than the perioperative mortality for the PCD™ System with Epicardial leads (4.7% - 35/742). Included in this table are the projected one year survival calculations for patients who ultimately received a PCD™ Transvene™ System (n = 757) and all patients that were screened for a PCD™ Transvene™ System (n = 854) regardless of implant outcome.

PCD™ Transvene™ System One Year Actuarial Survival		
	Received PCD™ Transvene™ System	**Screened for a PCD™ Transvene™ System**
Sudden Cardiac Death	99.8%	99.8%
Non-Sudden Cardiac	96.8%	97.1%
All Cardiac	96.6%	97.0%
Noncardiac	99.4%	99.4%
Perioperative	0.7%	1.5%
Overall	95.3%	94.8%

Table H-2: PCD™ Transvene™ System - One Year Actuarial Survival - 6/24/92

The positive impact of the PCD™ Transvene™ System on patient mortality is clearly obvious from this analysis. The sudden cardiac death survival rate in this patient group is 99.8%, both in the patient group that received a Transvene™ System and those who were screened for a Transvene™ System. This is marked improvement when compared with the reported survival of similar patient groups treated with drug therapy alone of between 34% and 73% at one year.

I. Clinical Experience By Primary Indication

Medtronic is requesting approval for use of the PCD™ Transvene™ System in the following patient population:

* Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or

* Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

Sudden cardiac death without recurrent VT (SCD) was the indication for implant in 37.1% of the patients, recurrent ventricular tachycardia without an episode of sudden cardiac death (VT) was the

indication for implant in 49.8% of the patients, and sudden cardiac death and recurrent VT (SCD/VT) was the indication for implant in 13.1% of the patients.

The performance of the PCD™ Transvene™ System in these three groups are summarized in Table I.1.

In all three patient groups, coronary artery disease was the predominant heart disease and the patients exhibited moderate left ventricular dysfunction as demonstrated by mean ejection fractions of less than 40%. The mean LED at the time of implant was similar among the patient groups as was the mean DFT.

The overall efficacy in terminating spontaneous VT/VF episodes in the SCD patient group was 99.1%, in the VT patient group 98.7%, and in the SCD/VT group 99.0%. Thus, independent of the indication for implant, the PCD™ Transvene™ System was highly effective in terminating spontaneous episodes of VT/VF.

The one year sudden cardiac death survival rates for all groups was greater than 99.7%

This analysis indicates that the PCD™ Transvene™ System has performed safely and effectively in the indicated patient groups and should be approved for use in the indicated patient population.

PCD™ Transvene™ System
Data Summary by Primary Indication

	SCD	VT	SCD/VT	All Patients
# of Patients	281 (37.1%)	377 (49.8%)	99 (13.1%)	757
Number, % Male Number, % Female	212 75.4% 69 24.6%	309 82.0% 68 18.0%	89 89.9% 10 10.1%	610 80.6% 147 19.4%
Mean Age	56.8 yrs	61.2 yrs	60.0 yrs	59.4 yrs
Coronary Artery Disease	191 68.0%	292 77.5%	78 78.8%	229 72.2%
Mean Ejection Fraction	39.1% (N=259)	33.7% (N=339)	32.5% (N=90)	35.6% (N=688)
Defibrillation Pathway: Sequential Simultaneous Single	 201 71.5% 74 26.3% 6 2.2%	 295 77.6% 82 21.6% 3 0.8%	 76 76.8% 22 22.2% 1 1.0%	 574 75.3% 178 23.4% 10 1.3%
Mean LED	15.3J (N=264)	16.2J (N=351)	17.3J (N=87)	16.0J (N=702)
Mean DFT	14.0J (N=117)	15.5J (N=155)	13.9J (N=44)	14.8J (N=316)
Spontaneous VT: # of Patients # of Episodes % Success	 39 765 99.6%	 144 3735 98.6%	 43 930 98.9%	 226 5430 98.7%
Spontaneous VF: # of Patients # of Episodes % Success	 58 296 97.6%	 109 421 99.8%	 31 256 99.6%	 198 973 99.1%
1 Year SCD Survival	100.0%	99.7%	100.0%	99.8%

Table I-1: PCD™ Transvene™ System Data Summary by Primary Indication - 6/24/92

J. Patients Not Meeting Implant Criteria

J.1 Overview

The PCD™ Transvene™ System offers a simpler and safer implantation technique for an implantable cardioverter defibrillator system. In addition, the PCD™ Transvene™ System decreases the potential perioperative and long term mortality associated with current epicardial system implantation approaches.

There is a class of patients who cannot tolerate the thoracotomy required for the utilization of the epicardial patch lead defibrillation lead system and who are at high risk of sudden cardiac death. Because of the surgical risks and postsurgical complications associated with the implant of an epicardial lead system, implantation in the following patient groups may not be desirable or possible:

(1) patients in whom there is no indication for concomitant cardiovascular surgery at the time of ICD implant;

(2) patients with severe pulmonary disease who can not tolerate prolonged anesthesia or an open chest procedure;

(3) patients with severe congestive heart failure (ejection fraction < 40%) who are at increased risk for perioperative mortality following a thoracotomy procedure;

(4) patients who may eventually require open chest procedures for treatment of their coronary artery disease or cardiac transplant.

For these patients, a transvenous ICD System is the only therapy available. The PCD™ Transvene™ System simplifies and greatly reduces the risk associated with lead introduction, making therapy available to these patient groups. Because there is no need to open the chest of these patients, more options for future therapy remain available; e.g. CABG is associated with increased morbidity and mortality if there has been prior open chest surgery.

However, it is expected that nonthoracotomy lead systems will have higher mean implant defibrillation thresholds as compared to traditional epicardial lead systems. In an

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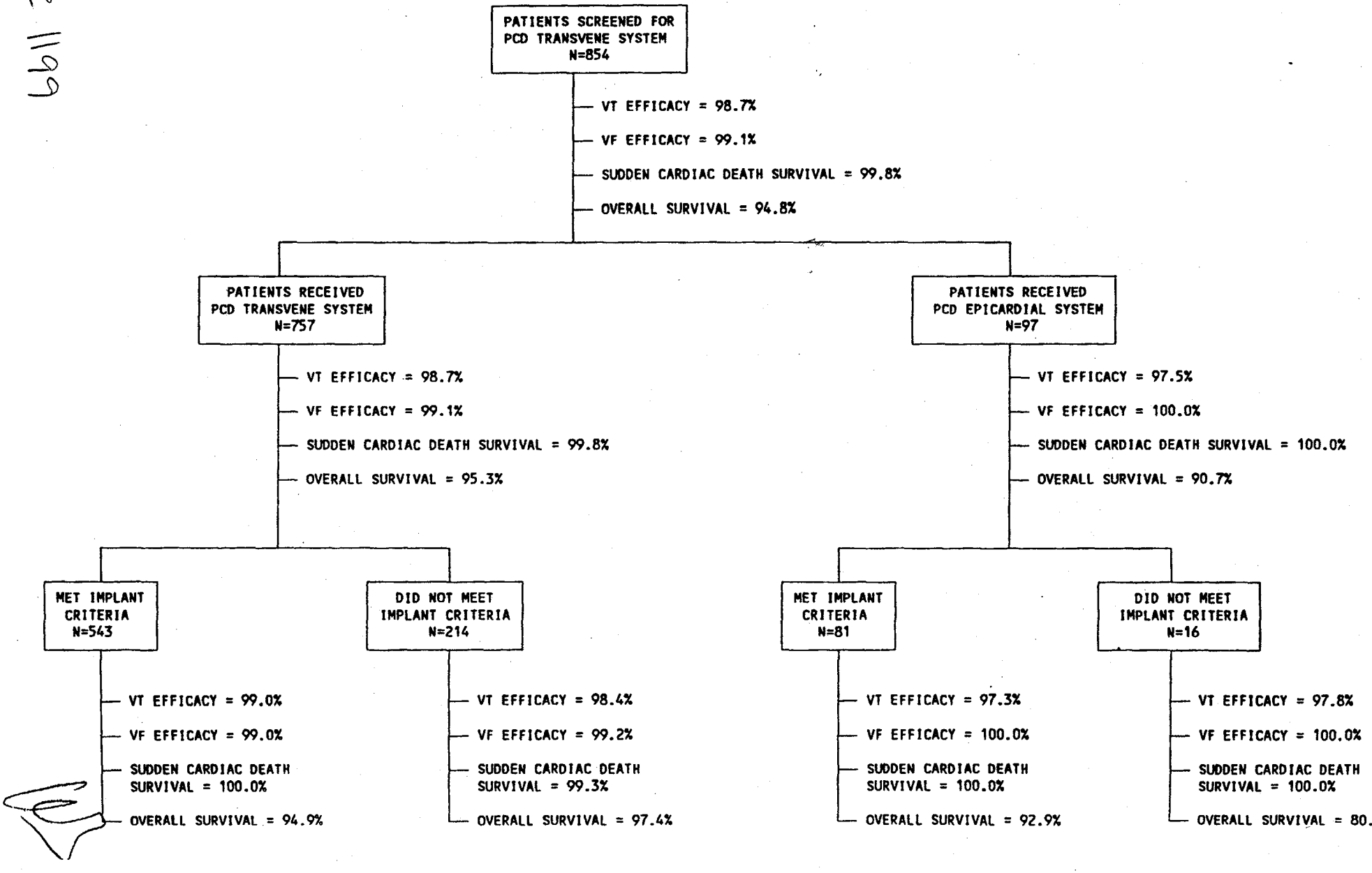
PCD™ TRANSVENE™ SYSTEM IMPLANT EVALUATION



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As can be seen, 88.6% (757/854) of the patients who were screened for a PCD™ Transvene™ System ultimately received the system. Of these 757 patients, 71.7% (543 patients) met the recommended defibrillation implant criteria which compares favorably with the predicted success rates published in the literature (Wilber et al). However, 28.3% (214/757) of the patients did not meet the recommended defibrillation efficacy implant criteria and still received the PCD™ Transvene™ System. It should be noted that 97.4% of the patients (737/757) received the PCD™ Transvene™ System with at least a 10 Joule defibrillation safety margin between the lowest energy of success (24J) and the maximum output (34J) of the PCD™ Device.

The investigators utilized this 10 Joule safety margin as a benchmark based on the clinical experience discussed in the article, Troup P., et al. The Implanted Defibrillator: Relation of Defibrillating Lead Configuration and Clinical Variables to Defibrillation Threshold. Journal of American College of Cardiology 1985; 6:1315-1321. Finally, and perhaps most importantly, the investigators also felt that for these patients the risk associated with not meeting the recommended implant criteria was outweighed by the risk of not implanting an ICD or implanting an epicardial system.

There were twenty patients (2.6%), who received a PCD™ Transvene™ System, whose cardiovascular condition precluded further completion of the PCD™ Transvene™ System and adequate definition of a defibrillation safety margin. In all cases, the physician felt that the benefit of the PCD™ Transvene™ System outweighed the risk of further inductions or the risk of a thoracotomy and elected not to evaluate or implant a PCD™ Epicardial System.

J.2 Patients Receiving PCD™ Transvene™ System & Did Not Meet Implant Criteria

For purposes of the PCD™ Transvene™ System, the implant criteria was defined as successful VF termination at least 3 times in 4 attempts with the final lead configuration at an output energy of 18 Joules or less. Of the 757 patients who **received** a PCD™ Transvene™ System, 214 patients (28.3%) did not meet the recommended defibrillation implant criteria and yet still received the PCD™ Transvene™ System. The physicians justification for implanting the PCD™ Transvene™ System despite not meeting the recommended defibrillation implant criteria are presented in Table J-1.

PCD™ Transvene™ System **Reasons for Not Meeting Implant Criteria Physician Justification**	
Reason	**Number of Patients**
Success at ≤ 24 Joules	170
Difficult/Unable to Induce VF	24
Patient Condition	20
TOTAL	214

Table J-1: PCD™ Transvene™ System: Physician Justification for Not Meeting Implant Criteria - 6/24/92

Further analysis of the patient who did not meet the recommended implant criteria indicates however, that 91% (194/214) had a 10 Joule safety margin between the lowest energy of successful defibrillation and the maximum output of the PCD Device (34J). Therefore, of the 757 patients who received a PCD™ Transvene™ System, 97.4% (737/757) had at least a 10 Joule defibrillation safety with the implanted lead configuration.

There were 20 patients (2.6%) in whom the implant procedure was terminated due to poor patient condition. These patients received a PCD™ Transvene™ System without at least a 10 Joule defibrillation safety margin. The implant circumstances of these patients is summarized as follows:

- At least one successful defibrillation was obtained at an energy level greater than 24 Joules and or equal to 34 Joules (N=11);

- Multiple inductions of VT were performed and successfully reverted with an energy level of 18 Joules or less. However, induced VF was not successfully reverted by an energy level of less than or equal to 34 Joules (N=6); and

- Physician elected to terminate the procedure due to the patient's condition before inductions with the final implanted lead configuration were performed (N=3).

Table J-2 provides a comparison of patient characteristics between patients who met the PCD™ Transvene™ System implant criteria and those patients who did not meet the implant criteria but still received the PCD™ Transvene™ System.

PCD™ Transvene™ System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Patient Characteristics		
Data	**Meeting Criteria**	**Not Meeting Criteria**
Number of Patients	543	214
Mean Follow-Up	6.2 months	4.0 months
Male*	422 (77.7%)	188 (87.9%)
Female	121 (22.35)	26 (12.1%)
Mean Age	59.4 yrs	59.6 yrs
Indication*		
SCD	209 (38.5%)	72 (33.6%)
VT	278 (51.2%)	99 (46.3%)
SCD/VT	56 (10.3%)	43 (20.1%)
Cardiovascular History		
CAD	396 (72.9%)	165 (77.1%)
Cardiomyopathy	173 (31.9%)	65 (30.4%)
Mean EF*	36.3%	33.7%
NYHA Class		
I	164 (30.9%)	53 (25.8%)
II	278 (52.4%)	114 (56.6%)
III	82 (15.4%)	34 (16.6%)
IV	7 (1.3%)	4 92.0%)
Number ON Drugs at Implant	223 (41.1%)	97 (45.3%)
Number ON Amiodarone	78 (14.4%)	38 (17.8%)

* (b)(4) (b)(4)

Table J-2: PCD™ Transvene™ System: Patients Meeting Implant Criteria vs Not Meeting Implant Criteria - Comparison of Pt Characteristics - 6/24/92

Statistical analysis indicated three significant differences between these two patient groups - patient sex, indication for implant and mean ejection fraction.

Patients not meeting implant criteria had a statistically higher percentage of patients who were male (b)(4) This difference reflects that the majority of patients with coronary disease with concomitant life threatening ventricular arrhythmias are males.

Analysis indicated the patients not meeting the implant criteria had a statistically higher percentage of patients whose primary indication for implant was sudden cardiac death associated with recurrent ventricular tachycardia (b)(4) This difference reflects the physicians use of the PCD™ Transvene™ System.

Finally, patients who did meet the implant criteria had a statistically lower mean ejection fraction ($p=0.0342$) which reflects a higher degree of underlying cardiovascular disease in these patients.

It should be noted, that none of these differences should be used as predictors for patients who should be screened for a PCD™ Transvene™ System.

In order to determine if the patient's not meeting implant criteria had higher risk for morbidity and mortality, a comparison of their clinical outcome was made with those patients who did meet the implant criteria. This comparison is provided in Table J-3.

PCD™ Transvene™ System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Implant Data		
Data	**Meeting Criteria**	**Not Meeting Criteria**
Number of Patients	543	214
Spontaneous VT Episode Efficacy	99.0%	98.4%
Spontaneous VF Episode Efficacy	99.0%	99.2%
Number of Patient Deaths	18	4
Perioperative Mortality	0.7%	0.5%
One Year Survival		
Sudden Cardiac	100%	99.3%
Non-Sudden Cardiac	96.4%	98.6%
All Cardiac	96.4%	97.9%
Noncardiac	99.2%	100%
Overall	94.9%	97.4%

Table J-3: PCD™ Transvene™ System: Patients Not Meeting Implant Criteria versus Patients Meeting Implant Criteria - Comparison of Clinical Outcome - 6/24/92

The two patient groups had similar efficacy in the treatment of spontaneous VT/VF episodes. Importantly, in the patient population who did not meet the implant criteria there were no patients who experienced actual spontaneous VF episodes where all programmed PCD™ Device therapies failed to terminate the episode.

In one patient (Patient ID (b)(4), (b)(4)) four programmed VF therapies were unsuccessful in terminating a spontaneous episode of VF. However, this was an inappropriate VF therapy delivered due to atrial fibrillation with a rapid ventricular response rather than VF. Reprogramming and modification of the patient's antiarrhythmic drug therapy corrected the problem. Thus, there were no patients who experienced an actual spontaneous VF episode where all four programmed VF therapies failed to terminate the episode.

There were eight patients (30 spontaneous VT episodes) where all four programmed VT therapies failed to terminate the episode. In four patients, the ventricular tachycardia was ineffectively terminated and the patient's drug therapy was modified in order to improve the efficacy of the programmed VT therapies. Four patients, three who experienced atrial fibrillation and the other sinus tachycardia, had episodes where all four VT therapies failed to terminate the " spontaneous VT episode". In all cases, the delivery of inappropriate VT therapy was resolved by modification of the patients' drug therapy.

There was no difference in the one year sudden cardiac survival or the overall survival in the two groups although follow-up was shorter for patients not meeting implant criteria (4.0 vs 6.2 months). This indicates, that despite not meeting the implant criteria these patients were not at higher risk of sudden cardiac death.

Finally, the survival of patients receiving a PCD™ Transvene™ System without meeting implant criteria (N=214) was compared to patients receiving a PCD™ Epicardial System without meeting implant criteria (N=92). This comparison is provided in Table J-4.

There were eight patients (30 spontaneous VT episodes) where all four programmed VT therapies failed to terminate the episode. In four patients, the ventricular tachycardia was ineffectively terminated and the patient's drug therapy was modified in order to improve the efficacy of the programmed VT therapies. Four patients, three who experienced atrial fibrillation and the other sinus tachycardia, had episodes where all four VT therapies failed to terminate the " spontaneous VT episode". In all cases, the delivery of inappropriate VT therapy was resolved by modification of the patients' drug therapy.

There was no difference in the one year sudden cardiac survival or the overall survival in the two groups although follow-up was shorter for patients not meeting implant criteria (4.0 vs 6.2 months). This indicates, that despite not meeting the implant criteria these patients were not at higher risk of sudden cardiac death.

Finally, the survival of patients receiving a PCD™ Transvene™ System without meeting implant criteria (N=214) was compared to patients receiving a PCD™ Epicardial System without meeting implant criteria (N=92). This comparison is provided in Table J-4.

PCD™ Transvene™ System Patients Not Meeting Implant Criteria Survival Analysis versus PCD™ Epicardial System Patients Not Meeting Implant Criteria Survival Analysis		
	PCD™ Transvene System Not Meeting Implant Criteria	PCD™ Epicardial System Not Meeting Implant Criteria
Number of Patients	214/757 (28.5%)	92/742 (12.4%)
Number of Deaths	4	13
Sudden Cardiac	99.3%	97.9%
Non-Sudden Cardiac	98.6%	100%
Noncardiac	100%	95.2%
Overall*	97.4%	83.8%

* Statistically Significant ($p \leq 0.05$)

Table J-4: PCD™ Transvene™ System: Patients Not Meeting Implant Criteria - PCD Transvene System vs PCD™ Epicardial System - 6/24/92

Though the PCD™ Transvene™ System had a higher incidence of patients not meeting implant criteria (28.5%) compared to the PCD™ Epicardial System (12.4%), there was no statistical difference in the sudden cardiac death patient survival. However, the overall survival of patients not meeting implant criteria with the Transvene™ System was significantly better ($p=0.001$) when compared to the PCD™ Epicardial System patients not meeting implant criteria, 97.4% and 83.3%, respectively.

The investigators felt in every case that the testing performed at the time of implant, though it did not meet the recommended implant criteria, did provide an adequate demonstration of device effectiveness and justified the implant of the PCD Transvene System. Finally, there have been no patients deaths secondary to unsuccessful termination of a spontaneous VT or VF episode in this patient population.

J.3 Description of Patients Not Meeting Implant Criteria

As noted previously, the patients not meeting implant criteria (N=214) were divided into three groups (1) Successful defibrillation

at an energy level of equal to or less than 24 Joules [79.4% of the patients]; (2) Difficult to induce VF [11.2% of the patients]; and (3) Implant procedure terminated due to poor patient condition [9.4% of the patients]. These patient groups are reviewed in the following discussion.

Lowest Energy of Defibrillation < 24 Joules

There were 170 patients in whom the PCD™ Transvene™ System was implanted with a defibrillation safety margin of at least 10 Joules. Table J-5 provides an overview of these patients clinical experience.

These data indicate that the final implanted PCD™ Transvene™ System was evaluated and significant attempts were made to meet the recommended implant criteria. In most of these patients (79.4%), a safety margin of 10 Joules was obtained between the successful defibrillation energy (24 J or less) for ventricular fibrillation and the maximum output of the PCD Device (34 J). The investigators decided in certain circumstances that this was appropriate demonstration of device effectiveness and that the PCD™ Transvene™ System could be implanted.

Of these patients, 148 (87.1%) have had VF induced at a chronic follow-up visit and in each case, VF was successfully terminated by the PCD Transvene System. In addition, 31 patients (18.2%) have experienced a spontaneous VF episode with an overall efficacy of 100%.

Thus, the clinical outcome in these patients was not adversely affected by not meeting implant criteria since their spontaneous VF episode efficacy was 100% and the one year sudden cardiac death actuarial survival was also 99.1%. The duration of follow up, however, is limited to an average of 4 months.

PCD™ Transvene™ System **Patients Not Meeting Implant Criteria** **10J Safety Margin Provided**	
Number of Patients	170
Lowest Energy of Defibrillation	
1 Success with 10J Safety Margin	87
2 Success with 10J Safety Margin	58
3 Success with 10J Safety Margin	18
> 3 Success with 10J Safety Margin	7
Overall Spontaneous VF Episode Efficacy	100%
One Year Survival	
Sudden Cardiac	99.1%
Overall	97.6%

Table J-5: PCD™ Transvene™ System: Patients Not Meeting Implant Criteria with 3/4 Successes at ≤ 24 Joules Clinical Experience - 6/24/92

Difficult to Induce VF

There were 24 patients who did not meet the recommended PCD™ Transvene™ System implant criteria because at least three episodes of VF were not induced at the time of implant. Of these, 15 patients had ventricular tachycardia induced and successfully reverted. The remaining 9 patients had ventricular flutter induced and successfully reverted. In all 24 patients, the lowest successful energy was equal to or less than 18 Joules.

The indication for implant was sudden cardiac death (SCD) in 6 patients (25%), recurrent ventricular tachycardia (VT) in 13 patients (54.2%) and sudden cardiac death associated with recurrent ventricular tachycardia (SCD/VT) in 5 (20.8%) patients. Thus the majority of the patients, 75%, had documented recurrent ventricular tachycardia as part of their ventricular tachyarrhythmia history. Eight of the these patients (33.0%) were on Amiodarone therapy which may have contributed to the inability to induce VF.

Of the 24 patients who did not meet the recommended PCD™ Transvene™ System implant criteria because at least three episodes of VF were not induced at the time of implant, 8 patients (33.3%)

have experienced a spontaneous VF episode and 19 patients (79.2%) have had VF induced during a chronic follow-up. In all cases, VF was successfully reverted by the PCD™ Transvene™ System.

There have been no reported patient deaths in the patient group with a resultant one year sudden cardiac death and overall actuarial survival of 100%.

Patient Condition

There were 20 patients in whom the implant procedure was terminated due to poor patient condition. These patients received a PCD™ Transvene™ System without at least a 10 Joule defibrillation safety margin. The implant circumstances of these patients is summarized as follows:

- At least one successful defibrillation was obtained at an energy level greater than 24 Joules but less than 34 Joules (**N=11 patients**);
- Multiple inductions of VT were performed and successfully reverted with an energy level of 18 Joules or less. However, induced VF was not successfully reverted by an energy level of less than or equal to 34 Joules (**N=6 patients**); and
- Physician elected to terminate the procedure due to the patient's condition before inductions with the final implanted lead configuration were performed (**N=3 patients**).

The mean ejection fraction of this group was 26.9%, indicating more severe underlying cardiovascular disease, and may have contributed to the physicians decision to terminate the implant procedure prior to meeting implant criteria. This group had a mean of 6.8 VF inductions, 2.2 lead configurations evaluated and a mean duration of VT/VF for the implant procedure of 220 total seconds. The circumstances of the implant procedures, mainly the duration of induced ventricular tachyarrhythmia and associated hemodynamic compromise, limited the number of inductions that could be performed and whether the recommended implant criteria could be met.

Of these twenty patients, ventricular fibrillation has been induced at a chronic follow-up visit in 15 patients (75%) and in all cases successful defibrillation with the implanted PCD™ Transvene™ System was documented.

The overall spontaneous VF episode efficacy for this patient group was 92.6% however further reviewed indicated that one patient experienced atrial fibrillation that was detected as VF and in whom all four programmed VF therapies were ineffective. This patient's antiarrhythmic drug therapy was modified and there were no further reports of ineffective therapies.

Thus there have been no patients who have experienced an actual spontaneous VF episode where all four programmed VF therapies failed to terminate the episode.

There has been one reported patient death, (Patient (b)(4), (b)(6)) which was classified as non-sudden cardiac secondary to end stage heart failure. The one year sudden cardiac death survival in this patient population is 100% while the overall one year survival was 93.8%. This lower overall one year survival may due to the lower mean ejection fraction of this patient group.

The clinical outcome in these twenty patients was not adversely affected by not meeting implant criteria since there was no reports of failure to terminate a spontaneous VF episode and the overall one year sudden cardiac death survival was 100%.

K. Comparison to AICD System Experience

K.1 Overview

The current AICD Epicardial System is implanted only with a defibrillation lead system requiring a thoracotomy. The PCD™ Transvene™ System allows the implantation of an implantable cardioverter defibrillator (ICD) system without the potential increased perioperative morbidity and mortality associated with a thoracotomy. This allows the application of ICD therapy in patients who may not otherwise be candidates for this type of therapy. Though the PCD™ Transvene™ System will have complications and observations that are specific to the lead system, the overall

performance should be at least equivalent to that reported with the current AICD Epicardial System.

This section provides a comparison of the PCD™ Transvene™ System clinical experience to that of the reported AICD Epicardial System clinical experience. The following areas will be discussed:

- Patient characteristics
- Clinical performance
- Survival analysis

For purposes of comparison, the Ventak-P Epicardial System patient population described in the Summary of Safety and Effectiveness Data (PMA Application Number P890061) dated May 2, 1991 will be used. A copy of this summary was obtained through the Freedom of Information Act.

K.2 Comparison of Patient Characteristics

In comparing the clinical experience with the PCD™ Transvene™ System to the reported Ventak-P Epicardial System clinical experience, it is important to determine that the patients who received the device are comparable.

The characteristics of the patients receiving the PCD™ Transvene™ System were compared to the characteristics of patients discussed in the Ventak-P Summary of Safety and Effectiveness Data and are presented in Table K-1. There were no differences between the two patient groups.

PCD™ Transvene™ System Comparison of Patient Characteristics PCD™ versus AICD		
	PCD™	**Ventak-P**
Number of Patients	757	292
Mean Follow-Up Time	5.6 months	6.8 months
% Males **% Females**	610 (81%) 147 (19%)	231 (79%) 61 (21%)
Mean Age	59.4 years	61.5 years
Primary Indication: **SCD** **VT** **SCD/VT**	 281 (37%) 377 (50%) 99 (13%)	 49 (16%) 169 (59%) 73 (25%)
Coronary Artery Disease	561 (74%)	228 (78%)
Mean Ejection Fraction	35.6%	34%
Drug Therapy at Implant	42%	45.0%
Concomitant Surgery	0%	18.0%

Table K-1: Comparison of Patient Characteristics, PCD™ versus Ventak-P 6/24/92

The two patient groups are comparable in mean age and mean ejection fraction. Both groups had moderately depressed left ventricular function demonstrated by the mean ejection of 35.6% for the PCD™ Transvene™ System patient group and 34% for the Ventak-P Epicardial System patient group.

Analysis indicated that no statistical differences between the PCD™ Transvene™ System and Ventak-P Epicardial System patient populations except in the category of patient indication. There are more patients that had Sudden Cardiac Death as the primary indication in the PCD™ Transvene™ population than in the AICD population ($p=0.001$).

K.3 Comparison of Clinical Performance

Areas of clinical performance that were compared were implant defibrillation thresholds, incidence of spontaneous VT/VF events,

incidence of complications and patient survival. These specific areas were selected in order to evaluate the system performance in the two patient populations.

Implant Defibrillation Thresholds

For the purposes of the PCD™ Transvene™ System clinical study, determination of defibrillation threshold was not mandatory. However, the preferred method of evaluating defibrillation efficacy was to determine the defibrillation threshold using a testing sequence of 18J, 15J, 10J, 5J with a failure at any level causing a return to 18 J for the remaining attempts. For the purposes of this report a defibrillation threshold was defined as the energy at the lowest successful defibrillation attempt, provided a patient had a failure below their lowest defibrillation success or a success at $\leq$ 5J. The rhythm treated must have been VF to be included in the analysis.

It should be noted, that it was expected that the PCD™ Transvene™ System would have a higher mean defibrillation threshold as compared to a traditional epicardial defibrillation lead system. In a epicardial system, the increased electrode surface area would theoretically decrease defibrillation requirements.

A total of 316 patients had a defibrillation threshold determined at the time of PCD™ device implant. The mean defibrillation threshold (DFT) for all lead systems was 14.8J. The recommendation for VF Therapy #1 is to program the stored energy to twice the implant DFT or 18 Joules, whichever is greater. Thus an adequate defibrillation safety margin was provided when following the VF therapy programming recommendations.

In the Ventak-P Epicardial System, the mean defibrillation threshold at implant was 13.4J. Thus the two systems had similar defibrillation thresholds at implant despite the fact that one system utilized an epicardial defibrillation lead system while the other utilized a transvenous defibrillation lead system.

These data indicate that the PCD™ Transvene™ System had comparable implant defibrillation threshold performance when compared to the reported Ventak-P Epicardial System clinical experience.

Incidence of Spontaneous VT/VF Episodes

The incidence of spontaneous VT/VF episodes in the Ventak-P Epicardial System and PCD™ Transvene™ System patient population was evaluated by utilizing the stored episode information provided by both devices.

In the Ventak-P device, the total number of shocks delivered to the patient is provided via interrogation of the device. The PCD™ device provides information on the total number of VT and VF episodes detected by the PCD™ device and the total number of VT and VF episodes successfully treated by the PCD™ device as well as the number of VT/VF episodes where the PCD™ device was ineffective. In addition, the last 20 intervals of the last episode satisfying detection criteria along with the first 10 intervals after the last therapy delivered are recorded by the device. These data assist the physician in evaluating the frequency of VT/VF episodes, the efficacy of the PCD™ device programmed parameters and the need for reprogramming.

In the Ventak-P Epicardial System experience of 292 patients with a mean follow-up of 6.8 months, 137 (46.9%) received a device countershock in response to a spontaneous ventricular tachyarrhythmia episode as defined by the Ventak-P Device detection criteria.

In the PCD™ Transvene™ System experience of 757 patients with a mean follow-up of 5.6 months, 311 patients (41%) have received device therapy in response to a spontaneous ventricular tachyarrhythmia episode as defined by the PCD™ Transvene™ System detection criteria.

A total of 5430 spontaneous VT and 973 spontaneous VF episodes have been recorded by the PCD™ device episode counters. Of the 5362 successfully treated spontaneous VT episodes, 92% were treated with one of the programmed antitachycardia pacing therapies incorporated in the PCD™ device. The clinical benefit of tiered therapy is the reduction of delivery of high energy shocks for the treatment of stable recurrent ventricular tachycardia that may be responsive to antitachycardia pacing.

Incidence of Complications

Table K-2 provides a comparison of reported complications and observations. The AICD clinical experience data is from the Winkle, et al Long Term Outcome with Automatic Implantable Cardioverter-Defibrillator; JACC, May 1989; 13(6); 135-161. This article was selected because it provides a detailed clinical complication experience on a large patient population, 270 patients. Note that the percentage reported in the PCD™ Transvene™ System includes **both complications and observations**. In the following table, the complications are reported for the categories of Fail to Cardiovert/Defibrillate, Pocket Infection, and Erosion. Observations are reported in the Inappropriate/Problematic VT/VF Therapy Delivery category.

PCD™ Transvene™ System
Comparison of Complication/Observation Rates
PCD™ versus AICD

Category	PCD™%	AICD%
Fail to Cardiovert/Defibrillate	0.8%	4.1%
Inappropriate/Problematic VT/VF Therapy Delivery	8.2%*	20%
Pocket Infection	2.0%	2.2%
Erosion	0.3%	0.7%

* Includes Observations only; there were no Complications in this category.

Table K-2: Comparison of Complication/Observation Rates: PCD™ Transvene™ System vs AICD Epicardial System - 6/24/92

The incidence of failure to cardiovert and/or defibrillate was lower in the PCD™ Transvene™ System patient population. The instances of failure to cardiovert and/or defibrillate in the PCD™ Transvene™ System patient population were associated with increased defibrillation requirements during induced episodes, none of which resulted in patient death. In six cases, the implanted system was modified to provide adequate defibrillation efficacy, in four cases the patient's drug therapy was modified and in the final two cases, reprogramming provided for adequate defibrillation efficacy.

The failures to cardiovert/defibrillate reported in the Winkle, et al article were associated with patch dislodgement, patch crinkling, lead conductor fracture and elevated defibrillation thresholds.

The incidence of inappropriate/problematic VT/VF therapy delivery was lower in the PCD™ Transvene™ System patient population. This is to be anticipated since the device incorporates independently programmable detection algorithms for VT and VF. The reasons for inappropriate VT/VF therapy delivery included sinus tachycardia being detected as VT or VF and atrial fibrillation with rapid ventricular response being detected as VT or VF.

The overdetection circumstances reported in Winkle, et al were nonsustained VT, VT, sinus tachycardia, atrial fibrillation with rapid ventricular response, sensing lead fracture and pacemaker interaction. The patients with VT complained of receiving multiple shocks with limited or no symptoms. The incorporation of antitachycardia pacing in the PCD™ device decreases the need for delivery of cardioversion shocks for the termination of stable VT and increases patient acceptance of ICD therapy.

In the Winkle, et al experience all patients with pocket infection had the devices explanted. In the PCD Transvene System experience, the incidence of device explant secondary to pocket infection was 2.0% which was comparable to Winkle's article.

Thus, the incidence of complications and observations was similar to that of the AICD Epicardial System in the categories of ineffective VT/VF therapies, infection requiring explant and erosion. The incidence of inappropriate delivery of therapy is lower in the PCD Transvene System experience than in the AICD Epicardial System experience, which is clinically significant.

This analysis indicates that the PCD™ Transvene™ System offers clinical advantages in reducing the need for a thoracotomy for implantation and reducing the number of shocks due to successful antitachyarrhythmia pacing.

K.4 Comparison of One Year Actuarial Survival

The Ventak-P Epicardial System produced by Cardiac Pacemaker, Inc, has obtained market approval from the U.S. FDA to date. While there are important differences in the function of the Ventak-P Epicardial System and the PCD™ Transvene™ System, there is a natural desire for comparison of the clinical outcome, particularly the impact of these devices on death rate.

A total of 22 deaths (2.9%) were reported in the PCD™ Transvene™ System patient population. Of the 18 cardiac deaths, 15 were non-sudden cardiac and 3 were sudden cardiac. Four deaths were classified as noncardiac. Five of the 22 total deaths occurred within the perioperative period (death less than 30 days post implant) with a resultant perioperative mortality of 0.7%.

In the Ventak-P Epicardial System patient population a total of 19 deaths (6.5%) were reported. Of the 12 cardiac deaths, 4 were classified as sudden cardiac and 8 were classified as non-sudden cardiac. Six of the deaths were classified as noncardiac and the cause of one was unknown. Eight of the deaths occurred within the perioperative period with a resultant perioperative mortality of 2.7%. The PCD™ Transvene™ System population had a lower perioperative mortality, 0.7% vs 2.7% ($p=0.006$).

For purposes of this comparison, only the **overall** actuarial survival rate includes perioperative deaths. All other calculations in both the PCD™ Transvene™ System and Ventak-P Epicardial System group exclude perioperative deaths.

For the Ventak-P Epicardial System, patient deaths were **censored** if the Ventak-P device had been either electively deactivated for various reasons prior to the patient's death, thus preventing the device from attempting to convert the arrhythmia or if the pulse generators were known to be nonfunctional and awaiting replacement. For purposes of this comparison, two patient deaths were **censored** in the PCD™ Transvene™ System patient population because the devices were deactivated at the time of patient death.

This PCD™ Transvene™ System sudden cardiac death survival of 100% at one year is comparable to that of the Ventak-P Epicardial System sudden cardiac death survival rate of 98.6 %. More importantly, the overall one year actuarial survival for the PCD™ Transvene™ System was 95.6% as compared to 90.8% for the Ventak-P Epicardial System. This difference was primarily due to the improvement in the reported perioperative mortality in the PCD™ Transvene™ System patient population. [Note: Confidence interval analysis was performed indicating that there was a statistical difference in the reported **Overall** mortality.]

This comparison of actuarial survival rates indicates that the projected sudden cardiac death survival of patients receiving a PCD™ System patient population is comparable to that reported for the Ventak-P Epicardial System. Thus, the incorporation of programmable VT/VF detection and therapy algorithms has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

In addition, the elimination of a surgical thoracotomy for implant in the PCD™ Transvene™ System has improved the perioperative mortality and overall one year survival when compared to the Ventak-P Epicardial System.

L. Comparison to PCD™ Epicardial System Clinical Results

The PCD™ Epicardial System uses the same tiered therapy device that combines features of bradycardia support pacing, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. This system has incorporated programmability and multiple detection and therapeutic options that allows the titration of device therapy to a patient's specific clinical arrhythmia history.

The PCD™ Epicardial System requires a thoracotomy for implantation because of the need to insert epicardial patch leads. This exposes the patient to surgical risk and potentially limits the type of patient who may be considered for implant of the system. The need for a simpler and safer implantation technique is widely recognized. The incorporation of a nonthoracotomy lead system, such as the PCD™ Transvene™ System, should

decrease the potential perioperative and long term mortality and morbidity associated with current epicardial system implantation approaches.

The PCD™ Epicardial System and PCD™ Transvene System are identical except for the implanted defibrillation lead system. Thus, the performance of the PCD™ device, associated support equipment, is similar in the two systems and therefore a comparison of clinical experience should focus on those areas where the implanted lead system may impact clinical outcome.

This section provides a comparison of the PCD™ Transvene™ System clinical experience to the reported PCD™ Epicardial System clinical experience. The following areas will be discussed:

- Patient characteristics
- Implant Data
- Spontaneous VT/VF Episode Efficacy
- Complications and Observations
- Survival analysis

This analysis will show that the incorporation of a nonthoracotomy defibrillation lead system has maintained the type of therapy available for the treatment of recurrent VT/VF and decreased the potential mortality and morbidity associated with epicardial implant approaches while maintaining the positive impact of ICD therapy on VT/VF episode efficacy and patient survival.

L.1 Comparison of Patient Characteristics

In comparing the clinical experience with the PCD™ Transvene™ System to the PCD™ Epicardial System clinical experience, it is important to determine that the patients who received the device are comparable.

Table L-1 contains the characteristics of the 757 patients receiving the PCD™ Transvene™ System versus the characteristics of the 742 patients who received the PCD™ Epicardial System as of 5/14/92.

PCD™ Transvene™ System Comparison of Patient Characteristics		
	PCD™ Transvene System	PCD™ Epicardial System
Number of Patients	757	742
Mean Follow-Up Time	5.6 months	9.7 months
% Males* % Females	610 80.6% 147 19.4%	637 85.8% 105 14.2%
Mean Age	59.4 years	59.6 years
Primary Indication* SCD VT SCD/VT	 281 37.1% 377 49.8% 99 13.2%	 214 28.8% 405 54.6% 123 16.6%
Cardiovascular History Coronary Artery Disease Cardiomyopathy	 561 74.1% 238 13.1%	 569 76.7% 222 29.9%
Mean Ejection Fraction	35.6%	34.0%
Number of Drugs Failed*	2.3	3.0

* Statistically Significant ($p \leq 0.05$)

Table L-1: Comparison of Patient Characteristics, PCD™ Transvene™ System versus PCD™ Epicardial System - 6/24/92

Both groups had moderately depressed left ventricular function demonstrated by the mean ejection of 35.6% for the PCD™ Transvene™ System patient group and 34.0% for the PCD™ Epicardial patient group.

Analysis indicated that the PCD™ Transvene™ System patient population had a higher percentage of patients whose indication for implant was sudden cardiac death ($p = 0.002$) and higher percentage of females ($p = 0.007$). It is not expected that these differences will result in a different clinical outcome in the PCD™ Transvene™ System patient population as compared to the PCD™ Epicardial System. This difference in patient indication is a reflection of the physicians use of the PCD™ Transvene™ System.

It is interesting to note, that there was a statistical difference in the number of antiarrhythmic drugs tested between the two patient groups ($p=0.001$). The PCD™ Transvene™ System patient group failed a mean of 2.3 antiarrhythmic drugs prior to implant while the PCD™ Epicardial System patient group failed a mean of 3.0 antiarrhythmic drugs. This difference is a reflection of the differences in the indications for implant between the two patient groups. The PCD™ Transvene™ System patient group had a higher incidence of patients whose primary indication for implant was sudden cardiac death. These patients have a higher probability of having experienced a sudden cardiac death episode but were non-inducible during electrophysiologic testing so that drug testing was not feasible.

L.2 Spontaneous VT/VF Episodes Efficacy Comparison

The primary benefits from the use of the PCD™ System center on the détection and termination of life-threatening ventricular tachyarrhythmias. An additional benefit of the PCD™ Transvene™ System is the elimination of the need for a thoracotomy for implantation of the defibrillation lead system and the resultant decrease in potential patient morbidity and mortality associated with a thoracotomy. This clinical benefit should not be gained at the expense of providing effective termination of spontaneous VT and VF episodes. Table L-2 provides a comparison of the efficacy of the PCD™ Transvene™ and PCD™ Epicardial System in treating spontaneous episodes of VT and VF.

PCD™ Transvene™ System Performance Comparison		
Spontaneous VT Episodes		
	PCD™ Transvene™ System	**PCD™ Epicardial System**
Mean Follow-Up	5.6 months	9.7 months
Number of Episodes	5430	13,706
% Overall Efficacy	98.7%	98.1%
% Unsuccessful Termination	0.4%	1.0%
Spontaneous VF Episodes		
	PCD™ Transvene System	**PCD™ Epicardial System**
Mean Follow-Up	5.6 months	9.7 months
Number of Episodes	973	1694
% Overall Efficacy	99.1%	98.6%
% Unsuccessful Termination	0.1%	0.5%

Table L-2: PCD™ Transvene™ System: Comparison of Spontaneous VT/VF Episode Efficacy - 6/24/92

The overall success rate of the PCD™ Transvene™ System in terminating spontaneous episodes of VT or VF is 98.7%. In addition, there have been no reported patient deaths due to ineffective termination of a spontaneous VT/VF episode. This success rate compares very favorably with the overall success rate of the PCD™ Epicardial System which was 98.2%. Therefore, the PCD™ Transvene™ System offers the potential of decreased patient morbidity and mortality without decreasing the treatment efficacy of spontaneous VT/VF episodes.

L.3 Incidence of Complications/Observations

A comparison of the reported complications and observations was made between the PCD™ Transvene™ System and the PCD™ Epicardial System. The PCD™ Epicardial System patient population used for comparison included clinical experience as of May 14, 1992 with 742 patients and a mean implant duration of 9.7 months. These two patient groups are similar in the patient demographics and indication for implant of the PCD™ System. In the PCD™ Transvene™ System patient population, 18.2% of the patients experienced a clinical complication and 20.8% of the patients experienced a clinical observation. In the PCD™ Epicardial System, 12.8% of the patients experienced a clinical complication and 25.7% of the patients experienced a clinical observation.

Table L-3 provides a comparison of the reported complications and the incidence in the two patient populations.

PCD™ Transvene System

PCD™ Transvene System versus PCD™ Epicardial System Reported Complications

Reported Complications	PCD™ Transvene™ System (N=757)	PCD™ Epicardial System (N=742)
Increased Defibrillation Requirements	0.8%	0.5%
Inappropriate Therapy	-	1.8%
Pace/Sense Related	0.9%	3.5%
Infection Related - Explant	2.0%	1.9%
Lead Related	6.6%	2.8%
Device Related	0.5%	0.9%

Table L-3: Reported Complications: PCD™ Transvene™ System versus PCD™ Epicardial System - 6/24/92

L.4 Survival Analysis Comparison

Despite their excellent clinical performance, epicardial defibrillation lead system have important limitations. The requirement for direct thoracic access contributes significantly to patient morbidity and mortality, patient discomfort and prolonged hospitalization. The availability of reliable nonthoracotomy lead systems should provide positive clinical impact on these issues while not negatively

impacting patient survival. Therefore, a comparison of the one year actuarial survival rates for the PCD™ Transvene™ and Epicardial System was performed.

Table L-4 provides a summary of the patient deaths reported in the two patient populations by classification. As a reference, the mean follow-up time for the PCD™ Transvene™ System patient population was 5.6 months while for the PCD™ Epicardial System it was 9.7 months.

PCD™ Transvene™ System **Death Classifications** **PCD™ Transvene™ System versus PCD™ Epicardial System**		
Death Classification	**PCD™ Transvene™ System (N=757)**	**PCD™ Epicardial System (N=742)**
Sudden Cardiac	3	20
Non-Sudden Cardiac	15	41
All Cardiac	18	61
Noncardiac	4	27
TOTAL	22	88

Table L-4: Death Classifications: PCD™ Transvene™ System versus PCD™ Epicardial System - 6/24/92

Table L-5 provides a comparison of actuarial survival rates between the PCD™ Transvene™ and PCD™ Epicardial patient populations. The actuarial survival projections include perioperative deaths only in the calculation of survival from death due to all causes (shown in table row labelled **Overall**). Perioperative mortality includes those deaths which occur in the first thirty days post implant of the PCD™ System.

PCD™ Transvene™ System Comparison of Actuarial Survival PCD™ Transvene™ System versus PCD™ Epicardial System			
One Year Survival	**PCD™ Transvene™ System**	**PCD™ Epicardial™ System**	**P-Value**
Number of Patients	757	742	-
Sudden Cardiac	99.8%	98.7%	0.144
Non-Sudden Cardiac	96.8%	95.7%	0.803
All Cardiac	96.6%	94.4%	0.656
Noncardiac*	99.4%	97.3%	0.022
Overall*	95.3%	87.2%	0.001

* Statistically Significant $p \leq 0.05$

Table L-5: Comparison of Actuarial Survival: PCD™ Transvene™ System versus PCD Epicardial System - 6/24/92

There was a significant increase in overall survival in the patients receiving a PCD™ Transvene System™. As previously noted, the Overall one year actuarial survival includes death from all causes. The overall one year survival for patients receiving the PCD™ Transvene™ System was 95.3%. This is significantly improved as compared to the overall one year actuarial survival for the PCD™ Epicardial System (87.2%) [p=0.001]. This improvement in overall survival is primarily due to the marked improvement in perioperative mortality, the PCD™ Transvene™ System having a 0.7% perioperative mortality versus the a perioperative mortality of 4.7% in the PCD™ Epicardial System. This improvement in perioperative mortality is primarily due to the elimination of the need for a thoracotomy and its associated morbidity and mortality.

M. PCD™ System Performance

M.1 PCD™ Device

Devices implanted for the treatment of recurrent ventricular tachyarrhythmias should perform safely and reliably in the indicated patient population. Device longevity, ventricular tachyarrhythmia detection, therapy performance, and analysis of explanted devices were evaluated to assess the performance of the PCD™ Device.

Extended longevity of implantable cardioverter defibrillators should decrease the number of device replacements a given patient would experience over their lifetime and decrease unnecessary patient morbidity. Thus, the PCD™ Device longevity, which is monitored utilizing battery voltage and charge time obtained via telemetry, was analyzed. The PCD™ Device longevity data collected is consistent with the longevity projections.

The combined experience of induced and spontaneous VT/VF episode experience has shown that the PCD™ Device VT/VF detection and therapies have performed safely and according to design specifications when required to treat induced and spontaneous VT/VF episodes.

There have been a total of 41 devices explanted. Reasons for explant were patient death (15), infection (17), cardiac transplant (5), low battery voltage (1) and PCD Device performance issues (3). The analysis of the device that was explanted due to lower than expected battery voltage indicated that the decreased battery voltage measurement was due to hermetic leakage at the input to one of the integrated circuits and this affected the battery indicator circuit only and did not affect the critical functions of the device. This leads to a voltage drop across a resistor where the voltage measurement is taken. Analysis indicated that the battery was performing to specifications and the hermetic leakage was a random event. Analysis of the other three devices indicated that two were due to random component failure and one due to shorting on Pulse 2 output. Thus, arcing occurred between the conductors inside the hermetically enclosed brazed ring of the high power hybrid. As a result, high voltage was momentarily applied to the low power circuitry, including the low power hybrid. This low power hybrid lost function including the capability to pace and transmit telemetry due to excessive voltage applied. Since this is the only device that exhibited this type of failure in the field and the hybrid manufacturing process has demonstrated that it will screen out infant mortality, this failure was assumed to be a random component failure.

Based on the clinical data collected, the PCD™ Device has performed safely and reliably in the indicated patient population.

M.2 Transvene™ Lead Performance

The Transvene™ Lead System consists of a Right Ventricular Lead, a Coronary Sinus/Superior Vena Cava lead, and a Subcutaneous Patch lead. There have been a total of 757 Right Ventricular leads (15 with the SP2100 and 742 with the Model 6884/6966), 796 Coronary Sinus/Superior Vena Cava leads (Model 6881/6963), and 718 Subcutaneous Patch leads (Models 6895/10317/6999) implanted with a cumulative implant duration of 4246 months. The reported incidence of conductor coil fracture is 0.5% (4/757).

Based on the clinical data collected, the Transvene™ leads have performed safely and reliably.

N. Summary

The overall clinical experience with the PCD™ Transvene™ System indicates that the system performed according to design and specification. The reported clinical complications and patient deaths are appropriately addressed in the required labelling for the system and the patient selection criteria for implant of the device is appropriate.

The following can be drawn from this analysis of the data collected in this clinical study:

Patient Deaths

- The projected one year survival probabilities for Sudden Cardiac Death, Non-Sudden Cardiac Death, all Cardiac Deaths and Noncardiac Death were found to be 99.8%, 96.8%, 96.6%, and 99.4%, respectively.

  The incorporation of programmable VT/VF detection and therapies has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

- The sudden cardiac death survival of 99.8% at one year is comparable to that of the AICD patient population 98.0%.

- There have been no deaths due to a PCD™ Device malfunction.

Complications/Observations

- Complications were reported in 18.2% of the patient population and observations were reported in 20.7% of the patient population.

- The incidence of complications was comparable to that of the market released AICD system in the categories of ineffective VT/VF therapy, pocket infection, and pocket erosion and was lower than the AICD in the category of inappropriate delivery of VT/VF therapy.

Patient Indications

- All of the patients entered into this clinical evaluation met at least one of the primary indications. Sudden cardiac death (SCD) was the primary indication in 37.1% of the patients, recurrent ventricular tachycardia (VT) was the primary indication in 49.8 % of the patients and SCD/VT was the primary indication in 13.1% of the patients.

- The number of patients (41.1%) receiving VT/VF therapy for spontaneous episodes of ventricular arrhythmias supports the conclusion that the patient selection criteria are appropriate and that the PCD™ Transvene™ System was implanted in patients who benefit from this therapy.

- The one year sudden cardiac death survival rates for the SCD patient group was 100.0%, for the VT patient group 99.7% and the SCD/VT patient group 100.0%.

VT/VF Detection and Therapy Performance

- The PCD™ Transvene™ System properly detects and treats VT as demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VT was 98.7%.

- The PCD™ Transvene™ System properly detects and treats VF as demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VF was 99.1%.

- There were no reported patient deaths due to the nondetection of a spontaneous VT or VF episode by the PCD™ Transvene™ System.

PCD™ Transvene™ System Performance

- The PCD™ Transvene™ System components (Model 7216A/7217B and Model 6884/6966, 6881/6963, 6895/6999 Transvene™ leads) have performed according to design and specification and are, therefore, considered safe and effective in the indicated patient population.

O. Clinical Experience Summary Conclusions

The PCD™ Transvene™ System is a tiered therapy device which combines features of bradycardia pacing support, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. The incorporation of these features has allowed the physician to titrate the ICD therapy to meet specific patient clinical needs, allowed fewer shocks to be delivered for recurrent ventricular tachycardia because of antitachycardia pacing features, allowed fewer cases of inappropriate therapy delivery due to programmable detection and allowed a sudden cardiac death survival rate identical to the Ventak-P Epicardial System.

The PCD™ Transvene™ System, due to the elimination of the need for a thoracotomy, has provided a marked improvement in both the perioperative and overall patient mortality as compared to the PCD™ Epicardial System. In addition, due to the decreased perioperative morbidity and mortality, the post implant hospital stay has been decreased to a mean of seven days as opposed to a mean of fourteen days for the PCD™ Epicardial System.

Medtronic asserts and the PCD™ Transvene™ investigators unanimously agree that the findings of the clinical study support the conclusion that the Medtronic Tachyarrhythmia Control System and the Transvene™ Cardioversion and Defibrillation Electrodes are safe and effective in the indicated patient population.

G. Summary of Safety and Effectiveness Conclusion

The efficacy and safety of implantable cardioverter defibrillator (ICD) therapy for recurrent ventricular tachycardia (VT) and ventricular fibrillation (VF) has been well established. The current market released device provides defibrillation therapy for VF or hemodynamically unstable VT, however this type of therapy may not be optimal for patients with stable, well tolerated VT that is amenable to antitachycardia pacing. The need to incorporate programmability and multiple detection and therapeutic options has lead to the development of a tiered therapy device, the Medtronic PCD System.

However, the current market released system requires a thoracotomy for implantation because of the need to insert epicardial patch leads. This exposes the patient to increased surgical risk an potentially limits the type of patient who may be considered for implant of the system. The need for a simpler and safer implantation technique is widely recognized. The incorporation of a nonthoracotomy lead system, such as the PCD™ Transvene™ System, would decrease the potential perioperative and long term mortality and morbidity associated with current epicardial system implantation approaches.

For the indicated patient population, the primary benefits from the PCD Transvene System center on the detection and termination of life threatening ventricular arrhythmias. The use of pacing therapies for the treatment of ventricular tachycardia reduces patient trauma associated with higher energy cardioversion pulses and extends the longevity of the PCD Device pulse generator. In addition, the PCD Transvene System offers the potential for decreased patient morbidity and mortality due to the elimination of the need for a thoracotomy.

Extensive laboratory and animal testing and human clinical trials of the PCD System were performed to demonstrate the safety and efficacy of the PCD Transvene System and its components in the indicated patient population.

Nonclinical laboratory studies included testing at the component, hybrid and system level. All requirements were satisfied and the components and device-level testing performed according to specification. Results of animal testing demonstrated safe and reliable performance of the PCD Transvene System.

The indications for use of the PCD System include:

- Patients who have survived at least one episode of cardiac arrest due to ventricular arrhythmia not caused by an acute myocardial infarction; or

- Patients with recurrent sustained, ventricular tachycardia that remains inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most effacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

The safety and efficacy of the PCD Transvene System in patients with VT and VF was evaluated in 757 patients with a mean implant duration of 5.6 months. The overall success rate in terminating spontaneous VT/VF episodes was 98.8%. The one year sudden cardiac death survival rate was 99.8% which was comparable to the reported sudden cardiac death rate of the PCD Epicardial System (98.7%) and Ventak-P Epicardial System (98.6%) patient populations. More importantly, the PCD Transvene System provided a significant improvement in overall one year survival (95.3%) when compared to the PCD Epicardial System (87.2%) and the Ventak-P Epicardial System (90.8%) patient populations. This improvement in overall survival was primarily due to the decreased perioperative mortality associated with the PCD Transvene System.

These data, in total, demonstrate the safe and effective performance of the PCD Transvene System in the indicated patient population. Therefore, the PCD Transvene System as reported in this PMA application is safe and effective for its intended use.

PS 015/S000 29-Mar-1993

FROM:	LETTER DATE	LOGIN DATE	DUE DATE
MEDTRONIC INC. ATTN: JENNIFER M. MARRONE 7000 CENTRAL AVENUE, N.E. MINNEAPOLIS,, MN 554323576	03/26/93	03/29/93	/ /
	DOCUMENT: PMA	CONTROL # P920015/S000 AMENDMENT	

SUBJECT:
MEDTRONIC(R) TRANSVENE LEAD SYSTEM

	OFFICE	DATE REFERRED
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T.C.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date May 10, 1993

From Mathematical Statistician (T. C. Lu) HFZ-162
Statistical Branch, Division of Biometric Sciences, OST

Subject Statistical Review of PMA P920015 Amendment, Medtronic Multiprogrammable Tachyarrhythmia Control System with Non-thoracotomy Cardioversion and Defibrillation Electrodes, Medtronic, Inc.

To Doris Terry - HFZ-450
Division of Cardiovascular, Respiratory, and Neurological Devices, ODE
Through: Director, Division of Biometric Sciences, OST
Through: Chief, Statistical Branch, DBS, OST

1. Background

The Medtronic Pacer-Cardioverter-Defibrillator (PCD) is an implantable, multiprogrammable, automatic tachyarrhythmia control device. This device is used for treatment of patients at risk of sudden cardiac death due to ventricular tachycardia (VT) and/or ventricular fibrillation (VF). The original PMA was submitted in April 1992. Amendment One was submitted in September 1992. Amendment Two was submitted for review in March 1993. The purpose of this memo is to review the response from the sponsor for the deficiencies stated in the FDA letter. Information provided in this amendment includes clinical experience of 757 patients through February 1, 1993.

2. Reviewer's Comments

2.1. Historical Control

Sponsor compared the PCD transvene system (treatment group) clinical experience to the reported PCD epicardial system (control group) clinical experience. Sponsor argued that patients were enrolled in the two studies concurrently and patients' indications, implant criteria and clinical data requirements were identical for the two patient groups. But, in Table 2-7, comparison of patient characteristics, PCD transvene system versus PCD epicardial system, as of February 1, 1993, page 19, gives different information. The p-values for sex and primary indication, (B)(4) and (B)(4) respectively, are statistically significantly different. Therefore, the sponsor's argument that the two groups are compatible is not correct.

2.2. Cox Regression

Sponsor stated, on pages 12 and 90, that: "Cox regression analysis was performed to see what effect gender, primary indication and system implanted (PCD transvene or PCD epicardial) had on survival outcome. This analysis showed that for overall survival at one year, the system implanted had an influence on the probability of survival but gender and primary indication had no influence". This reviewer would like to see the detailed evidence to support this claim, including the computer program, input, output and decision criteria.

2.3. Confidence Interval Analysis

Sponsor compared the PCD transvene system and Ventak-P epicardial system and claimed a statistically significant difference in one-year overall survival between the PCD transvene and AICD epicardial system, using confidence interval analysis, pages 13 and 256. This reviewer asked for this information in my December 16, 1992 memo to you and I would like to ask again for the computation of this confidence interval.

2.4. Actuarial Survival Comparison I

Table 2-16, page 24, depicts the actuarial survival of PCD transvene vs. PCD epicardial. This reviewer would like to see a more detailed Table such as this:

Month	Transvene	Epicardial
0-3	No.dead/No.at risk	No.dead/No.at risk
3-6	No.dead/No.at risk	No.dead/No.at risk
6-9	No.dead/No.at risk	No.dead/No.at risk
9-12	No.dead/No.at risk	No.dead/No.at risk

Then use the Mantel-Haenszel Chi-square test to compute the p-value for association between transvene and epicardial survival. Sponsor didn't discuss how the p-values in Table 2-16 were derived; it looks as if the binomial distribution was used for the computation. Sponsor should address this issue.

2.5. Please discuss the similarities/differences between Table 2-12 (page 22) and Table 3-3 (page 27).

2.6. Survival Probability I

Sponsor stated, on page 43, that the survival probabilities are calculated using a life-table survival analysis. For verification of survival probabilities, the data necessary to do calculations are available upon request. This reviewer would like to see this data set and the computation procedure.

2.7. Please discuss the similarities/differences between "one-year actuarial survival" of Table 1K-4 (page 43) and Table 8-5 (page 51). This reviewer would like to see the numerators and denominators actually used to derive the one-year actuarial survival shown in Table 8.5.

2.8. Survival Probability II

Sponsor stated, on page 83, that: "Presentation of the number of patients does not allow calculation of the survival probability. Therefore, a data set will be available upon request if you desire to verify the survival probability". This reviewer would like to see this data set and the computation procedure.

2.9. Actuarial Survival Comparison II

Table 1M-10 (page 84) depicts the comparison of actuarial survival: transvene vs epicardial as of June 24, 1992. Again, this reviewer would like to see the data set and the SAS procedure actually used to derive the p-values.

2.10. NYHA Classification

The p-value for the NYHA classification in Table IV-C (page 88) is (B)(4) as computed by the sponsor. Based on the data provided in this table, the reviewer calculated a p-value of (B)(4) Sponsor should address this difference in p-values.

2.11. Early Device Explant

There were four patients in whom the PCD device was explanted due to reasons other than death, infection or heart transplant. Analysis of one explanted PCD device indicated a random device failure in the microprocessor and low power hybrid. Another patient experienced a power on reset (POR) condition, see page 100. Please submit the other two results for review as soon as the results are available.

4

2.12. Lead Dislodgement

Lead dislodgements are reported as complications/observations in Table 27-2 (page 103). The sponsor should justify his choice of thirty (30) days as a cutoff.

2.13. Pooling

There are seventy eight (78) investigative centers participating in the clinical trial with thirty five (35) domestic centers and forty three (43) foreign centers. Please justify pooling all seventy eight centers together.

2.14. Follow-up Presentation

Table E-2, page 215, depicts the PCD transvene system follow-up. This is not an adequate presentation of the follow-up data. As I requested in my April 23, 1992 memo, the sponsor should refer to page 93, Table 4.6, in "Statistical Methods for Survival Data Analysis" by Elisa Lee for a more proper life-table analysis. Sponsor should also discuss the reasons why some patients dropped out of the follow-up study, i.e., either withdrawn alive or lost to follow-up.

2.15. Actuarial Survival Comparison III

Table 11-2 (page 231) depicts the PCD transvene system one-year actuarial survival as of 2/1/93. Again, this reviewer would like to see the actuarial survival table stratified by every month, similar to that in Section 2.4 above. Sponsor also stated "this table included the projected one year survival calculations for patients who ultimately received a PCD transvene system....". Please explain in detail the projected one-year survival calculations.

2.16. Data Summary by Primary Indication

Sponsor provided PCD transvene system data summary by primary indication as of 2/1/93 in Table I-1 (page 233). This reviewer would like to see the numerators and denominators for percent success from treating spontaneous VT and spontaneous VF. Sponsor provided similar information in Table IF-2 (page 287) and Table IF-4 (page 290).

2.17. Follow-up Evaluations

Sponsor indicated, on page 284, that clinical data were collected for follow-up evaluations at 1 and 3 months post-implant and at 3-month intervals. Please provide all of this information

2.18. P-values for Actuarial Survival

This reviewer calculated the p-values in Table 2-16 (page 24) as follows:

	P-Values	
Cause of Death	Sponsor	Reviewer
Sudden Cardiac	[(B)(4)]	[(B)(4)]
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Non-Cardiac	[(B)(4)]	[(B)(4)]
Overall	[(B)(4)]	[(B)(4)]

3. Conclusion

The sponsor needs to adequately address all issues raised in Section 2 above, mainly actuarial survival and follow-up, before the safety or effectiveness of the PCD transvene system relative to the PCD epicardial system can be evaluated from a statistical perspective.

T. C. Lu

T. C. Lu

cc: Abhijit Acharya, Ph.D. HFZ-450
Donald F. Dahms HFZ-450
Lynne A. Reamer HFZ-450
Medical Device File
Board File

I.C.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date May 10, 1993

From Mathematical Statistician (T. C. Lu) HFZ-162
Statistical Branch, Division of Biometric Sciences, OST

Subject Statistical Review of PMA P920015 Amendment, Medtronic Multiprogrammable Tachyarrhythmia Control System with Non-thoracotomy Cardioversion and Defibrillation Electrodes, Medtronic, Inc.

To Doris Terry - HFZ-450
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Through: Director, Division of Biometric Sciences, OST
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Q1

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9

Part 1- Page 1242

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Doris Terry 5

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T. C. Lu

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cc: Abhijit Acharya, Ph.D. HFZ-450
Donald F. Dahms HFZ-450
Lynne A. Reamer HFZ-450
Medical Device File
Board File

11

MEMORANDUM

From: Doris Terry (HFZ-450)
To: File # P920015
Subject: Transvene Lead System
Date: April 19, 1993
Office: DCRND/ODE

The manufacturer responded to the deficiencies listed in our letter of March 17, 1993. The data provided in the referenced amendment includes the experience of the PMA population (757 patients) as of a data cutoff of February 1, 1993. The letter contains deficiencies from a team of reviewers. The team consists of a medical officer, 3 scientific reviewers (including myself) and a statistician. The memos from the other reviewers will address specific requests.

Request # 1

We told the company to state the hypothesis and the objectives of the study. The hypothesis of the PCD Transvene clinical study is to demonstrate that the PCD Transvene System is safe and effective in treating VT and VF. We also asked the manufacturer to: (1) address the use of a control and the rationale for not using a concurrent control during the study; (2) randomization; (3) endpoints of the study; and (4) how the data will support the specified endpoints.

Objectives of the Study

The objectives are to determine the safety and effectiveness of the Transvene Lead System by:

- evaluating the sensitivity and specificity of the PCD with the Transvene lead system in detecting episodes of VT and VF. To evaluate the ability of the system to appropriately discriminate between VT and VF and other potentially nonmalignant rhythms;
- monitoring the efficacy of the PCD with the Transvene leads in treating VT and VF episodes;
- evaluating the performance of the Transvene leads;
- estimating one year sudden cardiac death survival and overall survival; and
- evaluating the safety and performance of the Model 9710 Programmer and the Model 9788 MemoryMod software cartridge in terms of effective programming.

Use of a Control

In addressing the use of a control, the PCD Epicardial (Epi)

system which is used as a control is similar to the PCD Transvene system with the exception of the lead system used. The manufacturer considers the PCD Epi group as the most closely matched population to the PCD Transvene population. This is because there is concurrent enrollment of the patients in the studies. In addition, the primary indications, implant criteria and clinical data requirements are identical for the two groups. A comparison between the PCD Transvene and Ventak P Epicardial lead system was also made. This was done essentially for comparison of the desired endpoints (overall survival and sudden cardiac death survival).

Randomization

In addressing the issue of randomization, the manufacturer identified patients who may not be able to withstand a thoracotomy. Therefore, randomization would not be feasible or clinically appropriate for these patients. These patients include: (1) those where there is no indication for concomitant surgery at the time of ICD implant; (2) those with pulmonary disease; (3) those with severe congestive heart failure; and (4) those who may require open chest procedures for treatment of their CAD or cardiac transplant. In these cases, the non-thoracotomy lead system is considered as the only therapy available for the ICD candidates.

Randomization was not employed, nor considered during the design of this study. This was due to: the investigators' preference; the known risks to the patient which are associated with a thoracotomy; and the urgency regarding the public health need for the product. A study such as the PCD Transvene will aid in determining, and/or making a case for or against a randomized trial involving nonthoracotomy and thoracotomy leads. The study could generate certain questions or concerns which could be answered through a randomized trial.

Endpoints of the Study

- freedom from sudden cardiac death and all causes of mortality shown through the 1 year survival; and

- treatment efficacy of spontaneous episodes of VT and VF episodes.

The data which will be used in the support of the endpoints will include data from the following: (1) patient deaths (sudden cardiac death survival and overall survival at 1 year); (2) complications and observations; (3) patient indications; (4) VT and VF detection and therapy performance; and (4) PCD Transvene System performance.

Request # 2

We asked that the manufacturer provide a side-by-side comparison between the PCD Transvene and the PCD Epi populations, and the PCD Transvene and the Ventak P AICD populations. The comparison between the named groups included: patient demographics; implant data (DFTs); programmed parameters; spontaneous VT and VF efficacy; complications an observations; and 1 year actuarial survival.

Comparison - PCD Transvene and Ventak P Epi

There were more patients with the indication of sudden cardiac death in the PCD Transvene group than in the Ventak P Epi group. The results of the Cox regression analysis showed that primary indication had no influence on the probability of survival. Therefore, it was considered that the two groups could be compared. Basically, the two groups were found to be comparable. The sudden cardiac death survival rates for the two patient groups were also comparable (99.7 percent for the PCD Transvene and 98.6% for the Ventak P Epi.

Comparison - PCD Transvene and PCD Epi

It was noted that there are more patients with the primary indication of sudden cardiac death in the PCD Transvene than in the PCD Epi population. As with the Ventak P analysis, the results showed that primary indication did not have an impact on patient outcome. The spontaneous VT episode efficacy for the PCD Transvene System was 98.4% which is comparable to that of the PCD Epi System of 98.3 percent. The spontaneous VF episode efficacy for the PCD Transvene System was 98.4 percent which is comparable to 98.7 percent reported for the PCD Epi System. The incidence of lead related complications is somewhat higher in the PCD Transvene population versus the PCD Epi population (15.1 percent versus 2.8 percent). The incidence of observations was statistically lower in the PCD Transvene group. The sudden cardiac death survival rate for the PCD Transvene was 99.5 percent and 98.9% for the PCD Epi group. The overall one year actuarial survival (including death from all causes for patients receiving the PCD Transvene System was 93.3 percent. A marked improvement of the overall one year survival for the PCD Epi of 88.6 percent. It is believed that the improvement is primarily due to the improvement in perioperative mortality of the PCD Transvene System (0.7 percent for the Transvene and 5.3 percent for the PCD Epi).

The implant pace/sense parameters (pacing threshold, R wave amplitude, slew rate and resistance) were found to be statistically significant. The mean implant DFT for the PCD Transvene System and PCD Epi System was 14.8 Joules (J) and 9.8 J respectively.

The majority (574 (75.3 percent)) of the patients in the PCD Transvene study had defibrillation programmed in the sequential pathway. Two hundred and fifty-one (33 percent) patients in the PCD Epi study were programmed in the sequential pathway. Four hundred and ninety-six (65.2 percent of the PCD Epi population were programmed with single defibrillation with only 10 (1.3 percent) patients in the PCD Transvene group with single.

Overall, the two groups were considered as closely matched as possible. The inherent difference being the design of the lead system.

Request # 3

The manufacturer provided an update of the PMA population (757 patients with a mean implant duration of 11.7 months) as of February 1, 1993.

Experience of Patients with the Dual Anchoring Sleeves

Two hundred and thirty-four patients (not included in the PMA population of 757 patients) were implanted with two anchoring sleeves. These patients received an additional sleeve due to the reported cases of lead dislodgement. This group of patients was similar to the PMA population with a slightly higher percentage of VT patients. Of the 234 patients, 186 have been followed for one month and 49 patients have been followed for 3 months. Only one lead dislodgement was reported in these patients.

Clinical Experience - Patients Followed for One Year or Greater

- 393 patients followed for one year or greater
- mean follow-up time 16.3 months
- primary indication: SCD - 150 (38.2 percent), VT - 191 (48.6 percent) and SCD/VT (52 (13.2 percent)
- defibrillation pathway: sequential - 296 (74.9 percent), simultaneous - 93 (23.6 percent) and single - 6 (1.5 percent)
- mean LED - 15.6 J (N= 365), mean DFT - 14.3 J (N=184)
- spontaneous VT success (99.0 percent)
- spontaneous VF success (98.6 percent)
- patient deaths - 7 (0 sudden cardiac, 4 nonsudden cardiac and 3 (noncardiac)

- complications - 89 in 76 patients (19.3 percent)

- observations - 122 in 99 patients (25.2 percent), forty of the observations involved inappropriate VT therapy delivery and 29 observations associated with oversensing

- none of the complications and observations resulted in patient death

Lead Dislodgements

Twenty-nine lead dislodgements occurred at greater than 30 days. None of these dislodgements resulted in ineffective therapy for the treatment of spontaneous episodes of VT or VF or patient death. The dislodgements were found during fluoroscopy at EP evaluation, chest x-ray or during pacing/sensing threshold evaluation during follow-up testing. In 29 cases, reoperation was necessary to reposition the lead.

Request # 4

A discussion of the implant criteria and how the implant testing attempted to satisfy the protocol requirements was provided.

The manufacturer described the patients who did not meet the implant criteria. These patients are among those patients referenced above who are at risk with a thoracotomy procedure. In these cases the investigators felt that if the patients had a lowest energy to defibrillate (LED) of 24 J, then they could be implanted with a 10 J safety margin (34 J max output of the device).

Request # 5

We requested that an update of the clinical experience of the patients who did not meet the implant criteria be provided. Also, a discussion regarding how the proposed labeling will address the deviation was requested.

One hundred and seventy patients did not meet the implant criteria, but had successful defibrillation at 24 J, were implanted with the PCD Transvene System. In determining if the patient's not meeting the implant criteria had a higher risk for morbidity and mortality, a comparison of their survival was made. There were no statistically or clinically significant differences in outcome between the patients who met the implant criteria and those who did not (one year survival - overall 93.8 percent for the patients not meeting the implant criteria and 93.2 percent for the patients who met the criteria).

Of the 170 patients, 41 complications were reported in 33 (19.4 percent) patients and 34 observations were reported in 31 (18.2 percent) patients. None of the complications and observations resulted in patient death.

Lead Dislodgements - Patients who did not Meet the Implant Criteria

There have been 14 lead dislodgements which occurred at greater than 30 days. The dislodgements were discovered and documented as described in the PMA application. In all 14 cases reoperation was required to reposition the lead.

There were no clinically significant differences in the characteristics and patient outcome of the patients who did not meet the implant criteria versus those who did. Based on these data, the manufacturer plans to recommend revising the defibrillation efficacy requirements to include the following: (1) two consecutive successful defibrillations with the final lead configuration with a stored output energy of 24 J or less; or (2) three successful defibrillations in four attempts with the final configuration at a stored output energy of 24 J or less.

Request # 6

Twenty patients who did not meet the implant criteria were implanted without the 10 J safety margin. We asked that an update of the clinical experience of these patients be provided. The mean ejection fraction of these patients was 26.9 percent. It is believed that the patient's condition was responsible for the termination of the implant procedure which resulted in the patients not meeting the implant criteria. Of these 20 patients, VT was induced at chronic follow-up in 16 patients and in all cases successful treatment was documented. The overall spontaneous VT episode efficacy was 98.9 percent. The spontaneous VF efficacy was 96 percent. There have been 2 deaths, both classified as nonsudden cardiac secondary to end stage heart failure. The one year sudden cardiac death survival in this population is 100 percent. The overall one year survival was 85.5 percent.

Request # 7

The manufacturer provided a table with percentages and the numerical support where appropriate.

Request # 8

An update of the patients who were implanted with the Transvene Lead system and were not counted in the PMA population was provided. The data covers a total of 1335 implants in 1330 patients with the PCD Transvene Lead System (757 patients in the PMA population and 573 additional patients). Of the 1330

patients, the primary indication was VT in 725 (54.5 percent). The spontaneous efficacy for VT and VF was 98.1 percent and 98.1 percent respectively. The overall survival was reported as 93 percent.

As of February 1, 1993, there have been 225 complications reported in 195 patients and 275 observations reported in 228 patients implanted with the PCD Transvene Lead System. How many of the complications and observations were from the additional 573 patients? According to the manufacturer, the percentage of patients with a complication or observation has decreased compared to the original PMA population of 757. Also, according to the applicant, the percentage of patients with lead dislodgements was reported to have also decreased from 12 percent of the population with a complication to 8.8 percent, and from 1.60 percent of the population with an observation to 0.9 percent.

Of the 1330 patients, there have been 30 (2.3 percent) complications involving pocket infection, and a total of 117 (8.8 percent) lead dislodgements. Included in the lead dislodgements, there were 36 cases which involved the SVC lead. (The manufacturer should discuss this information to clarify that every attempt has been made to address the complications. There should be evidence that the frequency of the complications has decreased.) There have been a total of 68 deaths (10 sudden cardiac, 37 nonsudden cardiac and 21 noncardiac) of the population of 1330 patients. The patients in whom the PCD was programmed OFF were included in the survival analysis. The perioperative death rate was 0.8% (10/1330). The one year actuarial survival rates were reported as follows: sudden cardiac death - 99.3 percent; nonsudden cardiac - 96.3 percent; all cardiac - 95.6 percent; noncardiac - 98.1 percent; perioperative - 0.8%; and overall - 93 percent.

Request # 9

We asked that the manufacturer differentiate between DFT testing and lowest energy to defibrillate (LED) testing. Also, we asked that samples of patient report forms which show the scheme of testing which was used in determining DFT and LED be provided. DFT testing was described as 3 out of 4 successes at 18 Joules. The protocol which included step down testing was included. The investigators were allowed to waive the step down testing if the patients could not tolerate the additional VF inductions. In these cases, the LED which is the lowest energy that successfully defibrillated the heart was programmed.

Request # 10

There was a statistically significant difference between the mean DFT obtained with the RV-CS-SQ lead configuration and other configurations. We asked the manufacturer to discuss the difference and the intended ramifications. The manufacturer

stated that the tests demonstrated that the RV-CS-SQ configuration had a lower DFT than the other configurations. This was simply due to the energy being better distributed throughout the myocardium with this configuration. It was pointed out that the intent of the study was not to show that lower DFTs result in better patient outcome. The primary emphasis was to demonstrate that the patient could be reliably defibrillated over time, and that there is a high probability of survival from sudden cardiac death regardless of the lead configuration or pathway chosen.

In terms of comparison of the PCD Transvene and PCD Epi groups, it was stated that the defibrillation efficacy protocol was identical for both groups.

Request # 11

The manufacturer provided a discussion of the DFTs or energy requirements obtained with the use of the single versus the sequential and simultaneous pathways. Essentially, even though the majority of the patients in both PCD populations were programmed with different defibrillation pathways, the DFTs were comparable (single - mean DFT 10.5 J and for sequential/simultaneous - mean DFT 8.8 J). It was reported that there was no difference in outcome for the patients with either of the systems.

Request # 12

According to the manufacturer, the time between detection and delivery of therapy of the PCD Transvene System is dependent upon the programmable VT and VF detection parameters. (The manufacturer should respond to the effect that an increase in lead impedance could have on the time from detection to delivery of therapy). In both of the PCD populations (Transvene and Epi), the majority (90 percent) of the spontaneous episodes of VT and VF were converted with the first shock. The most frequently programmed VT detection and therapy parameters were: VT number of intervals to detect (NID) - 16; VT tachycardia detection interval (TDI) - 400 ms; VT therapy # 1 type - ramp; VT therapy # 1 parameters - 91 percent rate adaption, 5 pulses, 3 sequences, 10 ms decrements; VT therapy # 2 type - cardioversion; and VT therapy # 2 parameters - 5 J. The most frequently programmed parameters for VF detection and therapy included: VF number of intervals to detect (NID) - 18; VF tachycardia detection interval (TDI) - 320 ms; VF therapy #1 type/parameter - defibrillation/34 J; charge time for VF therapy # 1 - 6.0 seconds; VF therapy # 2 type/parameter - defibrillation/34 J; and charge time for VF therapy # 2 - 3.0 seconds.

Request # 13

In response to the deficiency regarding the 2:1 VF sensing margin, the manufacturer provided the following information. The

recommendations for programming include a programmed sensitivity value of 0.3 mV for the PCD. During defibrillation testing, the ETCD is programmed with a nominal sensitivity value of 1.2 mV which is four times the nominal sensitivity setting (0.3 mV) of the PCD. When the PCD is programmed at 0.3 mV, it provides a four step safety margin (because sensing was evaluated at a value four times less sensitive than the programmed value). When the device is programmed at 0.6 mV, there would be a 2:1 VF sensing margin. It was stated that all of the patients who received the PCD Transvene System had a 2:1 VF sensing margin. At the last known follow-up, the manufacturer mentioned that 76.6 percent of the patients were programmed to 0.3 mV and 22.3 percent were programmed to 0.6 mV. There have been no reports of undersensing during induced VF episodes and no deaths due to the nondetection of a spontaneous VF episode.

Request # 14

As of the June 24, 1992 data cutoff, 130 of the 329 patients followed for 6 months or greater had a spontaneous VT episode with a mean of 28.9 (3752/130) episodes per patient. One hundred and twenty patients had a spontaneous VF episode with a mean of 5.6 (667/120) episodes per patient. A total of 179 patients had either spontaneous VT or VF episodes with a mean of 24.7 (4419/179) episodes per patient.

Of the 115 patients followed for 12 months or greater, 60 patients had a spontaneous VT episode with a mean of 29.5 (1770/60) episodes per patient. Thirty-seven patients had a spontaneous VF episode with a mean of 6.7 (248/37) episodes per patient. A total of 67 patients had either spontaneous VT or VF episodes with a mean of 30.1 (2018/67) spontaneous episodes per patient (will be updated).

Request # 15

We asked that clarifications be provided regarding how the treated episodes, designated as success or failure, were categorized. The manufacturer reiterated that spontaneous episodes (VT and VF) are defined as those which satisfy the detection criteria for VT and VF. A table which included the spontaneous VT and VF experience was provided. The table clearly outlined the experience which included a breakdown of the number of episodes and patients and the ineffective episode experience.

It was noted that 60 patients had 163 VT episodes in which the PCD was ineffective in terminating the spontaneous episode of VT despite the delivery of all four therapies. No patient deaths occurred as a result of the ineffective VT therapy. Reprogramming and an adjustment of the patient's drug regimen resolved the problems. There are no concerns regarding the data as presented.

Sixteen patients experienced 31 episodes of VF in which the PCD

was ineffective in terminating the episodes despite the delivery of all four programmed VF therapies. Three of the patients experienced ineffective therapy of a spontaneous VF episode due to lead performance or "secondary to a terminal event." One patient had an episode of ineffective VF therapy due to lead dislodgement. A second patient had an episode of ineffective VF therapy due to lead fracture which generated "noise" which was detected as VF by the PCD. The third patient had two episodes of ineffective therapy at the time of his "monitored" death. Pharmacologic intervention and reprogramming was used in resolving the events associated with the majority of the 16 patients.

Request # 16

The Table IM-6 was modified to include the episodes which were unsuccessfully terminated due to atrial fibrillation or sinus tachycardia. The percent of unsuccessful termination (ineffective in terminating the arrhythmias despite the delivery of all four therapies) is also included for VT and VF. There was a higher incidence (0.9 - Epi and 0.4 Transvene) of unsuccessful termination of VT with the PCD Epi System versus the PCD Transvene System. The information in the Table is as of the June 24, 1992 cutoff date. It is unclear if the data on the proceeding pages are as of the updated cutoff (February 1, 1993). These data state that 30 patients out of 757 had 68 spontaneous VT episodes where the PCD was ineffective in terminating the episode despite delivery of all four therapies. Twenty-five of the patients experienced 45 (0.9%) episodes which were due to sinus tachycardia or atrial fibrillation/flutter with a rapid ventricular response which were detected as VT. Five patients in the Transvene population had 9 spontaneous VF episodes where the device was ineffective in terminating the episode despite the delivery of all four VF therapies. This was due to the detection of sinus tachycardia and atrial fibrillation with a rapid for The device responded appropriately as programmed. However, the rhythms were not VF as seen by the device. Reprogramming and pharmacologic intervention resolved these problems and those mentioned regarding the detection of the spontaneous episodes of VT.

Request # 17

We asked for a clarification regarding the category "Failure to Cardiovert/Defibrillate" and how an episode of an inappropriate therapy is categorized. The manufacturer reported that the incidence of "Fail to Cardiovert/Defibrillate" was 0.8 percent is now 1.2 percent due to the increased follow-up time. The manufacturer stated that the instances of failure to cardiovert and/or defibrillate were due to increased defibrillation requirements during induced episodes of VF. It was stated that the failures reported in the article by Winkle, et. al, (AICD patient population used for comparison to the PCD Transvene population) were associated with patch dislodgement, patch

crinkling, lead conductor fracture and elevated defibrillation thresholds due to changing patient condition. The comparison between the complications/observations of the PCD Transvene and the AICD showed a somewhat greater incidence of pocket infection within the PCD Transvene population.

Request # 18

We asked the manufacturer to differentiate between the 38 inactive patients reported in Table IH-1 (previous amendment) and the 34 patients who were reported as no longer active. The manufacturer stated that the amendment contained an error. According to the manufacturer, the text preceding the Table should have read, "there are a total of 38 patients who had received a PCD System and are no longer active in the study as of 6/24/92." As of the data cutoff, it was reported that 82 patients (patient deaths - 51, infection (explant) - 22 and heart transplant - 9) who received a PCD system are no longer active in the study.

Request # 19

This request had to do with how the sudden cardiac death survival was calculated and if all patients who had a prior cardiac arrest were included in the analysis. The manufacturer adequately responded to the request. It was mentioned that additional data regarding the statistics would be available upon request if there was a need to verify the survival probability. It was mentioned that all patients in the Transvene study were included in the analysis regardless of the indication or prior cardiac arrest status.

Request # 20

At our request the manufacturer included the number of patients in the referenced Table with the percentage and calculated p-values. It was again referenced that verification of the percentages and p-values are available upon request.

Request # 21

As requested, the manufacturer stated that the null hypothesis was that the patient characteristics are equivalent for the three lead configurations: RV/SVC/SQ, RV/CS/SQ and RV/CS/SVC. The [(B)(4) (B)(4)]was used to test for association between variables (the Pearson chi-square statistic was used). The commercial statistical software package was used in calculating the statistical information presented in Table IV-C. The validity of the statistical analyses performed along with statistical methods employed will be reviewed by FDA's statistician.

Request # 22

In order to justify data pooling and data analysis, the FDA

statistician questioned the statistical procedure which was used. The manufacturer responded by saying that there is no reason to

[(B)(4)]

significance level. However, the adequacy of the response will be addressed by the statistician.

Request # 23

The manufacturer discussed how the confidence interval was calculated. According to the manufacturer, [

(B)(4)

] The statistician should review this response. provided.

Request # 24

Clarifications regarding the information presented in Table XB-1, page 378 of Volume 2 were requested. The response involved the use of the (B)(4) computer software in analyzing whether there were significant differences between the PCD and Ventak P populations. The FDA statistician should also address the adequacy of this response.

Request # 25

The manufacturer discussed the instances of inappropriate therapies. The majority of the cases involved atrial fibrillation with a rapid ventricular response or sinus tachycardia. In these cases the rhythms overlapped the programmed detection criteria. In cases like these, the investigator either reprogram the device or modifies the patient's drug regimen. The manufacturer stated that the labeling for the PCD contains programming recommendations and warnings for potential programming problems.

The Manual also contains explicit recommendations for programming the Onset Criterion and the Stability Criterion. It was reported that as of February 1, 1993, 33 of the 757 Transvene patients had the Onset Criterion enabled and 55 patients had the Stability Criterion enabled. Eleven of the patients had both the Onset and the Stability algorithms enabled. The majority of the patients with the Onset and Stability enabled had the algorithms programmed ON within 30 days of implant. However, many patients had the algorithms programmed ON for the first time very late in the follow-up period. The efficacies for the treatment of VT and VF (induced and spontaneous episodes) when the algorithms are programmed ON were provided. In the cases of induced episodes, it was reported that the PCD performed appropriately. Specifically, the spontaneous experience includes the following:

The efficacies for VT and VF of the patients with the Stability Criterion programmed ON was 94.8 percent and 100 percent respectively. The efficacy for VT and VF in patients with the Onset Criterion programmed ON was 97 percent and 100 percent respectively.

Request # 26

We asked the manufacturer to provide a discussion of the "device related" complications reported for the Transvene and the PCD epicardial populations. The manufacturer stated that "device related" complications have reference to the complications which resulted in explantation of the device for reasons other than death, infection or transplant.

There were 4 patients within the Transvene population who were explanted due to reasons other than those named above. Reasons for explant included: (1) low battery voltage due to leakage at the input of one of the integrated circuits; (2) failure to appropriately synchronize and deliver cardioversion therapy for an induced VT episode; (3) Power on Reset condition which was not related to the delivery of external defibrillation or cautery; and (4) inappropriate delivery of VF therapy during manual capacitor charge time. In all cases, it was reported that the devices were safely replaced with no adverse consequences to the patient.

There were 7 patients in the PCD Epi population in whom the PCD was explanted due to reasons other than death. The reason for explant in all 7 cases was because of lower than expected battery voltage. The causes for low battery voltage included the following: (1) failure of the integrated circuit; (2) leakage at the input of one of the integrated circuits; and (3) tantalum capacitor leakage. In all of these cases, the devices were also safely removed with no adverse effects on the patients.

There were 4 patients in whom the PCD was explanted due to reasons other than those mentioned above. In these cases the events were classified as complications. These cases involved: low battery voltage (1); inappropriate VF therapy (1); failure to synchronize and delivery therapy (1);and Power On Reset condition due to electrocautery or external defibrillation (1). (The results of all pending analyses should be provided.

Request # 27

The manufacturer discussed complications reported in the patients followed for one year or greater. As of February 1, 1993, there have been 393 patients implanted for one year or greater. There have been 89 complications reported in 76 patients and 122 observations reported in 99 patients. Therefore, 19.3 percent (76/393) of the patients had an event categorized as a

complication and 25.2 percent (99/393) had an event categorized as an observation. The observations included 40 cases of inappropriate VT therapy and 29 cases of oversensing.

The complications included 5 cases of pocket infection, 6 cases of lead fracture and 56 cases of total lead dislodgement. Of these there were 29 dislodgements which occurred at greater than 30 days. Reoperation was required in all cases to reposition the lead.

None of the complications and observations have resulted in a patient death.

Request # 28

We questioned the infection rate reported for the Transvene study. The manufacturer stated that the incidence of infection in the Transvene study is not significantly different form that reported for the Ventak P epicardial lead system (2.3 percent for the Transvene and 2.4 for the Ventak P). The manufacturer feels that there is no substantial increase in the infection rate. Therefore, the current labeling is appropriate.

Request # 29

The manufacturer discussed the experience in the use of the different entry sites. We wanted to know whether the labeling would aid in the selection of an entry site. The manufacturer stated that the left subclavian vein was the most frequently used entry site regardless of the lead and location. It was stated that the physician makes the decision about the specific entry site. However, the technical manuals contain information about the selection of a entry site, and cautions regarding the different entry sites. There are no specific concerns regarding this information.

Request # 30

This deficiency asked about the Transvene Systems that were explanted, returned and analyzed. Of the 762 implants in 757 patients, 41 units were explanted. Fifteen systems were explanted due to patient death, infection (17), cardiac transplant (5) low battery voltage measurement (1) and PCD performance issues (3). Fifteen systems of the 22 deaths were explanted and returned to the company for analysis (five systems were interred with the patients). Of the 15 systems which were returned, ten were analyzed and found to be performing to specifications. Of the 41 devices explanted, final analysis on 19 systems showed that the systems were performing to specifications. It was reported that final analysis is pending on 17 units. The report of the analyses of these units should be provided. The manufacturer mentioned that of the 41 lead

systems, 21 lead systems or portions of the systems were returned. Of these 21 lead systems, the helix of one 6966 lead was damaged (explant data will be updated in requested volumes).

Request # 31

The manufacturing discussed the death of the patient who died 22.5 months post implant. The manufacturer stated that the patients was admitted to the hospital for heart failure and increased episodes of VT and VF. In addition, the patient was reported to have digitalis toxicity. The patients later expired, described as secondary to heart failure due to LV dysfunction. The death was categorized as nonsudden cardiac and not related tot e PCD Transvene System. Interrogation of the device at the explant revealed a normal battery voltage and charge time. Therefore, the patient had experienced no new episodes of VT or VF since the last follow-up visit. The analysis showed that the PCD was performing to specifications. Were the leads returned and analyzed?

The manufacturer provided all relevant data (implant and follow-up data, programmed status of the PCD, etc.) pertaining to the patient (PCD Serial Number [B6] implanted for 22.5 months.

Request # 32

We asked about the number of perioperative deaths, and if in these cases there were devices programmed OFF. As of February 1, 1993, there have been 51 deaths in the Transvene PMA population. Five (0.7 percent) of the deaths were perioperative (sudden cardiac (2, nonsudden cardiac (2) and noncardiac (1)). The patient death in which the PCD was programmed OFF, was classified as non-sudden cardiac not related to the tachyarrhythmia episode. A copy of the death summaries was provided for our review.

Request # 33

This deficiency deals with the 1 year sudden cardiac death survival and overall actuarial survival of the patients followed for a year. According to the manufacturer, the survival calculations took in to account the following: all of the patients were alive at one year post implant so their survival from all causes of death was 100 percent. Patients who died within 30 days are not counted within this group. There are no concerns about how the manufacturer addressed this deficiency.

Data (treatment efficacy, lead orientation, complications and survival rates, etc.) of the patients who have been followed for 1 year or more were provided. Of the 115 patients followed for one year or more, the majority (94.7 percent), the primary indication was recurrent, sustained VT without an episode of sudden cardiac death. The treatment efficacy for the patient

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population was 98.9 percent for spontaneous VT and 98.8 percent for VF. The treatment efficacy is equivalent to the overall patient population. Twenty-four of the patients followed for 1 year or more had a complication. There are no specific concerns regarding the data submitted.

Request # 34

The manufacturer provided an engineering drawing of the Transvene lead models and a description of the testing of each segment and the full lead body. These data have been reviewed in the IDE application. However the adequacy of the response will be assessed by one of the reviewers on the team.

Request # 35

We asked that the manufacturer discuss the adequacy of the flexing procedures employed [(B)(4)] [(B)(4)] The manufacturer discussed the life testing protocol and how the leads were tested. [(B)(4)] [(B)(4)] We asked that the manufacturer document, for clarity, all relevant testing of the Transvene leads. The response will be reviewed further by one of the reviewers on the team.

Request # 36

The manufacturer provided documentation regarding the potential for failure of the platinum sputtered Transvene Model 6966. A side-by-side comparison of the Model 6966 and the 4,000 series bradycardia leads (platinum sputtered leads where failure was noted) was included. The review of other team members will specifically address the specifics of the response.

Request # 37

The manufacturer provided a copy of the Summary of Safety and Effectiveness with the updated clinical data.

The manufacturer submitted copies of the technical manuals for our review. Data as referenced in the review will be considered for incorporation into the labeling. At this time there are no specific concerns. The Transvene Lead System will be labeled for use with the pulse generator with which it has been tested. Namely the Medtronic Model 7217B PCD.

It should be noted that as a condition for approval of expansion (allotment of 200 patients per month), the manufacturer has agreed to submit monthly reports. The reports should include a

trend analysis of the observations and complications, returned devices and deaths. These data will be a beneficial adjunct to the data contained within the PMA application. These data will lend support and help to alleviate any concerns which might be related to the incidence of complications and observations reported for the PCD Transvene System.

Discussion of the Review of the PMA Application for the PCD Transvene System

The manufacturer has responded satisfactorily to the deficiencies listed in our letter of March 17, 1993. Several issues which are noted in the teleconference memo (attached) were discussed with the manufacturer. Namely, presentation of the data for Panel review, questions pertaining to the performance of the PCD Transvene and the reported observations and complications. The manufacturer adequately responded to our questions and/or agreed to include specific data in the Panel PMA volumes.

Teleconference

Between: Medtronic Representatives
And: Doris Terry (HFZ-450)
Date: April 29 - May 17, 1993

We discussed and/or requested the following:

1. Updated information on patients with non-standard Transvene configurations should be provided. It was stated that twenty-four patients received the Transvene leads initially (not counted in the 757). Need data on this group. Four of the patients with non-standard configurations received the leads after implant and are counted. Data are not separated out. The manufacturer will provide a "patient tree" which includes all patients.

2. Updated data on the 97 patients who were screened for the Transvene and went on to receive the Epi system should be provided.

3. How many of the patients followed for a year or greater did not meet the implant criteria? Need to know the experience of these patients.

4. The PMA Data should be arranged to include the following sections for panel review:

   Preclinical Tests (Bench, Animal, Life)

   Investigational plan (protocol, hypothesis, objectives of the study, patient report forms)

   Updated clinical report

      Patients who did not meet the implant criteria.
      Patients in the non-standard lead configuration
      Patient followed for one year and greater
      patient followed for 6 months and greater
      (spontaneous experience)
      experience by primary arrhythmia
      Foreign patients

   Observations and Complications

   Additional Transvene patients

   Pertinent Data from June 24, 1993
   Clinical Report

   Comparison Data

Explants

Deaths

Labeling

Summary of Safety and Effectiveness

Survival curves (statistics)

Pertinent Articles (when referring to an article, please include)

Patient Manual

Responses to FDA Concerns (Reviewers and Statisticians). All questions will be included and addressed. If data are incorporated into other sections of the volumes, the section and page number will be referenced.

4. A comparison table of mortality and survival data for the PCD Epi and PCD Transvene and the Ventak P should be provided.

5. Number of patients followed for one year or greater who had spontaneous episodes or were induced after 6 months. Update of Table, page 73.

6. Update of table (complications and observations by follow-up interval) as presented in Volume 2, September 21, 1992 amendment. Complications and observations for the two patient populations (PMA cohort and additional Transvene patients) should be reported separately.

7. Update on foreign experience, namely complications and observations.

8. Trend analysis of the incidence of complications observations and complications within the patient groups (patients followed for 1 year and more, patients implanted with nonstandard lead configuration, etc.) and by primary indication (VT, VF, and VT/VF). These data should be updated. Statistical methods employed should be identified.

9. The complications and observations of the 573 additional Transvene patients should be reported separately. How many have dual sleeves?

Update on experience with dual anchoring sleeves. Update on

573 patients, complications and observations by follow-up.

10. There should be a section which includes ineffective therapies. The Section should report the circumstances surrounding these patients.

11. There should be an update on the reprogrammings (Table VIIF-5, September amendment).

12. Incidence of ineffective therapies with the PCD Epi and PCD Transvene. Updated data as reported in Table IM6, page 78 of the March amendment should be provided.

13. Data obtained from interrogation of the device upon the patient's death should be provided. The data should be referenced as explant data.

14. On Page 338, it was stated that all 58 devices were returned. A Table which contains these data should be prepared.

Continued - May 12, 1993

15. Evidence to support the claim that gender, primary indication and the system implanted (PCD Epi or PCD Transvene) had no impact on survival outcome. The evidence would consist of a description of the computer program used, data input and output, and the decision criteria.

26. A statistically significant difference between the PCD Transvene and the AICD Epicardial System using the confidence interval analysis was found. How was the confidence interval computed?

27. The table on page 24 shows the actuarial survival of PCD Transvene versus PCD Epi. The statistician would like to see a Table which includes mortality data according to monthly intervals, e.g., number dead/number at risk for the Transvene and Epi systems. Then the Mantel Haenszel Chi square test should be used to compute the p-values. The manufacturer should also discuss how the p-values in Table 2-16, page 24 were derived.

28. Based on the clinical experience, will include addition to the labeling: different positions for patch placement. Majority (75 percent) of patients had patch leads placed at the mid axillary line or fourth or fifth intercostal space. Data will be provided about surgical approach.

29. In support of the chronic performance and integrity of the lead system, We asked the manufacturer to provide data regarding the induced and spontaneous activity of the

patients followed for 6 months and beyond. We reiterated that they should be able to account for the experience of each patient. Each of the patients should have been tested or should have had spontaneous episodes. The data can be presented at 90 days and beyond, 6 months and beyond, 12 months and beyond, etc.

30. Results of remaining analyses on all device explants. should be provided. Note: There was a total of 58 explants.

31. Update of the observations and complications as per the time interval. The data in Table XII-E-2 in the September amendment will be updated.

32. In response to Albert Moyal's review, I asked the company about the use of a two lead configuration. The manufacturer stated that the patients who were implanted with a two lead configuration are counted within the group of patients (43) with a non-standard configuration. Among these, 6 patients have a RV-SVC or RV-SQ; and 10 patients have three leads, programmed in a two lead configuration.

    The 702 patients counted in the table on page 289, March Amendment, include only those patients who had LED and/or DFT testing. Other concerns included in the reviewer's memo will be documented in a phone conversation by the reviewer.

The manufacturer agreed to provide the requested information.

Response to Statistician's Review

Items # 2.1 and 2.2

The statistician stated that the p-values for sex and primary indication rendered the two groups (PCD Transvene and PCD Epi) significantly different. Therefore, the statistician contends that the two groups are not "compatible." According to the manufacturer, primary indication and gender did not impact survival. However, the implanted system did influence the probability of survival. The manufacturer used the Cox Regression Analysis to support this position. The statistician asked that the manufacturer provide evidence (description of the computer program, the data input and output and the decision criteria which were used) to support the claim. The request was discussed with the manufacturer. Appropriate data will be submitted in the Panel Volumes to address this issue.

Item # 2.3

The manufacturer was asked to provide data regarding how the confidence interval (as referenced on pages 13 and 256, March Amendment) for the one year overall survival data was computed. The response will be included in the Panel volumes.

Item # 2.4

The manufacturer was asked to prepare a table which depicts the number of patients dead versus the number at risk or total patient population at the different monthly intervals, e.g. 0-3, 3-6, 6-9 and 9-12. In addition, the manufacturer was asked to use a specific Chi square test to compute the p-value for the "association" between the Transvene and Epi survival. It was unclear how the p-values were derived. The requested data will be submitted in the Panel volumes.

Item # 2.5

The similarities and differences between Table 2-12 and Table 3-3 essentially involve data presented for the entire population versus patients followed for one year.

Item # 2.6

The data set and a description of the computation procedure for calculating the survival probabilities were requested. These data are necessary for verification purposes. A response will be

included in Panel volumes. The manufacturer mentioned that the requested data consists of reams of raw data. However, a response which includes a description of the statistical procedure utilized and how the probabilities were calculated will be provided.

Item # 2.7

The similarites and differences between the one year actuarial survival in Table 1K-4, page 43 and Table 8-5, page 451 should be discussed. The numerators and denominators used to derive the one year actuarial survival shown in Table 8.5 should be provided in the requested volumes.

Item # 2.8

The data set and the computation procedure (as referenced on page 83) used in the calculation of the survival probability should be provided for verification. Same as in Item # 2.6. However, the requested data will be condensed, and included in the Panel volumes.

Item # 2.9

The manufacturer should provide the data set and the SAS procedure (statistical software package) used to derive the p-values for the data provided in Table 1M-10, page 84. Information will be included in the Panel volumes.

Item # 2.10

The manufacturer reported a p-value of (B)(4) The statistician calculated a p-value of (B)(4) . The manufacturer should discuss how the p-value was calculated. The manufacturer will address the difference in the calculations.

Item # 2.11

We requested that the results of the analyses pending on the devices that underwent early explant should be provided. Data will be included in the requested volumes.

Item # 2.12

The choice of 30 days (in reporting lead dislodgement) can be justified because of its use historically on an acute basis. Acute is described as within the first 6 weeks.

Item # 2.13

The concern deals with justifying pooling the data from all 78 centers which participated in the PCD Transvene clinical trial. It should be noted that all centers used the same protocol or investigational plan (patient selection criteria, follow-up plan, data collection procedures, etc.) for the PCD Transvene study. The manufacturer will also address this issue in the data which will be submitted.

Item # 2.14

The statistician stated that Table E-2, page 215 does not provide an adequate presentation of the follow-up data. The statistician directed the manufacturer to Table 4.6 as published in Lee, Elisha, "Statistical Methods for Survival Data Analysis", page 93 to see how the data could be best presented. This was considered as a good reference for preparing a life table analysis. It was pointed out that the manufacturer should also discuss the reasons why some of the patients were not represented in the follow-up data. It should be noted if the patients were withdrawn alive or lost to follow-up. The statistician's request was relayed to the manufacturer. The response will be provided in the Panel volumes.

Item # 2.15

The statistician would like to see the survival table (page 231) stratified monthly as referenced in Item # 2.4. How the projected one year survival calculations were done should be explained. The manufacturer agreed to provide the data for our review.

Item # 2.16

The numerators and the denominators for the percent success (Table I-1, page 233; Table IF-2, page 287 ; and Table IF-4, page 290) for the treatments of spontaneous episodes should be provided. These data will be included in the Panel volumes.

Item # 2.17

The data collected at the designated follow-up intervals will be included in the updated report and reflected throughout the Panel volumes.

Item # 2.18

The manufacturer was asked to address the calculation of the p-values reported in Table 2.16, page 24. FDA's statistician calculated the p-values and obtained different values than those reported by the manufacturer. This will be addressed in the

Panel volumes.

Note: These data are for clarification and verification purposes. The data do not significantly impact upon the safety and effectiveness of the PCD Transvene System. Therefore, the request for these data are being made via a telephone conversation to the manufacturer.

3fc

Memorandum

June 11, 1993

To: Doris Terry, B.S., M.S., Medical Reviewer, DCRND

From: Jeffrey D. Jones, M.D., F.A.C.C., Medical Officer, DCRND

RE: Medtronic PCD Transvene Lead System, PMA Amendment P920015

At your request I have reviewed the relevant clinical aspects of the Medtronic PCD Transvene PMA amendment. The clinical study involved 757 patients followed for a mean of 11.7 months. 657 patients were followed for 6 months or greater and 393 patients were followed for 1 year or greater. Inclusion criteria were as follows:

1. Those patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction.

2. Those patients who have recurrent sustained ventricular tachycardia that remains inducible via programmed electrical stimuli or exercise, or occurs spontaneously despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

The 757 patient population was compared to three (3) different historical controls in a retrospective fashion. The three historical controls were 1) the Ventak-P Epicardial system PMA (which was obtained through the freedom of information act), the published AICD clinical experience published from Winkle et al, in the May 1989 JACC (copy attached to this consult for reasons described below) and the PCD Epicardial System clinical experience.

This retrospective picking and choosing of historical controls is not only not scientifically sound (B5) [redacted] historical data. For example, the JACC article by Winkle which was referenced by Medtronic was conducted over a seven (7) year period. It is inappropriate to use these total complication rates as a comparison. To do so markedly minimizes the "complication and observation" rates presented in this study of lesser duration than the control. Specifically, it minimizes the significance of the incidence to failure to cardiovert or defibrillate, of inappropriate VT/VF therapy delivery, pocket

infection (explant) and erosion rates. Approximately half of the infection in the control was due to generator replacement at end of life. It clearly is misleading to compare this to the incidence of primary infection in the study population. In addition, I was unable to determine how the 4.1% failure to cardiovert or defibrillate that is presented by Medtronic was calculated from this article.

Regardless of their flawed scientific approach and manipulation of the historical data several important clinically relevant statements can be made based on the data provided by the company.

1. The patient population of the Ventak-P is likely similar enough to the PCD Transvene study population to allow the comparison of carefully selected endpoints.

2. The one year actuarial survival from SCD in probably comparable between the PCD Transvene and the Ventak-P Epicardial system. Regardless of the fact that survival distributions were not compared by an acceptable statistical method (eg: Mentel-Haenszel), the conclusion is probably a reasonable one.

3. The perioperative mortality of the PCD Transvene is **comparable** to the Ventak-P patient population but **not** statistically lower. When all patients screened for a PCD Transvene are included into the study group (as is clinically appropriate) the perioperative mortality increases from 0.7% to 1.6% and is no longer statistically significantly different than the 2.7% in the Ventak-P population which Medtronic chose as their comparison.

4. The PCD Transvene and the PCD Epicardial patient populations are likely similar enough to allow the comparison of carefully selected endpoints.

5. The one year actuarial survival from SCD is probably comparable between the PCD Transvene and the PCD Epicardial system. Again however, survival distributions were not compared.

The comparison of spontaneous VT/VF episode efficacy is so inconsistently performed and contradictory[B5 B5]. In addition, R-R interval analysis is not accurate enough to make the bold claims of the high success rates of appropriate therapy that are made by the company. [B5 B5 B5 s. In other]

Medtronic recognizes this and states that "the philosophy behind Medtronic's labeling recommendations and the practice of PCD

investigators is to[B4 B4] tachycardia." At this stage in the development of these devices this is a very reasonable approach. Therefore, the PCD Transvene [B5 B5] in the PMA.

Of continued concern is the very high incidence of lead dislodgment (15.7% total, 9.7% for SVC, 10% for CS) with a reported lead related complication rate of 15.1%. Recall that Medtronic defines complications as requiring invasive interventions to correct. This explains the 5.3% infection rate in the PCD Transvene patient population compared to the 2.5% in the PCD Epicardial system population. Re-operation and repositioning of the lead contributes to the iatrogenic infection rate. This absolute difference is even more alarming when one considers that the mean follow-up in the epicardial group was 16.3 months compared to the lesser 11.7 months is the Transvene. The infection related explant was 2.9% in the PCD Transvene patient population compared to 2.3% in the PCD Epicardial study and 2.4% in the Ventak-P study. No statistical analysis was provided by Medtronic between these comparisons.

In response to FDA's deficiency letter, Medtronic has submitted data in an additional 234 patients which have been implanted with two (2) separate anchoring sleeves. These patients were not included in the 757 patients in the study population. 186 patients completed their one (1) month follow-up and 49 completed a 3 month follow-up. Reportedly, there has been only a single documented dislodgment. Additional follow-up on these patients is needed. If prior to panel review, the follow-up data appears favorable, changing the labeling to emphasize the need for the use of 2 anchoring sleeves should be adequate. FDA should inquire as to the recruitment method used to obtain these additional 234 patients. It could be phrased in the following question:

In reference to the 234 patients who received 2 anchoring sleeves, please explain how these patients were chosen. For example, were they consecutive patients from selected institutions or were consecutive patients from all institutions represented? Are all patients currently undergoing implantation implanted with 2 anchoring sleeves? If not, why not and how are you assured that alternative methods are as effective as the two anchoring sleeve method?

In summary, this collection of clinical data presented by Medtronic in support of their PMA has demonstrated the following:

1. In a similar patient population the PCD Transvene had an equivalent 1 year SCD survivorship when compared to the PCD epicardial system and the Ventak-P systems.

2. A higher incidence of lead dislodgment and infection and probably infection related explant is present in the PCD Transvene PMA patient population when compared to controls.

3. No definite improvement in perioperative mortality has been demonstrated in the PMA population when compared to the Ventak-P study population.

4. No definite conclusions can be drawn about the appropriateness or "efficacy" of spontaneously delivered VT or VF therapy.

The above conclusions can be summarized in the following question which can be posed to the panel:

Has Medtronic demonstrated in its clinical study that the increased risk of lead dislodgment and potential iatrogenic infection justifies a small but statistically insignificant decrease in perioperative mortality?

Lastly, I have a continued concern regarding the perioperative death of patient ZB1100718R. This death was classified as Sudden Cardiac and rightfully so; however, even though the device was interrogated, we have not been told of the results of that interrogation. This information was to be provided to us with this submission but as with the last update Medtronic states, "The results of this analysis are not available as of this submission but will be provided to the FDA." I suggest we require this information before the device is allowed to be reviewed by the panel.

If I may be of further assistance please do not hesitate to ask.

UD

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CARDIAC PACING

Long-Term Outcome With the Automatic Implantable Cardioverter-Defibrillator

ROGER A. WINKLE, MD, FACC, R. HARDWIN MEAD, MD, MICHAEL A. RUDER, MD, VINCENT A. GAUDIANI, MD, NELLIS A. SMITH, MD, WALLY S. BUCH, MD, PAULA SCHMIDT, RN, TAMARA SHIPMAN, RN

Redwood City, California

The automatic implantable cardioverter-defibrillator was implanted in 270 patients because of life-threatening arrhythmias over a 7 year period. There was a history of sustained ventricular tachycardia or fibrillation, or both, in 96% of these patients, 80% had one or more prior cardiac arrests and 78% had coronary artery disease as their underlying diagnosis. The average ejection fraction was 34%, and 96% of these patients had had an average of 3.4 antiarrhythmic drug failures per patient before defibrillator implantation. There were four perioperative deaths and eight patients had generator infection or generator erosion, or both, during the perioperative period or during long-term follow-up. Concomitant antiarrhythmic drug therapy was given to 69% of patients.

Shocks from the device were given to 58% of patients, and 20% received "problematic" shocks. The device was removed from 16 patients during long-term follow-up for a variety of reasons. There were 7 sudden cardiac deaths and 30 nonsudden cardiac deaths, 18 of which were secondary to congestive heart failure. The actuarial incidence of sudden death, total cardiac death and total mortality from all causes was 1%, 7% and 8%, respectively, at 1 year, and 4%, 24% and 26% at 5 years.

The automatic implantable cardioverter-defibrillator nearly eliminates sudden death over a long-term follow-up period in a high risk group of patients. It has an acceptable rate of complications or problems, or both, and most late deaths in these patients are nonsudden and of cardiovascular origin.

(J Am Coll Cardiol 1989;13:1353–61)

Patients who have survived out of hospital cardiac arrest or who have recurrent sustained ventricular tachycardia have a high long-term total and sudden death mortality rate when their arrhythmias cannot be controlled with antiarrhythmic drug therapy (1,2). Previous reports (3–6) have shown a remarkably low short-term sudden death mortality rate in patients receiving the automatic implantable cardioverter-defibrillator (AICD). Although most centers have reported an acceptable rate of complications, others have emphasized certain problems with the device (7). There is undoubtedly a "learning curve" that exists for the implantation of these devices, with fewer complications and problems occurring as a center gains additional experience.

In the near future, there will be tremendous changes in the types of devices being implanted, the lead configurations and defibrillating waveforms used and, over the next few years, in patient selection. Devices will soon include features such as backup bradycardia pacing, antitachycardia pacing and low energy cardioverting capabilities (8–10). Lead configurations will include three epicardial patch lead systems, transvenous catheters (11) and transvenous catheters coupled with subcutaneous patches (12). In addition to the standard monophasic truncated exponential waveform now utilized, devices with sequential pulses (13,14) and biphasic pulses (15–17) will become available. These newer devices may be better suited than the current device to treat patients with more frequent episodes of arrhythmia recurrence, and the indications for implantation may therefore broaden. There have been no significant changes in patient selection criteria for the currently available defibrillator from the inception of the program in 1980. Although there have been improvements in the device and implant techniques, they have been relatively minor compared with changes that will likely occur during the next few years. Therefore, it seems an appropriate time to report our long-term experience with the automatic implantable cardioverter-defibril-

From the Department of Cardiology and Cardiovascular Surgery, Sequoia Hospital, Redwood City, California.

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Address for reprints: Roger A. Winkle, MD, Cardiovascular Medicine, 770 Welch Road, Suite 100, Palo Alto, California 94304.

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lator. In the present study, we report our seven year experience with regard to clinical observations, complications, modifications of implantation techniques over time and long-term survival.

Methods

Study patients. This study describes our experience with 273 consecutive patients undergoing surgery for implantation of the automatic implantable cardioverter-defibrillator between March 2, 1981 and March 2, 1988. This experience represents the personal experience of one of the authors (R.W.), and includes 88 implantations at Stanford University Medical Center, Stanford and 185 at Sequoia Hospital, Redwood City, California. Our early experience after the first 70 implantations was reported in detail in 1985 (3). All patients undergoing initial implantation at our centers are included even if they were subsequently followed up at other implanting centers. Patients undergoing initial implantation elsewhere and followed up by our center are not included in this analysis. All patients signed written informed consent before device implantation, and implantation protocols were approved by the Human Subjects Committee of Stanford Medical Center and the Institutional Review Board of Sequoia Hospital for all implantations done before Food and Drug Administration approval of the device.

Patient selection and preoperative evaluation. Patients were offered the automatic implantable cardioverter-defibrillator as a therapeutic alternative if they had at least one cardiac arrest caused by ventricular tachycardia or ventricular fibrillation, or both, or had recurrent episodes of sustained life-threatening ventricular tachycardia. Patients were excluded from implantation if their cardiac arrest was due to acute myocardial infarction, antiarrhythmic or other drug toxicity or severe electrolyte abnormalities. A small number of patients had either syncopal episodes that were unmonitored or known to be due to nonsustained ventricular tachycardia with sustained hypotensive ventricular tachycardia inducible at electrophysiologic study, or had a familial sudden death syndrome with inducible sustained ventricular tachycardia at electrophysiologic study.

Except for unusual circumstances, all patients underwent complete cardiac evaluation, including right and left heart catheterization, coronary and left ventricular angiography, a complete baseline intracardiac electrophysiologic study and an extensive period of in-hospital telemetry monitoring. Patients with inducible sustained ventricular tachyarrhythmia underwent serial electrophysiologic studies in an effort to find an antiarrhythmic drug that would prevent arrhythmia induction. Patients whose arrhythmia could not be induced while they were receiving antiarrhythmic medication were not offered a defibrillator implant. Patients with a single out of hospital cardiac arrest whose arrhythmia was not inducible at baseline electrophysiologic study were offered a defibrillator implant as a therapeutic option if they had poor ventricular function and repetitive forms on noninvasive monitoring, or if they had the long QT syndrome or primary ventricular fibrillation. When an implantable defibrillator was contemplated for a patient, the patient and his or her family underwent extensive preoperative education, including provision of audiovisual and written materials, extensive sessions with specially trained nurses as well as ample time to discuss the therapy with one or more physicians (18).

All patients with episodes of nonsustained ventricular or supraventricular tachycardia that could trigger the committed device had these arrhythmias controlled with antiarrhythmic drugs. Patients with extremely frequent episodes of sustained ventricular tachycardia had these episodes controlled with antiarrhythmic medication or were excluded from device implantation, as were most patients whose rate of ventricular tachycardia was <140 beats/min. After early 1985, most patients with significant organic heart disease were routinely treated with digoxin to slow episodes of atrial fibrillation, even if they had never had this arrhythmia. Treadmill exercise tests were routinely performed early in our experience to evaluate peak sinus rate, but they were not performed routinely after 1984. Review of previous spontaneously occurring ventricular tachyarrhythmias, in-hospital monitoring data and the arrhythmias induced at electrophysiologic study was utilized to select the cutoff rate of the implanted device. Whenever possible, antiarrhythmic therapy was discontinued shortly before defibrillator implantation to avoid myocardial depression during surgery.

Device and lead selection. Devices implanted before July 1982 (Patients 1 to 5) were the original automatic implantable defibrillator (AID) models, which sensed only sinusoidal ventricular tachycardia or fibrillation. From July 1982 until October 1986, the automatic implantable cardioverter-defibrillator (AICD) was used, after which time the Ventak model 1520 was utilized. All devices were manufactured by Intec Systems or Cardiac Pacemakers, Inc. Ninety-nine percent of all devices used were rate only/high energy models. The first four patients received spring and patch leads made of silver tinsel. All other cardioverting-defibrillating leads were made with drawn braised strands of conducting material. For Patients 1 to 13, only spring-patch lead configurations were utilized. For Patients 14 to 109, spring-patch lead systems were the standard configuration but, if unacceptable defibrillation thresholds were obtained, two patch lead systems were utilized. After Patient 109, nearly all patients received large patch-large patch configurations. Epicardial screw-in leads manufactured by Medtronic Corp., Daig Corp. or Cardiac Pacemakers, Inc. were used in most patients. Transvenous endocardial sensing leads were utilized only when patients had unacceptable R wave amplitudes at several ventricular sites or when the sensing leads needed late revision because of insulation or conductor

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malfunction, or both, of previously implanted epicardial leads.

Surgical technique. Except for the first two patients who underwent median sternotomy, all patients undergoing only automatic implantable cardioverter-defibrillator implantation had this done by a limited left thoracotomy performed for patch lead and epicardial sensing lead placement. After September 1984, a double lumen endotracheal tube was utilized to deflate the left lung transiently to facilitate posterior patch placement. When one patch lead was used in conjunction with the superior vena cava spring, it was the cathode and was positioned near the apex of the heart. When two patch leads were used, the cathode was positioned on the posterolateral left ventricular wall and the anode over the anterior right ventricular walls. When superior vena cava spring leads or transvenous endocardial leads were utilized, they were inserted percutaneously through the left subclavian vein. The distal ends of all leads were tunneled below the costal margin to the deep subcutaneous space in the mid left abdomen and connected to the generator, which was placed in a deep subcutaneous pocket. Patients undergoing patch implantation by means of a median sternotomy had the left cathodal patch placed near the inferoapical left ventricle and the right patch placed along the right atrial border.

All patients with significant (>70%) coronary artery lesions supplying viable myocardium had the lesions bypassed or (less frequently) treated with percutaneous transluminal angioplasty. Most patients undergoing other major cardiac procedures in addition to defibrillator implantation had a two stage operation, with the patch leads implanted initially at the time of their primary cardiac surgical procedure and the generator placed after recovery from surgery. All patients undergoing endocardial resection had patch leads left in place pending the outcome of postoperative electrophysiologic studies. In these patients, an automatic implantable cardioverter-defibrillator generator was placed if ventricular tachycardia occurred spontaneously or remained inducible after endocardial resection. Patch leads were sutured to the outside of the parietal pericardium. Only when defibrillation thresholds were unacceptable were the patches placed inside the pericardium or was the polarity of the shocking leads reversed.

Most patients undergoing generator changes for depleted batteries were admitted on the morning of the generator change and discharged the next day. Prophylactic cephalosporin antibiotic agents were given to patients before early 1985. Since then, all nonallergic patients undergoing either new system implantation or generator changes underwent preoperative povidone iodine (Betadine) showers and received prophylactic antibiotics using both a cephalosporin and vancomycin.

Intraoperative testing. After Patient 14, extensive defibrillation threshold testing (19) was performed routinely for new implants and generator changes utilizing the Intec/CPI external cardioverting defibrillator (ECD) box or the Ventritex HVS-02 testing device. Ventricular fibrillation was induced in all patients, utilizing either alternating (AC) current or bursts of rapid pacing with a cycle length of 10 to 20 ms. Testing of cardioversion thresholds was not routinely carried out at the time of device implantation. Patients undergoing a two stage procedure who had a prolonged cardiopulmonary bypass time during their primary cardiac operation had only limited initial testing to be certain that 15 J was effective, with extensive defibrillation threshold evaluation at the time of generator implantation. In order for a "defibrillation threshold" to be acceptable, 25 J was required to reliably provide a "clean defibrillation" on essentially every test. It was also desired to have 20 J be nearly uniformly effective, and 15 J was expected to be effective approximately half the time. Lower energies were routinely tested, with 25 J rescue shocks being given for ineffective low energy defibrillations.

If the defibrillation threshold was considered unacceptable and the patient had a spring-patch lead system, it was upgraded to a two patch system. For patch-patch lead systems, an unacceptable defibrillation threshold led to further attempts at lead repositioning, placement of the patches inside the pericardium or reversal of defibrillating lead polarity. If these maneuvers failed to result in an acceptable defibrillation threshold, the device was not implanted, the leads were left in place and the patient returned to the operating room approximately 7 to 10 days later when the leads had a chance to approach "chronic" thresholds. If the defibrillation threshold remained unacceptable, a decision was made regarding the advisability of device implantation, or the patient was considered for a reoperation to try a different patch placement. When a satisfactory defibrillation threshold was obtained with the external testing equipment, the permanently implanted leads were attached to the AICD generator and the arrhythmia was induced one or more additional times to be certain that the device to be implanted would effectively terminate the arrhythmia with a single shock.

Pacemaker evaluations. Only bipolar pacemakers were utilized in conjunction with the automatic implantable cardioverter-defibrillator. Care was taken to avoid double counting of atrial and ventricular pacing stimuli or a ventricular pacing stimulus and its evoked local potential if this occurred >150 ms beyond the pacing spike. All implanted pacemakers were chosen to have maximal programmability of pacemaker output. Testing was performed to avoid this potential double counting by evaluating the pacemaker when programmed to its maximal output, and the defibrillator in the electrophysiologic test mode. In addition, the pacemaker was generally programmed to values of heart rate less than half the automatic implantable cardioverter-defibrillator rate cutoff so that if double counting did occur, the defibrillator would not be triggered. To be certain that the pacemaker did not cause undersensing of a sustained ventricular tachy-

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arrhythmia by causing the automatic gain control circuits of the defibrillator to "lock-in" on the pacing spike and ignore the underlying ventricular tachyarrhythmia, arrhythmia episodes were induced with the pacemaker programmed to maximal output in an asynchronous pacing mode. Finally, pacemakers were ultimately programmed to the lowest voltage output consistent with a reasonable margin of safety for atrial or ventricular capture, or both.

Postoperative care. All newly implanted automatic implantable cardioverter-defibrillators were kept inactive during the early postoperative period. Antiarrhythmic medications, if indicated, were restarted in the postoperative period. Encainide was not given to any patient receiving an automatic implantable cardioverter-defibrillator because of the possibility of increasing defibrillation thresholds (20). Patients undergoing therapy with other type IC drugs always underwent generator testing while taking the drug being used. Patients undergoing a staged procedure had no further testing of the device. Patients with an initial complete system implant had follow-up electrophysiologic studies at approximately 5 to 7 days postoperatively. The clinical arrhythmia was induced at this study on the antiarrhythmic medication to be given on a long-term basis. The device was left in the active mode after this study. A 24 h ambulatory electrocardiographic (ECG) recording was obtained during the first 24 h after all newly implanted devices were placed in the active mode. Patients were generally discharged the day after device activation unless other medical conditions required them to stay in the hospital. Operative deaths were defined as those occurring within 30 days of the initial implantation or during the initial hospitalization if it was >30 days and the death was thought to be a direct complication of the surgery.

Long-term follow-up. Two hundred twenty-three of the 273 patients were followed up primarily by us in conjunction with each patient's personal cardiologist. The remaining 50 patients were followed up primarily at other implanting centers. Follow-up evaluation was by direct communication with the patient or patient's physician, or both, mailed questionnaires or data obtained from the Cardiac Pacemaker Inc. computer data base. Patients were seen every 2 months for the first 14 months after each new generator was placed and 1 month thereafter. At each visit a physical examination, charge time to evaluate battery status and the number of shocks delivered by the device were recorded. Patients were generally not reevaluated extensively for single defibrillator shocks; they were hospitalized promptly when a barrage of defibrillator shocks developed. For intermittent but frequent discharge of devices, continuous 24 h ambulatory ECG recordings were obtained until 1984. After that time, generous use was made of transtelephonic devices with a memory loop to determine the cause of frequent discharges. Once the cause of the defibrillator shocks was confirmed, drug therapy was modified to prevent these discharges.

Throughout the study, aggressive therapy was given for underlying congestive heart failure and, since 1986, the oral inotrope vasodilator enoximone has been utilized for patients, followed up primarily by us, who failed to respond to diuretic drugs and vasodilators. Patients with uncontrolled heart failure who were otherwise appropriate candidates were referred for cardiac transplantation.

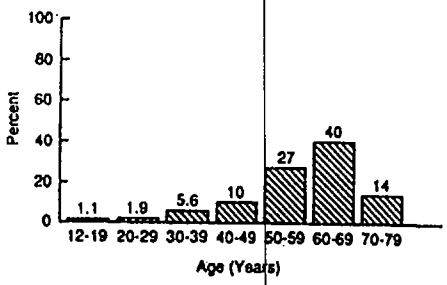

Figure 1. Distribution of ages of 270 patients receiving an automatic implantable cardioverter-defibrillator. The average age was 58.2 ± 11.8 years.

For the purposes of this study, sudden cardiac death was defined as witnessed instantaneous death. All unwitnessed out of hospital deaths were considered to be sudden. All patients whose deaths were classified as due to congestive heart failure were under observation in a medical facility at the time of death and died after a progressive course of worsening heart failure unresponsive to maximal medical therapy. Deaths were considered as arrhythmic but nonsudden when they occurred in-hospital as a result of uncontrolled ventricular tachyarrhythmias.

Statistical analysis. All data are presented as mean values ± SD unless otherwise specified. Life table analysis of survival was evaluated by the Kaplan-Meier method.

Results

Patient characteristics. The average age of the patients undergoing defibrillator implantation was 58.2 ± 11.9 years (range 12 to 77) (Fig. 1). Two hundred seventeen of the 270 patients were male and 53 were female. The underlying heart disease is summarized in Table 1. Ejection fraction, available for 200 patients (73%), had a median value of 34 ± 15% (Fig. 2). The primary underlying cardiac arrhythmia is summarized in Table 2. Fifty-three patients (20%) had not expe-

Table 1. Underlying Cardiac Disease in 270 Patients

Coronary artery disease	211 (78.2%)
Dilated cardiomyopathy	22 (8.1%)
Valvular	13 (4.8%)
Primary electrical	7 (2.6%)
Long QT syndrome	6 (2.2%)
Hypertrophic cardiomyopathy	3 (1.1%)
Other (hypertension 2, Marfan's syndrome 2, right ventricular dysplasia 2, congenital 1, myasthenia gravis 1)	8 (3.0%)

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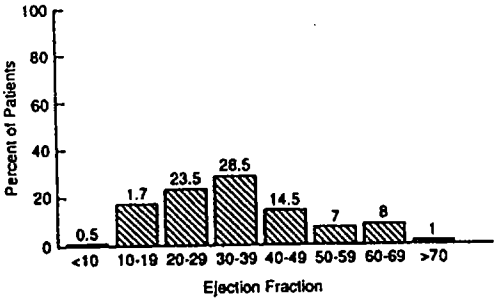

Figure 2. Distribution of ejection fractions of 200 patients receiving an automatic implantable cardioverter-defibrillator. Ejection fraction averaged 34%; it was <40% in 70% of patients.

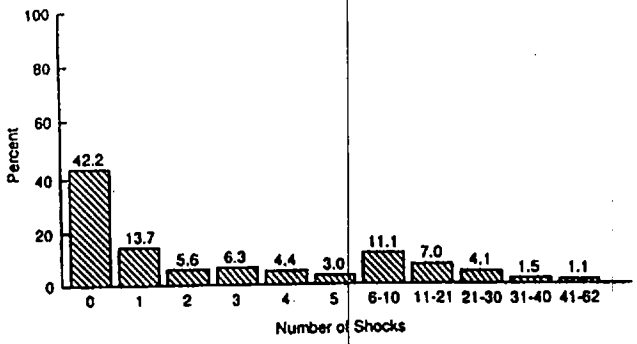

Figure 3. Number of device shocks per patient. The average number was 4.8 per patient.

rienced prior cardiac arrest, 136 (50%) had had a single cardiac arrest and 81 (30%) had had more than one cardiac arrest (average = 1.5 cardiac arrests per patient). At baseline electrophysiologic study, 231 patients (86%) had sustained ventricular tachyarrhythmias reliably induced. Ten patients (4%) had ventricular tachyarrhythmias induced, but induction was not reliable enough for serial drug testing; in 27 patients (10%), tachyarrhythmias were not inducible, and 2 patients (1%) had no baseline electrophysiologic study. Eighty-six patients (32%) had undergone previous cardiac surgery, including coronary artery bypass grafting alone in 53 patients, prosthetic valve replacement in 7 patients, bypass surgery plus valve replacement in 10 patients, aneurysm resection with bypass grafting in 12 patients and other procedures in 4 patients. Two hundred sixty-nine patients (96%) had had at least one antiarrhythmic drug failure clinically or at electrophysiologic study, and the average number of drug failures for the entire group was 3.4 ± 1.8 per patient.

Operative procedure. Two hundred seventy patients received an automatic implantable cardioverter-defibrillator generator; three patients did not undergo generator implantation despite operation for lead placement because of elevated defibrillation thresholds (see later discussion). The initial shocking lead configuration was large patch-large patch in 183 patients (68%), spring-small patch in 71 patients (26%), spring-large patch in 9 patients (3%), large patch-small patch in 5 patients (2%) and small patch-small patch in 2 patients (1%). The sensing lead configuration was epicardial screw-in leads in 242 patients (90%) and endocardial sensing leads in 27 patients (10%). One patient received only the AID device, which required no sensing leads. A total of 189 patients (70%) received the AICD generator as the only operation performed. Eighty-one patients (30%) underwent AICD system implantation as part of a concomitant cardiac surgical procedure. These procedures included coronary bypass surgery alone in 54 patients, endocardial resection alone in 8, valve replacement alone in 2, endocardial resection plus bypass surgery in 12, endocardial resection plus plus valve replacement in 2 and other operations in 3. Among the patients receiving the AICD in conjunction with additional cardiac surgery, the generator was implanted at the time of initial surgery in 21 patients and at a second procedure before hospital discharge in 60. Subsequent generator replacements were for the standard indications of battery depletion, excessive capacitor charge times or device malfunction. Only a single generator was implanted in 148 patients, two generators in 75, three generators in 36, four generators in 10 and five generators in 1 patient.

Table 2. Problematic Device Shocks in 270 Patients

Sinus tachycardia (one nonfatal arrest)	7
SVT including atrial fibrillation	13
NSVT	3
VT	7
NSVT/VT	7
Unknown	10
Misdirection (one nonfatal arrest)	3
Sensing lead fracture	2
Screw caps off	1
Generator malfunction	1
Pacemaker interaction	1
Total	55 (20.5%)

NSVT = nonsustained ventricular tachycardia; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

Concomitant pacemakers. A total of 29 patients (11%) had a bradycardia pacemaker used simultaneously with the AICD. These included 10 (VVI) pacemakers, 16 (DDD) pacemakers, 1 (AAI) pacemaker and 2 Intermedics InterTach antitachycardia pacemakers. One patient with the antitachycardia pacemaker has terminated a number of episodes of slow ventricular tachycardia with the antitachycardia device. The other patient had significant interactions between the InterTach and the AICD at the time of implantation, and the combination was a clinical failure.

Defibrillator shocks. A total of 156 patients (58%) received shocks from their AICD generator (Fig. 3). For most patients receiving occasional infrequent shocks, no effort

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was made to determine whether the shocks were "appropriate" or "inappropriate" because our previous experience indicated this was difficult on clinical grounds. A total of 55 patients (20%), however, had episodes of problematic shocks; the causes for these are listed in Table 2. Once the cause for the problematic shocks was identified, all but five patients had them controlled by changes in drug therapy.

Lead problems. Eight (10%) of 80 patients receiving superior vena cava spring leads had a total of 12 episodes of complications. These included five instances of lead migration and seven instances of lead fracture. One sudden death occurred when a device failed to terminate ventricular tachycardia/fibrillation because of the migration of a spring lead. Eight patients (2%) experienced problems with 462 patch leads. One of these was a crinkled patch lead that resulted in late elevation of the defibrillation threshold and the lead was replaced. Several other patients have crinkled patches on chest X-ray study, but defibrillation thresholds remain acceptable. One patient had an insulation break near the header that was successfully repaired. Six patients had a lead conductor fracture in the abdomen. Repair was successful in two patients and required repeat thoracotomy with patch lead replacement in four patients. One of the patch lead fractures was detected when a patient had an out of hospital cardiac arrest that the device did not terminate and from which he was successfully resuscitated by paramedics. The other patch lead fractures were diagnosed at the time of elective generator replacement. Six patients (1%) experienced problems with 511 sensing leads. One patient had a bad signal whose precise cause was never determined. In two patients with insulation breaks, the leads were replaced with new endocardial lead systems. One patient had an epicardial screw-in lead accidently cut at the time of generator change, and two patients received inappropriate shocks (the sensing lead was found to be loose in the header in one patient, and the screw caps had been inadvertently left off at the time of original generator implantation in the other).

Three of the four patients with the originally used silver tinsel leads had these changed. Two patients had spring leads and patches electively replaced because of a known history of a high incidence of lead fracture with this system. One patient had the spring lead electively replaced and subsequently had the patch lead replaced when it became infected.

System infections/erosions. Six patients had AICD system infection, one had erosion with subsequent infection and another had erosion without infection. For the six system-induced infections not due to erosion, three occurred at the time of new implantation, two at the time of generator change and one when a lead was repositioned. One of the seven infections was due to *Serratia* and was treated with generator removal and antibiotics, with the patch lead left intact. The remaining infections were due to *Staphylococcus aureus*, and one patient with this infection died from overwhelming sepsis. In the remaining five patients, the entire AICD system was removed. Three of the five patients had the system reimplanted at a new surgical procedure after full recovery from the infection.

Operative complications. There were four postoperative deaths (1.5%). One of these occurred in a patient with amiodarone pulmonary toxicity preoperatively who developed adult respiratory distress syndrome postoperatively. A second was due to perforation of the superior vena cava at the time of pacemaker implantation, which was performed immediately after placement of an automatic defibrillator. A third death was related to amiodarone toxicity postoperatively; the fourth occurred in a patient who had intractable ventricular tachycardia postoperatively that required emergency endocardial resection on the fourth postoperative day and who subsequently died of overwhelming sepsis related to the endocardial resection. Other perioperative complications included an infected chest tube site in one patient, staphylococcal sepsis caused by a central venous pressure catheter in one patient and a pacemaker infection that required revision of the pacemaker generator in one patient. Four patients experienced a perioperative cerebrovascular accident, none of which resulted in permanent sequelae. There were two pocket hematomas related to anticoagulant therapy. Two patients were taken back to the operating room because of bleeding related to their patch leads.

Elevated defibrillation thresholds. A total of seven patients had an unacceptable defibrillation threshold at the time of implantation or at a 7 to 10 day follow-up assessment of defibrillation threshold, or both. Five (6%) of these patients were in our first group of 88 patients and only 2 (1%) were in the last group of 182 patients. In three of these patients, including one who underwent reoperation with a three patch configuration, the generator was never implanted because it was believed that it would be totally nonfunctional. In one patient, the device was removed before hospital discharge because it was found to accelerate ventricular tachycardia to fibrillation that it could not terminate. Two of these seven patients had good defibrillation thresholds achieved by reoperation. One (the first patient known to receive two patches) was reoperated on the day after the initial operation, and successful defibrillation thresholds were achieved with use of two patches; the other patient required mitral valve replacement 2 years after the original implantation, and underwent lead revision at the time of sternotomy, with excellent defibrillation thresholds. One patient whose ventricular fibrillation was terminated approximately 50% of the time with 25 J had the device left in place. Two patients had subsequent late elevation of previously acceptable defibrillation thresholds. One of these patients, with a spring-patch lead system, refused reoperation for revision to a patch-patch system and had the device removed after it failed to work for sustained ventricular tachycardia on several occasions. The other patient had a crinkled patch lead and

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Table 3. Concomitant Drug Therapy in 270 Patients

	No. (%)
Antiarrhythmic drugs	
Amiodarone alone	61 (22.6)
Amiodarone plus a type I agent	10 (3.7)
Procainamide	22 (8.1)
Sotalol	22 (8.1)
Propafenone	18 (6.7)
Mexiletine plus a type I agent	13 (4.8)
Mexiletine alone	12 (4.4)
Quinidine	10 (3.7)
Tocainide	9 (3.3)
Flecainide	3 (1.1)
Lorcainide	3 (1.1)
Other	3 (1.1)
Total	186 (68.9)
AV node blocking drugs	
Digoxin alone	102 (37.8)
Digoxin plus a beta-blocker	11 (4.1)
Digoxin plus a calcium channel blocker	11 (4.1)
Beta-blocker alone	19 (7.0)
Calcium channel blocker alone	3 (7.1)
Calcium channel blocker plus a beta-blocker	1 (0.4)
Total	147 (54.5)

AV = atrioventricular.

underwent reoperation with revision of the crinkled patch lead with restoration of excellent defibrillation thresholds.

Concomitant drug therapy. One hundred eighty-six patients (69%) received one or more antiarrhythmic drugs to suppress nonsustained or sustained tachyarrhythmias that might cause frequent device discharges, and atrioventricular (AV) node blocking drugs were given to 147 patients (55%) (Table 3).

Long-term follow-up. There was a total of 40 deaths among the patients undergoing continuous treatment with the AICD. Seven of these deaths were sudden, including two in patients who were believed to have battery depletion (one on the basis of glass corrosion and one because of reaching generator end of life) and one patient who experienced sudden death and was not resuscitated by his defibrillator because of spring lead migration. Three of the 40 deaths were noncardiac as a result of pneumonia in one patient, a primary respiratory arrest in one patient and exsanguination from end stage lung cancer in one patient. The cause of death among the 30 patients with nonsudden cardiac death was slow progressive congestive heart failure in 18 patients, cerebrovascular accident in 3, clotted prosthetic valve in 1 patient, postoperative death in 4, infection after generator change in 1 patient, subsequent myocardial infarction in 1, subacute electromechanical dissociation in 1 and uncontrolled slow ventricular tachycardia in 1. Except for one patient who refused hospitalization despite severe end stage congestive heart failure and the patient with end stage lung cancer, all patients classified as having a nonsudden death

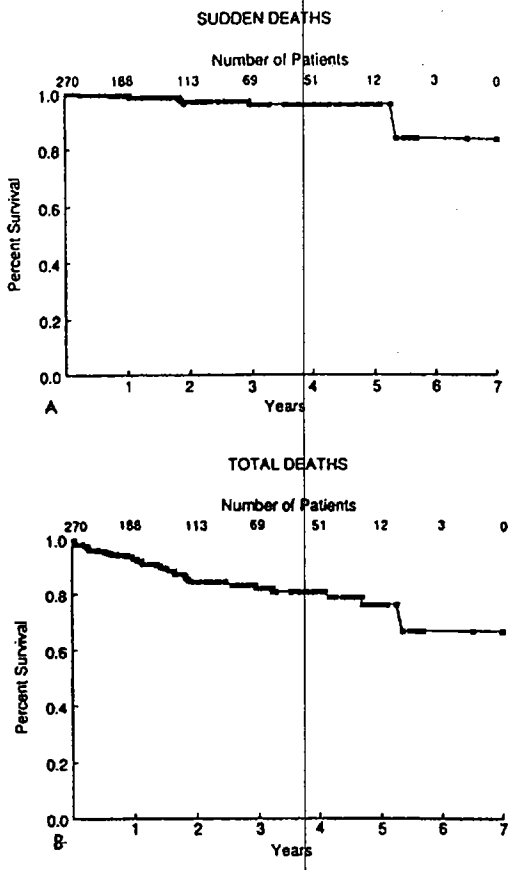

Figure 4. Survival of patients receiving an automatic implantable cardioverter-defibrillator. A, Actuarial survival rate with regard to sudden death. B, Total survival rate, including operative deaths (see Table 4).

died under direct medical observation, generally after a prolonged downhill hospital course.

Figure 4 shows the actuarial survival curves for these patients. Exact yearly survival data are listed in Table 4.

Six patients experienced nonfatal out of hospital cardiac arrest, and were not successfully resuscitated by their device. Two of these episodes were induced by the device in an outpatient medical setting; one occurred in the patient with a crinkled patch who was undergoing a treadmill exercise test when the device fired and precipitated a malignant ventricular arrhythmia that it could not terminate, and the other occurred during a magnet test with a misdirected initiating ventricular fibrillation that the device could not terminate because of a device malfunction. Both patients were successfully resuscitated by medical personnel in attendance. Of the four additional nonfatal out of hospital cardiac arrests, one was due to complete heart block and a second was a result of documented cardiac asystole. The device appropriately did not fire for either of the bradyarrhythmic arrests. A third episode occurred in the patient who subsequently was found to have a fractured patch lead. In this patient, the

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Table 4. Kaplan-Meier Actuarial Mortality Rate in 270 Patients

	1 Year (n = 188)	2 Years (n = 113)	3 Years (n = 69)	4 Years (n = 51)	5 Years (n = 12)
Sudden death	0.9%	3.1%	4.4%	4.4%	4.4%
Cardiac (nonsudden)	6.2%	13.0%	13.9%	15.3%	20.3%
All cardiac	7.0%	15.6%	17.8%	19.1%	23.8%
Total	7.7%	16.3%	18.4%	19.7%	26.2%

device had attempted to terminate the arrhythmia with four shocks, but these were obviously unsuccessful. The fourth patient, who received a series of shocks that failed to abort the cardiac arrest, was successfully externally resuscitated by bystanders. The device functioned normally when it was subsequently tested at electrophysiologic study. The reason for its failure to abort the cardiac arrest is unknown.

Among the 270 patients receiving an AICD generator, 16 living patients were withdrawn from the series. Four of these patients had the device explanted because it proved to be ineffective; one of these had one of the original defibrillator units that could not sense ventricular tachycardia, one had ventricular tachycardia that accelerated to ventricular fibrillation that could not be terminated, one had a high defibrillation threshold at implantation and one had late elevation of the defibrillation threshold. Three patients asked to have the device removed because they thought it was no longer needed, three underwent subsequent cardiac transplantation and three did not have the device replaced after it became infected; in three other patients it was removed because their personal physician believed it was no longer needed. One patient withdrawn alive from this series was lost to follow-up study. Three of the 19 patients who never had the device placed because of high defibrillation thresholds or were withdrawn from the series alive experienced subsequent sudden cardiac death.

Discussion

Improvements during the past 7 years. This report describes our 7 year experience with the automatic implantable cardioverter-defibrillator (AICD). It considerably expands on the number of patients (70) we had previously reported on (3) and gives a much longer-term follow-up assessment. Over the past 7 years, our indications for implantation of this device, the patients in whom it has been used, the number of antiarrhythmic drug failures and the use of other therapies have not changed remarkably. However, several changes have occurred with regard to implantation technique and follow-up of these patients, and our experience contains an ongoing "learning curve." Very early in our experience, it became apparent that the devices needed to sense ventricular tachycardia as well as fibrillation, and the original automatic implantable defibrillator (AID) generator was modified to include cardioverting capabilities. The high incidence of silver tinsel lead fractures led to the development of sturdier leads with a much lower failure rate. Failure to defibrillate with the implanted device led to the utilization of extensive defibrillation threshold testing (19) and two large patch leads rather than the original spring-patch lead configuration for delivering the defibrillating shocks (21). We have incorporated into our operative routines more extensive antibiotic prophylaxis to protect against *Staphylococcus aureus*. Because of the occurrence of rather unpleasant AICD shocks for nonsustained ventricular tachyarrhythmias and supraventricular tachycardia, we have made generous use of antiarrhythmic drugs and AV node blocking drugs to prevent these shocks. Finally, improved therapy for congestive heart failure has become possible through the use of the angiotensin-converting enzyme inhibitors and the oral inotrope enoximone. Finally, the skills of the investigators have improved remarkably in the management of patients with end stage congestive heart failure.

Follow-up mortality and complications. The present study demonstrates that the extremely low 1 and 2 year sudden death rates previously reported (3,4,6) in patients receiving the automatic implantable cardioverter-defibrillator continue to be maintained for as long as 5 years. During the longer follow-up period, the largest number of deaths are nonsudden and of cardiovascular origin, with more than half of these a result of progressive congestive heart failure. The longer follow-up period and larger number of patients have uncovered relatively few problems and complications not previously appreciated, but have served to provide a better assessment of their frequency of occurrence.

Device improvements. The knowledge obtained during the past 7 years has already resulted in some device improvements. This experience also provides data on which to base recommendations for improvements needed in future devices. The shocks given for nonsustained supraventricular and ventricular tachycardia could be eliminated if the device had programmable sensing times and was a noncommitted device that did not fire if an arrhythmia terminated before the defibrillating shocks had been delivered. Patient acceptance would probably be improved even further if the device provided antitachycardia pacing and programmability for shock output to reduce the discomfort from the shocks. The large number of generator changes required because of short battery life would be substantially reduced with greater battery longevity. The >10% incidence of need for a sepa-

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rate concomitant backup bradycardia pacemaker as well as the two documented bradyarrhythmic aborted cardiac arrests indicate that backup bradycardia pacing would be a desirable feature in these devices. The ability to reliably distinguish supraventricular from ventricular tachycardia would also reduce the number of unnecessary shocks. Despite the limitations of the present device, its remarkable success in preventing sudden death supports its widespread use in high risk patients.

We thank Edward Stinson, MD and Debra Echt, MD, who participated in the early care of these patients. We also thank Thomas Fogarty, MD, Duncan Mason, MD and Tamara Ellis, PA, who participated in the care of the latter patients in this series. We thank all of the nurses and support staff of the Sequoia Hospital intensive care unit and cardiac surveillance unit for their assistance in the management of these patients, as well as the efforts of all other physicians involved in the care of these patients. We acknowledge Glenda Rhodes for secretarial support throughout the duration of this study and for manuscript preparation. We thank Margie Bodeman for excellent assistance with the AICD patient data base. We thank Andra Thomas, RN, Susan Moser, RN, Stan Bach, Jr, MD and their colleagues at Intec Systems and Cardiac Pacemakers Incorporated for their technical assistance and cooperation throughout the study. Finally, we thank Michel Mirowski, MD and Morton Mower, MD for their enthusiastic support during the entire 7 years covered by this report.

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DOCU#: P920015/A **DATE:** 6/93
TO: Record, PEDB
FROM: Albert E. Moyal, PEDB **COMP:** Medtronic, Inc.
DEVICE: Transvene NTL System
SUBJECT: Phone MEMO, re: Questions on Amendment

I phoned and spoke with Ms. Jennifer Marrone, Regulatory Affairs Manager, regarding several questions that I had concerning the file P920015/A.

The first question concerned the use of a two-lead Transvene system. The amendment stated the use of an RV/SQ or RV/SVC configurations. Ms. Marrone stated that there were several of these configurations present within the group of patients implanted in the non-standard configuration. A total of 37 patients were implanted in this group. Most of the implant population, about 80-90% were implanted with a three-lead configuration.

I asked if these configurations would be included in the final labeling. Ms. Marrone responded by stating that they would be included in the final labeling under "Alternate Configurations". Data on those implanted with a two-lead configuration will be needed before the final review is completed on this device.

Regarding question 1b, the disparity was explained as being 24 couldn't be induced into VF/VFlutter and those patients who couldn't get an LED were also excluded.

Regarding question two, the peri-operative deaths are not included in the overall death calculations. They are stated to be reflected in the duration.

Concerning question number three, the entry sites for the SQ patch are between the first and fifth intercostal muscles.

DOCU#: P920015 **DATE:** 5/17/93

TO: Record, PEDB

FROM: Biomedical Engineer, PEDB
Albert E. Moyal

COMP: Medtronic, Inc.

DEVICE: Transvene NTL System

SUBJECT: Review of Amendment: Response to FDA Questions.

Medtronic has responded to the questions asked in the FDA Letter March 17, 1993. They have responded to the various concerns raised in the evaluation of the Transvene Non-Thoracotomy Lead System.

A total of 1330 patient have been implanted with the Transvene NTL System. The PMA total number of Transvene patients followed up until February 1993 is 757 patients. Out of this number, 657 have been followed for greater than six months, with 393 patients followed for greater than one year.

The one year survival rate for SCD is 99.3%. There were 458 spontaneous episodes of VT that occurred. Sixty (60) patients experienced 163 episodes that were ineffectively treated terminated. This represents a company claim of 1.6%, although 60 patients out of 757 represents 7.9% of the population.

Other information provided included patients meeting, and not meeting implant criteria, clinical experience, survival rates, clinical complications and observations, and comparisons between the PCD Transvene with the PCD Epicardial and AICD Ventak P historical data.

The concerns that I have with this amendment are as follows:

1. On page S12, the company describes the lead configurations that may be done with the leads making up the transvene system. In the first paragraph, they mentioned a three lead system that includes the RV/CS/SQ, RV/SVC/SQ, RV/SQ, and RV/SVC.

   Does Medtronic plan on including the use of a one lead/patch (RV/SQ) and/or a two lead (RV/SVC, RV/CS) system as a recommended implant technique? Have they tested this type of two lead system? Does the use of the RV/CS/SVC configuration in only 37 out of 702 lead system preclude the use of this configuration, in comparison the configurations using the SQ patch?

   It is stated on page S21, table IF-3, the breakdown of the of the lead systems used. The total is 702, yet, there are 757 patients implanted with the PCD Transvene system. Please explain the disparity, and describe what, if any, other implant configurations used with the Transvene Leads.

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2. Table IK-5 on page S45 lists the Survival Analysis for patients not meeting the implant criteria for the PCD Transvene System and the patients not meeting the implant criteria for the PCD Epicardial System.

   Please explain the breakdown of survival rates for those patients not meeting the PCD Epicardial Implant Criteria when there is a total of 92 patients, of which there are 17 patient deaths (18.5%).

3. On page 105 of the amendment, the response to question 26, listed in tabular form is the breakdown of venous entry sites for the RV and CS/SVC leads. What about a breakdown of the entry sites for the SQ lead? Please provide.

These are initial concerns that I have with this amendment, that I am submitting to comply with the May 17,18 Panel decision date. I will submit further concerns if and when they arise.

SUMMARY: The company has provided the responses to the questions asked in the FDA letter sent to them regarding the review of this Non-Thoracotomy Lead System. The data provided appears to be satisfactory, although several concerns have arisen regarding the presentation of this data. The course of action to be taken is to explore any and all concerns questions that may arise from the review of the amendment prior to the panel taking place.

The recommendation for this application is to submit this to the panel at the earliest time possible.

Albert Moyal M.D.
Albert Moyal.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

227-8627

Public Health Service

Memorandum

Date May 10, 1993

From Mathematical Statistician (T. C. Lu) HFZ-162
Statistical Branch, Division of Biometric Sciences, OST

Subject Statistical Review of PMA P920015 Amendment, Medtronic Multiprogrammable Tachyarrhythmia Control System with Non-thoracotomy Cardioversion and Defibrillation Electrodes, Medtronic, Inc.

To Doris Terry - HFZ-450
Division of Cardiovascular, Respiratory, and Neurological Devices, ODE
Through: Director, Division of Biometric Sciences, OST
Through: Chief, Statistical Branch, DBS, OST

1. Background

The Medtronic Pacer-Cardioverter-Defibrillator (PCD) is an implantable, multiprogrammable, automatic tachyarrhythmia control device. This device is used for treatment of patients at risk of sudden cardiac death due to ventricular tachycardia (VT) and/or ventricular fibrillation (VF). The original PMA was submitted in April 1992. Amendment One was submitted in September 1992. Amendment Two was submitted for review in March 1993. The purpose of this memo is to review the response from the sponsor for the deficiencies stated in the FDA letter. Information provided in this amendment includes clinical experience of 757 patients through February I, 1993.

2. Reviewer's Comments

2.1. Historical Control

Sponsor compared the PCD transvene system (treatment group) clinical experience to the reported PCD epicardial system (control group) clinical experience. Sponsor argued that patients were enrolled in the two studies concurrently and patients' indications, implant criteria and clinical data requirements were identical for the two patient groups. But, in Table 2-7, comparison of patient characteristics, PCD transvene system versus PCD epicardial system, as of February 1, 1993, page 19, gives different information. The p-values for sex and primary indication [(b)(4)] respectively, are statistically significantly different. Therefore, the sponsor's argument that the two groups are compatible is not correct.

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2.2. Cox Regression

Sponsor stated, on pages 12 and 90, that: "Cox regression analysis was performed to see what effect gender, primary indication and system implanted (PCD transvene or PCD epicardial) had on survival outcome. This analysis showed that for overall survival at one year, the system implanted had an influence on the probability of survival but gender and primary indication had no influence". This reviewer would like to see the detailed evidence to support this claim, including the computer program, input, output and decision criteria.

2.3. Confidence Interval Analysis

Sponsor compared the PCD transvene system and Ventak-P epicardial system and claimed a statistically significant difference in one-year overall survival between the PCD transvene and AICD epicardial system, using confidence interval analysis, pages 13 and 256. This reviewer asked for this information in my December 16, 1992 memo to you and I would like to ask again for the computation of this confidence interval.

2.4. Actuarial Survival Comparison I

Table 2-16, page 24, depicts the actuarial survival of PCD transvene vs. PCD epicardial. This reviewer would like to see a more detailed Table such as this:

Month	Transvene	Epicardial
0-3	No.dead/No.at risk	No.dead/No.at risk
3-6	No.dead/No.at risk	No.dead/No.at risk
6-9	No.dead/No.at risk	No.dead/No.at risk
9-12	No.dead/No.at risk	No.dead/No.at risk

Then use the Mantel-Haenszel Chi-square test to compute the p-value for association between transvene and epicardial survival. Sponsor didn't discuss how the p-values in Table 2-16 were derived; it looks as if the binomial distribution was used for the computation. Sponsor should address this issue.

2.5. Please discuss the similarities/differences between Table 2-12 (page 22) and Table 3-3 (page 27).

2.6. Survival Probability I

Sponsor stated, on page 43, that the survival probabilities are calculated using a life-table survival analysis. For verification of survival probabilities, the data necessary to do calculations are available upon request. This reviewer would like to see this data set and the computation procedure.

2.7. Please discuss the similarities/differences between "one-year actuarial survival" of Table 1K-4 (page 43) and Table 8-5 (page 51). This reviewer would like to see the numerators and denominators actually used to derive the one-year actuarial survival shown in Table 8.5.

2.8. Survival Probability II

Sponsor stated, on page 83, that: "Presentation of the number of patients does not allow calculation of the survival probability. Therefore, a data set will be available upon request if you desire to verify the survival probability". This reviewer would like to see this data set and the computation procedure.

2.9. Actuarial Survival Comparison II

Table 1M-10 (page 84) depicts the comparison of actuarial survival: transvene vs epicardial as of June 24, 1992. Again, this reviewer would like to see the data set and the SAS procedure actually used to derive the p-values.

2.10. NYHA Classification

The p-value for the NYHA classification in Table IV-C (page 88) i (BY4) as computed by the sponsor. Based on the data provided in this table, the reviewer calculated a p-value of (BY4) ponsor should address this difference in p-values.

2.11. Early Device Explant

There were four patients in whom the PCD device was explanted due to reasons other than death, infection or heart transplant. Analysis of one explanted PCD device indicated a random device failure in the microprocessor and low power hybrid. Another patient experienced a power on reset (POR) condition, see page 100. Please submit the other two results for review as soon as the results are available.

2.12. Lead Dislodgement

Lead dislodgements are reported as complications/observations in Table 27-2 (page 103). The sponsor should justify his choice of thirty (30) days as a cutoff.

2.13. Pooling

There are seventy eight (78) investigative centers participating in the clinical trial with thirty five (35) domestic centers and forty three (43) foreign centers. Please justify pooling all seventy eight centers together.

2.14. Follow-up Presentation

Table E-2, page 215, depicts the PCD transvene system follow-up. This is not an adequate presentation of the follow-up data. As I requested in my April 23, 1992 memo, the sponsor should refer to page 93, Table 4.6, in "Statistical Methods for Survival Data Analysis" by Elisa Lee for a more proper life-table analysis. Sponsor should also discuss the reasons why some patients dropped out of the follow-up study, i.e., either withdrawn alive or lost to follow-up.

2.15. Actuarial Survival Comparison III

Table 11-2 (page 231) depicts the PCD transvene system one-year actuarial survival as of 2/1/93. Again, this reviewer would like to see the actuarial survival table stratified by every month, similar to that in Section 2.4 above. Sponsor also stated "this table included the projected one year survival calculations for patients who ultimately received a PCD transvene system....". Please explain in detail the projected one-year survival calculations.

2.16. Data Summary by Primary Indication

Sponsor provided PCD transvene system data summary by primary indication as of 2/1/93 in Table I-1 (page 233). This reviewer would like to see the numerators and denominators for percent success from treating spontaneous VT and spontaneous VF. Sponsor provided similar information in Table IF-2 (page 287) and Table IF-4 (page 290).

2.17. Follow-up Evaluations

Sponsor indicated, on page 284, that clinical data were collected for follow-up evaluations at 1 and 3 months post-implant and at 3-month intervals. Please provide all of this information

2.18. P-values for Actuarial Survival

This reviewer calculated the p-values in Table 2-16 (page 24) as follows:

	P-Values	
Cause of Death	Sponsor	Reviewer
Sudden Cardiac	[(B)(4)]	[(B)(4)]
Non-Sudden Cardiac	[(B)(4)]	[(B)(4)]
All Cardiac	[(B)(4)]	[(B)(4)]
Non-Cardiac	[(B)(4)]	[(B)(4)]
Overall	[(B)(4)]	[(B)(4)]

3. Conclusion

The sponsor needs to adequately address all issues raised in Section 2 above, mainly actuarial survival and follow-up, before the safety or effectiveness of the PCD transvene system relative to the PCD epicardial system can be evaluated from a statistical perspective.

T. C. Lu

T. C. Lu

cc: Abhijit Acharya, Ph.D. HFZ-450
Donald F. Dahms HFZ-450
Lynne A. Reamer HFZ-450
Medical Device File
Board File

Medtronic

Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576
Telephone: (612) 574-4000
Cable: Medtronic Telex: 29-0598
FAX: (612) 574-4879

March 26, 1993

Office of Device Evaluation
PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

RECEIVED
29 Mar 93 12 02
FDA/CDRH/ODE/DMC

Re: Transvene Lead System, PMA Amendment
(Document Control Number P920015)

AC2V1

The purpose of this submission is to respond to the deficiencies described in FDA's letter, dated March 17, 1993, see Attachment 1. Deficiency responses are presented in Attachment 2. An updated Summary of Safety and Effectiveness is provided in Attachment 3.

Information provided in this amendment includes clinical experience of 757 patients through February 1, 1993. Additional information is provided on virtually all clinical Transvene system implants, N = 1330, relative to patient complications and observations (including lead dislodgements), patient deaths and survival. This is provided in deficiency response #8. Again, the data cutoff date for these 1330 patients is February 1, 1993. A stand-alone, Clinical Summary Report is provided in Attachment 4 for convenient reference.

Clinical data presented in this amendment continues to demonstrate the PCD Transvene system performs as specified and is, therefore, safe and effective for its intended use. Results include 99.3 percent survival from SCD at one year. Additionally, Transvene system perioperative mortality and hospital stay compares dramatically to that of epicardial systems, 0.7% mortality and 7 days in hospital, versus 5.3 percent mortality and 11 days in hospital, respectively.

Copies of Transvene labeling (technical manuals) are provided in Attachment 5 for reference.

The existence of this PMA Amendment and the data and other information it contains are confidential, and the protection afforded to such confidential information by 18 USC 1905 and other applicable laws is hereby claimed.

Three copies of this PMA Amendment are provided. Should additional information be required by the Agency, please contact the undersigned.

Sincerely yours,

MEDTRONIC, INC.

Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
(612) 574-4688
(612) 574-6424 FAX

Attachment

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Appendix A: Nonclinical Testing Transvene Models 6963, 6966, 6999

Appendix B: Technical Report for Medtronic, Inc.

Appendix C: Medtronic Product Performance Report, February 1993

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

MAR 17 1993

Ms. Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

RE: P920015
Transvene™ Lead System
Filed: April 1, 1992
Amended: September 21, 1992

Dear Ms. Marrone:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial scientific review of the above referenced premarket approval application (PMA). We regret to inform you that on the basis of this review, we have concluded that the PMA lacks information needed to complete the review and determine whether there is reasonable assurance that the device is safe and effective for its intended use.

We recognize the potential public health significance of this device and acknowledge the separate discussions underway to expedite the review. However, because of this lack of information, review of the PMA cannot continue and, accordingly, we have listed the following significant deficiencies which require the responses as indicated:

1. To clearly establish the purpose of the clinical data in the PMA application, please provide the following:

   a. the hypothesis and the objectives of your clinical study;

   b. a discussion of (i) how your clinical study addresses the use of a control, which is relevant to all clinical studies, (ii) the appropriateness of the AICD™ as a historical control, and (iii) your rationale for not using a concurrent control during an implantable cardioverter defibrillator (ICD) study;

   c. the endpoints of your study; and

   d. how the data provided in the PMA application support the specified endpoints.

2. Based on data provided in your PMA application, please prepare table(s) which include a side-by-side comparison of the PCD® Transvene™ and the PCD® Epicardial System and the PCD® Transvene™ and Ventak P AICD™ populations. The table must also include the inclusion and exclusion criteria which were used for each study. You must include a discussion of how these data may or may not represent a valid comparison, and other comments which justify and support the use of these groups as controls.

3. An update of the PMA clinical study population must be provided. The update must include the data as presented in the PMA application, and must include the clinical experience in the use of the new anchoring sleeves, which are aimed at decreasing the incidence of dislodgement, and a summary of the clinical experience (spontaneous treatment efficacy of ventricular tachycardia (VT) and ventricular fibrillation (VF), observations and complications, number of patient deaths and overall survival) of the patients followed for a year or more.

4. Please provide a clear description of how you identified the "patient who did not meet the implant criteria." Please discuss your implant criteria and how implant testing attempted to satisfy protocol requirements.

5. Of the 214 patients who did not meet the implant criteria and yet were implanted with the device, 170 patients had successful defibrillation with 24 Joules (J). Please provide an update of the clinical experience on these patients, as described in item 3 above. Also, please discuss how your proposed labeling will address this protocol deviation. Will implant criteria be changed?

6. There were 20 patients among the 214 who did not meet the implant criteria and were implanted without the 10 J safety margin. An update of the spontaneous episode experience in the treatment of VT and VF in these patients and the overall survival must be provided.

7. Table IK-4, page 151, compares the patients meeting the implant criteria to those who did not meet the criteria. However, many of the percentages were presented without numerical support. Please provide the appropriate numbers.

8. Please provide an update on the patients who are implanted with the Transvene™ System and were not counted in the PMA population. The update must include a summary of the clinical experience as referenced in item 3 above.

9. Based on your study protocol, please differentiate between defibrillation threshold (DFT) testing and lowest energy to defibrillate (LED) testing. Based on the individual patient report forms of the 757 patients, how many patients underwent what is described as DFT testing and how many had LED testing? Samples of the patient report forms showing the scheme of testing which was

categorized as DFT and LED testing must be provided. Please discuss how the DFT and LED data were reported and presented in the PMA application.

10. There is a statistically significant difference between the mean DFT obtained with the RV-CS-SQ lead configuration and the mean DFT obtained with the other lead configurations. How do you account for this difference? Was the DFT as reported and discussed for all lead configurations obtained using an identical or similar scheme? Please discuss. You must document that there were no significant differences between the scheme for performing DFT and LED testing between the Transvene™ and PCD® Epicardial patient populations, if that is the case.

11. Please elaborate on how the comparison of DFTs obtained from the PCD® Epicardial Lead study and the Transvene™ study can be considered as a valid comparison in that the majority of the patients (574 (75.3 percent)) in the Transvene™ study were programmed with the sequential pathway and 178 (23.4 percent) were programmed via the simultaneous pathway. The majority of the patients (496 (65.2 percent)) in the PCD® Epicardial study were programmed with the single pathway. Based on your PCD® Epicardial study, please discuss the DFTs or energy requirements obtained with the use of the single defibrillation pathway versus the sequential and simultaneous pathways.

12. Please discuss the time between detection and delivery of therapy of the Transvene™ System versus the PCD® Epicardial System.

13. On page 125 of the application, please explain and/or discuss what is meant by "a 2:1 VF sensing margin", how it is determined, and if the patients met the criteria.

14. Of the 329 patients who were followed for 6 months, 130 patients had spontaneous episodes. What was the average number of VT and VF episodes per patient? Of the patients followed for a year, how many had spontaneous episodes of VT and VF and what was the mean number of episodes per patient in this group?

15. On page 130, Table IF-4, you report that there were 5362 episodes of VT successfully terminated. On page 131, paragraph 2, you state that 25 patients experienced 45 (0.8 percent) episodes of sinus tachycardia or atrial fibrillation. Are these patients included in the success or failure category? Nine hundred and sixty-four episodes of VF were reported, however, 75 episodes were not actual VF. You must clarify how the successful and ineffective therapies and failures are discerned and categorized. Please prepare a table which includes a category of ineffective therapies with actual patient numbers and percentages. In addition, what assurance is there that an episode of supraventricular tachycardia or atrial fibrillation is not misinterpreted as VT or VF by the physician and considered a successful therapy?

16. Table IM-6, page 173 must be modified to include a column on inappropriate therapy or therapies delivered as the device was programmed so that the percentages add up to 100 percent.

17. On page 162, Table IL-2 lists a category "Fail to Cardiovert/Defibrillate" as 0.8 percent. Please clarify. If a patient survives an episode of an inappropriate therapy, is it categorized as a success? Please discuss. The tables must include percentages with the representative numerical support.

18. There were 38 inactive patients reported in Table IH-1, however, 34 patients were reported to be no longer active. Please clarify.

19. Please discuss how the 1 year sudden cardiac death survival, as reported in Table IF-2 page 128, was calculated. The numbers and an explanation of patient classification must be included. Was every patient included who had a prior cardiac arrest regardless of the arrhythmia?.

20. On page 177, the number of patients must be provided so that the percentages and calculated p-values can be confirmed.

21. Table IV-C, page 649 of the original submission shows a comparison of patient variables for the three lead systems and provides p-values for the variables tested, but the hypothesis was not clearly stated. Please state the hypothesis and discuss the p-values obtained when reporting by primary indication, and the chi-square test of the data set and how it was computed.

22. For purposes of justification of data pooling and data analysis of Table IV-C, please discuss why the multiple statistical significant difference was not adjusted at a 0.05 significance level using a more widely accepted procedure such as the Hochberg procedure (Dunnett and Tarnhoue: A Step-up Multiple Test Procedure, Journal of the American Statistical Association, March, 1992, Vol 87: pp.162-170).

23. You claim that confidence interval analysis was performed to compare the overall mortality of the PCD® and AICD™ populations. What was the confidence interval?

24. Please clarify and/or discuss the following regarding Table XB-1, page 378, Volume 2:

    a. the total number of patients in the Ventak P population (292) versus those reported by primary indication (291); and

    b. a chi-square test of primary indication, using the StatXact computer software, yields a p-value of nearly 0. This is statistically significant, indicating the PCD® and Ventak P populations are significantly different.

25. Please discuss the incidence of inappropriate therapies reported as observations in the Transvene™ study. It appears as if there has only been a slight improvement over the PCD® Epicardial study as it relates to programming and patient management (drug therapy). Please discuss the experience of both studies and how the labeling supports effective programming of the device parameters and the use of the Onset and Stability algorithms. How many patients in the Transvene™ study have the Onset and Stability algorithms programmed ON? At what interval during the study were the majority of patients programmed with the algorithms? Your experience in the treatment of induced and spontaneous episodes with use of the algorithms must be discussed.

26. Please discuss the "device related" complications reported for the Transvene™ and the PCD® Epicardial System.

27. Please describe in detail the complications reported in the patients followed for a year.

28. There was a substantial increase in the number of infections reported in the Transvene™ study. Even though you discussed why there was an increase, based on your experience, how will your labeling address the procedures for reduction in the number of infections? Please validate these procedures.

29. A discussion of your experience in the use of the different entry sites for the placement of the Transvene™ leads, and how your labeling assists in the selection of an entry site, must be provided.

30. Of the 22 deaths, 15 systems were explanted and returned for analysis. The results of the analyses (PCD® and Transvene™ leads) must be provided. What did device interrogation reveal? How many of the 41 Transvene™ lead systems which were explanted were returned and analyzed? How long were the leads implanted? A description of the protocol for analysis and the results of the analyses on all leads and devices must be provided. The PMA application must document how your study has addressed the need for the return and analysis of all Transvene™ leads and the PCD®.

31. Please discuss the circumstances surrounding the death of the patient who died 22.5 months post implant. What did interrogation of the device reveal?

32. Of the perioperative deaths, how many devices were programmed OFF? Please discuss the circumstances surrounding each death. The number of perioperative deaths must be reported in a table and be identified as sudden cardiac, non-sudden cardiac or non-cardiac. Were there other deaths when the device was programmed OFF?

33. You state that there have been no reported patient deaths in the group with a 1 year sudden cardiac death survival and overall

actuarial survival of 100 percent. Does this include the perioperative deaths and the patients who have been followed out for a year?

34. Please provide an engineering drawing of each Transvene™ lead model which identifies the segments of the lead and a description of the tests that each segment and the full lead body underwent.

35. Since flex testing exerts a considerable amount of stress on the lead, and is essential to life testing, why was it considered that [(B)(4)] month period would be sufficient? Describe how the full lead and different segments were flexed. Did you do a finite element stress analysis to validate the flex testing stress?

36. In light of the failure of your platinum (B)(4) polyurethane bradycardia pacing leads, and since the Transvene™ lead Model 6966 is also a platinum (B)(4) polyurethane lead, please provide documentation regarding the failure mechanism of the pacing leads and all relevant information pertaining to these cases. How can we be assured that the failure may be restricted to the bradycardia pacing leads? Based on your testing to date regarding the pacing leads and the testing of the Model 6966 lead, discuss the potential and the probability of failure of the Model 6966 lead. A side by side comparison of the Model 6966 and the 4,000 series bradycardia pacing leads must be provided. The comparison must include material, design, dimensions, function, tests performed and a schematic drawing.

37. A copy of the Summary of Safety and Effectiveness which includes the updated data must be provided.

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period up to 180 days. As provided by 21 CFR 814.37(c), you may decline to submit a major amendment requested by FDA in which case the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

As provided under 21 CFR 814.44(g), FDA will consider this PMA to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA amendment. You may, however, amend the PMA within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA with in the 180-day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA and will be assigned a new number.

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You may amend the PMA to provide the above requested information (12 copies), voluntarily withdraw the PMA (3 copies), direct CDRH to complete processing the PMA without the submission of additional information (3 copies) or request an extension. The required copies of the amended PMA should include the FDA reference number for this PMA and should be submitted to the following address:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

Upon receipt of an amendment adequately addressing the above requests or a written response declining to submit the requested amendment, CDRH may schedule an advisory panel meeting at which your PMA will be reviewed. You will be notified of the location and date of this meeting should one be necessary. In order to provide adequate time for CDRH and advisory panel review, information received by FDA less than 6 weeks in advance of any scheduled advisory committee meeting will not be considered or reviewed at the meeting and may delay consideration of your PMA until a subsequent advisory committee meeting.

If you have questions concerning this deficiency letter, please contact Doris Terry at (301) 427-1018 or Arnold Alpert, Ph.D., at (301) 427-1186.

Sincerely yours,

F. Alan Andersen

F. Alan Andersen, Ph.D.
Acting Director
Office of Device Evaluation
Center for Devices and
Radiological Health

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1. **To clearly establish the purpose of the clinical data in the PMA application, please provide the following:**

   a. **the hypothesis and the objectives of your clinical study;**

   RESPONSE:

   The hypothesis and objectives of the Medtronic Transvene clinical study are as follows. Note that this has been presented in each clinical summary report provided to FDA over the past two years including our previous deficiency responses provided on September 18, 1992.

   Hypothesis

   The objectives of the Transvene clinical study, described below, are intended to demonstrate the hypothesis that the Transvene PCD system is safe and effective in treating VT and VF, versus the null hypothesis that the system is not safe and effective in the treatment of VT and VF tachyarrhythmias.

   Objectives

   The safety and efficacy of the Transvene system is/was determined by:

   - Evaluating the sensitivity and specificity of the PCD device with Transvene lead systems to detect episodes of VT and VF, and to evaluate the ability of the system to appropriately discriminate between VT/VF and other potentially nonmalignant rhythms.

   - Monitoring the efficacy of the PCD device with Transvene lead systems in treating VT and VF episodes. VT/VF therapy efficacy is determined as the ratio of successful termination of episodes detected to the total number of episodes detected in which one or more therapies were delivered (successful termination/number of detected episodes with therapy delivered). Investigators are able to choose from any of the available leads and VT/VF therapies that the efficacy was first evaluated acutely.

   - Evaluating the performance of the Model 6966, 6963 and 6999 Transvene leads.

- Estimating the one year SCD and overall survival of the patients implanted with the PCD® Transvene™ System.

- Monitoring the patient selection criteria and patient management methods required by the PCD device and Transvene leads.

- Evaluating the safety and effectiveness of the Model 5355 ETCD device when used during the implant procedure. Specifically, tachyarrhythmia episode induction, detection, termination and ease of use are analyzed.

- Evaluating the safety and performance of the Model 9710 programmer and the Model 9788 MemoryMod software cartridge in programming sensing and therapy parameters and the appropriate delivery of noninvasive electrophysiologic stimulation.

b. a discussion of (i) how your clinical study addresses the use of a control, which is relevant to all clinical studies, (ii) the appropriateness of the AICD™ as a historical control, and (iii) your rationale for not using a concurrent control during an implantable cardioverter defibrillator (ICD) study;

RESPONSE:

i. how your clinical study addresses the use of a control, which is relevant to all clinical studies,

Background

The PCD Epicardial System, is a tiered therapy device that, combines features of bradycardia support pacing, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. This system has incorporated programmability and multiple detection and therapeutic options that allows the titration of device therapy to a patient's specific clinical arrhythmia history.

The PCD Epicardial System requires a thoracotomy for implantation because of the need to insert epicardial patch leads. This exposes the patient to surgical risk and potentially limits the type of patient who may be considered for implant of the system. The need for a simpler and safer implantation technique is widely recognized. The incorporation of a nonthoracotomy lead system, such as

the PCD Transvene System, should decrease the potential perioperative and long term mortality and morbidity associated with current epicardial system implantation approaches.

The PCD Epicardial System and PCD Transvene System are identical except for the implanted defibrillation lead system. Thus the performance of the PCD device, and associated support equipment, is similar in the two systems and therefore a comparison of clinical experience should focus on those areas where the lead system implanted may impact clinical outcome. This would include spontaneous VT/VF episode efficacy, complication/observation rates and patient survival.

The Use of a Control

Medtronic provides a comparison of the PCD Transvene System clinical experience to the reported PCD Epicardial System clinical experience. **A historical control comparison was performed using the Medtronic clinical database on the PCD Epicardial System since patients were being enrolled in the two studies concurrently and the patient indications, implant criteria and clinical data requirements were identical for the two patient groups.**

At the start of the PCD® Transvene™ System clinical study a randomized controlled study was not performed since the investigators felt strongly that it was not clinically appropriate to randomize to a surgical procedure when a less invasive implant procedure was available. The investigators believed that the ability for Medtronic to do a historical control comparison between the PCD® Transvene™ and PCD® Epicardial System would provide sufficient data to allow a comparison of the clinical outcome of the two patient groups. A historical comparison would be appropriate

A historical comparison to the Ventak-P Epicardial System was also feasible since it was the most similar system that was market released and the patient indications were similar to that of both the PCD® Transvene™ and PCD® Epicardial Systems.

The premise of the PCD® Epicardial and Transvene™ studies was to demonstrate that if a patient was evaluated at

implant and shown to meet implant criteria, that they would be reliably defibrillated over time, and therefore, have a high probability of survival from SCD regardless of which lead system or defibrillation pathway was chosen. The Epicardial System is a valid comparison since the same PCD® was used in both systems, the same indications were used, the same implant criteria, the same protocol and data requirements and the studies were performed concurrently at the same centers. There is no other system that is currently market released that is a better, or more applicable control. We have shown for both studies that freedom from SCD at one year is at least equivalent to that afforded by the commercially available AICD for patients who meet the implant criteria regardless of lead system. All of the transvenous defibrillation systems that are available are currently under investigation and, as such, limited or no data exists with which to compare our performance.

The investigators believe that there is a class of patients who cannot tolerate the thoracotomy required for the utilization of the epicardial patch lead defibrillation lead system and who are at high risk of sudden cardiac death. For these patients, the PCD Transvene System is the only therapy available. Because of the surgical risks and postsurgical complications associated with epicardial lead system, implantation in the following patient groups may not be possible:

(1) patients in whom there is no indication for concomitant cardiovascular surgery at the time of ICD System implant;

(2) patients with severe pulmonary disease who cannot tolerate prolonged anesthesia or an open chest procedure;

(3) patients with severe congestive heart failure (ejection < 40%) who are at increased risk for perioperative mortality post a thoracotomy procedure;

(4) patients who may eventually require open chest procedures for treatment of their coronary artery disease or cardiac transplant.

For these patients, the PCD Transvene System is the only therapy available. The PCD Transvene System simplifies and greatly reduces the risk associated with lead introduction, making therapy available to these patient

groups. Because there is no need to open the chest of these patients, options for future therapy remain available; e.g. CABG is associated with decreased morbidity and mortality if there has been no prior open chest surgery. **Thus randomization would not be feasible or clinically or ethically appropriate in these patient groups.**

ii. **the appropriateness of the AICD™ as a historical control, and**

The AICD clinical experience was compared to that of the Transvene system, i.e., the AICD served as a control of sorts, because the AICD system **was the only commercially available, FDA approved ICD system,** at the time of our analysis and documentation of the PCD® Epicardial and Transvene™ clinical experience. The Ventak-P System was chosen since it was the most similar to PCD® and the patient indications were similar. For purposes of comparison, the Ventak-P epicardial system patient population described in the (Ventak-P) Summary of Safety and Effectiveness, P890061, dated May 2, 1991, was used. A copy of this summary was obtained through the Freedom of Information Act.

A detailed comparison has been provided in the Transvene PMA application and subsequent amendments. It is also provided in this amendment, see Deficiency Response Number 2.

iii. **your rationale for not using a concurrent control during an implantable cardioverter defibrillator (ICD) study;**

A concurrent market release control was not used because of the reasons previously stated in Deficiency Response 1.b.(i) and because another transvenous defibrillation lead system was/is not commercially available. Other manufacturers simply do not allow their systems, clinical or market release, to be used by competitors due to the need to protect trade secrets. A concurrent control was also not used because an appropriate historical control was available, that is, the PCD Epicardial System. The PCD® Epicardial System is an appropriate historical control. Since patients were being enrolled in the two studies concurrently, the patient indications, implant criteria and clinical data requirements were identical for the two groups.

Specifically, the PCD Epicardial System uses the same tiered therapy device that combines features of bradycardia support pacing, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. This system has incorporated programmability and multiple detection and therapeutic options that allows the titration of device therapy to a patient's specific clinical arrhythmia history.

The PCD Epicardial System and PCD Transvene System are identical except for the implanted defibrillation lead system. Thus, the performance of the PCD device and associated support equipment, is similar in the two systems and therefore a comparison of clinical experience should focus on those areas where the implanted lead system may impact clinical outcome.

Analysis provided in this clinical update, and also provided in previous Transvene PMA documents, shows that the incorporation the of nonthoracotomy defibrillation system has maintained the type of therapy available for the treatment of recurrent VT/VF and decreased the potential mortality and morbidity associated with epicardial implant approaches while maintaining the positive impact of ICD therapy on VT/VF episode efficacy and patient survival.

This analysis is thoroughly discussed in this amendment. See Deficiency Response Number 1 and the Clinical Update.

c. **the endpoints of your study; and**

d. **how the data provided in the PMA application support the specified endpoints.**

RESPONSE:

The following is a description of the endpoints of the Transvene clinical study and how the data collected support these endpoints.

Endpoint: Freedom from sudden cardiac death (SCD) and all cause mortality as shown through one-year survival.

Endpoint: Treatment efficacy of spontaneous VT/VF episodes.

Data supporting these endpoints are as follows. (See also the Clinical Update included in this PMA amendment.)

Patient Deaths

- The estimated one-year survival probabilities for Sudden Cardiac Death, Non-Sudden Cardiac Death, all Cardiac Deaths and Noncardiac Death were found to be 99.5%, 96.2%, 95.8%, and 98.1%, respectively.

  The incorporation of programmable VT/VF detection and therapies has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

- The sudden cardiac death survival of 99.5% at one year is comparable to that of the AICD™ patient population 98.0%.

- There have been no deaths due to a PCD Device malfunction.

- Overall survival at 93.3% is better than that afforded by the Ventak-P Epicardial System.

Complications/Observations

- Complications were reported in 19.4% of the patient population and observations were reported in 23.8% of the patient population.

- The incidence of complications was comparable to that of the market released AICD™ system in the categories of ineffective VT/VF therapy, pocket infection and pocket erosion, and was lower than the AICD™ in the category of inappropriate delivery of VT/VF therapy.

Patient Indications

- All of the patients entered into clinical evaluation met at least one of the primary indications. Sudden cardiac death (SCD) was the primary indication in 37.1% of the patients, recurrent ventricular tachycardia (VT) was the primary indication in 49.8% of the patients and SCD/VT was the primary indication in 13.1% of the patients.

- The number of patients (60.5%) receiving VT/VF therapy for spontaneous episodes of ventricular arrhythmias supports the conclusion that the patient selection criteria

are appropriate and that the PCD Transvene System was implanted in patients who benefit from this therapy.

- The one year sudden cardiac death survival rates for the SCD patient group was 100.0%, for the VT patient group 99.4% and the SCD/VT patient group 98.6%.

VT/VF Detection and Therapy Performance

- The PCD Transvene System properly detects and treats VT as demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VT was 98.4%.

- The PCD Transvene System properly detects and treats VF as demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VF was 98.4%.

- There were no reported patient deaths due to the nondetection of a spontaneous VT or VF episode by the PCD Transvene System.

PCD Transvene System Performance

- The PCD Transvene System components (Model 7216A/7217B and Model 6884/6966, 6881/6963, 6895/6999 Transvene leads) have performed according to design and specification and are, therefore, considered safe and effective in the indicated patient population.

Clinical Experience Summary Conclusions

The PCD Transvene System is a tiered therapy device which combines features of bradycardia pacing support, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. The incorporation of these features has allowed the physician to titrate the ICD therapy to meet specific patient clinical needs, allowed fewer shocks to be delivered for recurrent ventricular tachycardia because of antitachycardia pacing features, allowed fewer cases of inappropriate therapy delivery due to programmable detection and allowed a sudden cardiac death survival rate identical to the Ventak-P Epicardial System.

The PCD Transvene System, due to the elimination of the need for a thoracotomy, has provided a marked improvement in both the

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perioperative and overall patient mortality as compared to the PCD Epicardial System. In addition, due to the decreased perioperative morbidity and mortality, the post implant hospital stay has been decreased to a mean of 7.6 days as opposed to a mean of 10.6 days ($p=0.001$) for the PCD Epicardial System.

Medtronic asserts and the PCD Transvene investigators unanimously agree that the findings of the clinical study support the conclusion that the Medtronic Tachyarrhythmia Control System and the Transvene Cardioversion and Defibrillation Electrodes are safe and effective in the indicated patient population.

2. **Based on data provided in your PMA application, please prepare table(s) which include a side-by-side comparison of the PCD® Transvene™ and the PCD® Epicardial System and the PCD® Transvene™ and Ventak P AICD™ populations. The table must also include the inclusion and exclusion criteria which were used for each study. You must include a discussion of how these data may or may not represent a valid comparison, and other comments which justify and support the use of these groups as controls.**

RESPONSE:

The efficacy and safety of implantable cardioverter defibrillator (ICD) therapy for recurrent ventricular tachycardia (VT) and ventricular fibrillation (VF) has been well established. The Ventak-P Epicardial System provides cardioversion and defibrillation therapy for VT and hemodynamically unstable VT. However, this type of therapy may not be optimal for patients with stable, well tolerated VT that is amenable to antitachycardia pacing due to the pain associated with cardioversion shock therapy. The need to incorporate programmability, multiple detection and therapeutic options has lead to the development of the PCD® Device.

However the Ventak-P Epicardial System and PCD® Epicardial System are implanted only with a defibrillation lead system requiring a thoracotomy. The PCD® Transvene™ System allows the implantation of an ICD System without the potential increased perioperative morbidity and mortality associated with a thoracotomy. This allows the application of ICD therapy in patients who may not otherwise be candidates for this type of therapy.

In the PCD® Transvene™ System PMA Application a comparison of the PCD® Transvene™ System clinical experience was made to both the Ventak-P Epicardial System and the PCD® Epicardial System. (Reference: Clinical Experience Report Section X, Comparison to AICD Clinical Results and Section XI, Comparison to PCD® Epicardial System Clinical Results). A comparison to the Ventak-P Epicardial System was done because this was the only FDA approved ICD System available at the time of the original submission. A comparison to the PCD® Epicardial System was done since this system incorporated the same tiered therapy ICD Device as well as being a concurrent clinical study.

The comparison between the Ventak-P Epicardial System and the PCD® Transvene™ System was limited in scope due to the availability of clinical data from the Ventak-P Epicardial System Summary of Safety and

Effectiveness but included patient characteristics, implant defibrillation thresholds, incidence of spontaneous VT/VF episodes, incidence of complications and one year actuarial survival.

The comparison between the PCD® Transvene™ System and the PCD® Epicardial System included patient characteristics, implant data, implant defibrillation thresholds, programmed parameter status, spontaneous VT/VF episode efficacy, incidence of complications and observations and one year actuarial survival.

At the start of the PCD® Transvene™ System clinical study a randomized controlled study was not performed since the investigators felt strongly that it was not clinically appropriate to randomize to a surgical procedure when a less invasive implant procedure was available. The investigators believed that the ability for Medtronic to do a historical control comparison between the PCD® Transvene™ and PCD® Epicardial System would provide sufficient data to allow a comparison of the clinical outcome of the two patient groups. A historical comparison would be appropriate since patients were being enrolled in the two studies concurrently and the patient indications, implant criteria and clinical data requirements were identical for the two patient groups.

A historical comparison to the Ventak-P Epicardial System was also feasible since it was the most similar system that was market released and the patient indications were similar to that of both the PCD® Transvene™ and PCD® Epicardial Systems.

The **indications for the Ventak-P Epicardial System** are:

1. Patients who have survived at least one episode of cardiac arrest presumably due to hemodynamically unstable ventricular tachycardia unassociated with acute myocardial infarction; and

2. Patients who have experienced recurrent ventricular tachyarrhythmias in the absence of previous arrest and are inducible into sustained hypotensive ventricular tachycardia or fibrillation despite conventional antiarrhythmia drug therapy.

The patient **indications for the PCD® Transvene™ and PCD® Epicardial System** are as follows:

1. Patients who have survived at least one episode of cardiac arrest presumably due to a ventricular tachyarrhythmia not caused by an acute myocardial infraction; or

2. Patients with recurrent sustained ventricular tachycardia that remain inducible via programmed electrical stimulation or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

The Ventak-P Epicardial System is contraindicated in the following patients:

1. Patients who ventricular tachyarrhythmias may have a reversible cause;
2. Patients who require a pacemaker that causes Ventak-P pulse generator nondetection or oversensing;
3. Patients whose ventricular tachyarrhythmias occur so frequently that device's batteries would be depleted soon after implantation; and
4. Patients who are prone to supraventricular tachyarrhythmias despite conventional drug therapy.

The PCD® Transvene™ and PCD® Epicardial System are contraindicated in the following patient groups:

1. Patients with transient ventricular tachyarrhythmias due to reversible causes;
2. Patients with transient ventricular tachyarrhythmias due to other causes such as acute myocardial infarction; and
3. Sole use of detection and treatment of atrial arrhythmias.

The following tables provide a side-by-side comparison of the PCD® Transvene™ System to both the Ventak-P Epicardial System and the PCD® Epicardial System. These tables are identical to those presented in the PCD® Transvene™ System PMA application but have been updated to reflect clinical experience with the PCD® Transvene™ System with a data cutoff of 2/1/93. The clinical experience with the PCD® Epicardial System reflects a data cutoff of 1/5/93 and the Ventak-P Epicardial System clinical experience is that presented in the Summary of Safety and Effectiveness that is available via the Freedom of Information Act.

A comparison of the Ventak-P Epicardial System clinical experience and the PCD® Transvene™ System clinical experience indicates that the devices are being used in patients with similar cardiovascular disease history. There is a statistical difference in the primary indication for implant between the two systems. There were more patients that had Sudden Cardiac Death as their primary indication in the PCD® Transvene™ System population than the AICD Epicardial System population ($p = 0.001$).

Cox regression analysis was performed to see what effect gender, primary indication and system implanted (PCD® Transvene™ or PCD® Epicardial) had on survival outcome. This analysis showed that for overall

survival at one year the system implanted had an influence on the probability of survival but gender and primary indication had no influence.

Thus, since primary indication has no impact on survival outcome, the PCD® Transvene™ System and Ventak-P Epicardial System can be compared. There was a statistical difference (Confidence Interval Analysis) in one year overall survival between the PCD® Transvene™ (94.2%) and AICD Epicardial System (90.8%). This difference is due to the implanted defibrillation lead system.

The mean DFT value at implant of the PCD® Transvene™ System falls well below the maximum output (34J) of the PCD® Device and is comparable to that reported with the Ventak-P Epicardial System.

The percentage of patients receiving therapy from the PCD® Transvene™ System is comparable to that reported with the Ventak-P Epicardial System. However, greater than 90% of the VT episodes are treated by antitachycardia pacing in the PCD® Transvene™ System versus cardioversion shocks in the Ventak-P Epicardial System experience. This reduction in shocks is a clinical benefit to the patients.

The reported incidence of most complications is comparable between the two systems. The incorporation of programmable VT/VF detection has decreased the delivery of inappropriate therapy for sinus tachycardia and/or atrial fibrillation with a rapid ventricular response. The incorporation of programmable VT/VF detection and therapy algorithms has not resulted in an increase in reported complications.

The reported Sudden Cardiac Death survival rates in the two patient groups is comparable (PCD® Transvene™ System - 99.7%; Ventak-P System - 98.6%). This indicates that the programmable features within the PCD® Transvene™ System have improved the types of therapy available for the treatment of recurrent VT and VF while maintaining a positive impact on sudden cardiac death survival.

More importantly, the overall one year actuarial survival for the PCD® Transvene™ System was 94.2% as compared to 90.8% for the Ventak-P Epicardial System. This difference was primarily due to the improvement in the reported perioperative mortality in the PCD® Transvene™ System patient population.

The PCD® Transvene™ System incorporates additional detection and therapy features as compared to market released Ventak-P Epicardial System and has been used in a comparable patient population. In that patient population the PCD® Transvene™ System has allowed for fewer

shocks to be delivered because of the antitachycardia pacing features, fewer cases of inappropriate therapy delivery due to programmable detection and a comparable sudden cardiac death survival rate.

In addition, the elimination of a thoracotomy for implant in the PCD® Transvene™ System has improved the perioperative mortality and overall one year survival when compared to the Ventak-P Epicardial System.

A comparison of PCD® Transvene™ System clinical experience and PCD® Epicardial System clinical experience indicates that the devices are being used in patients with similar cardiovascular disease history. There is a statistical difference in the primary indication for implant between the two systems. There were more patients that had Sudden Cardiac Death as their primary indication in the PCD® Transvene™ System population than the PCD® Epicardial System population ($p = 0.002$). However, as with the Ventak-P Epicardial System analysis indicated that this difference in indication did not have an impact on patient outcome.

The mean DFT value at implant of the PCD® Transvene™ System falls well below the maximum output (34J) of the PCD® device and are comparable to those obtained with the PCD® Epicardial System.

The differences in PCD® device programmed status in the two groups is a reflection of the patients receiving the PCD® Transvene™ System and the defibrillation energy requirements of a nonthoracotomy lead system. However, despite differences in the programmed status, the PCD® device performed safely and effectively in both patient groups.

The spontaneous VT episode efficacy for the PCD® Transvene™ System was 98.4% which was comparable to that reported with the PCD® Epicardial System, 98.3%. The spontaneous VF episode efficacy for the PCD® Transvene™ System was 98.4% which again was comparable to that reported with the PCD® Epicardial System, 98.7%. Thus the incorporation of a nonthoracotomy lead system had no effect on the efficacy of the PCD® Device in detecting and terminating spontaneous VT/VF episodes.

The reported incidence of complications is comparable between the two systems. The reported incidence of observations was statistically lower in the PCD® Transvene™ System.

Finally, the reported Sudden Cardiac Death survival rates in the two patient groups is statistically the same (PCD® Transvene = 99.5%; PCD® Epicardial = 98.9%). However, there is statistical improvement in the overall survival in the PCD® Transvene™ System patient population. There was a significant improvement in overall survival in the patients

receiving a PCD® Transvene™ System. The Overall one year actuarial survival includes death from all causes. The overall one year survival for patients receiving the PCD® Transvene™ System was 93.3%.

This is significantly improved as compared to the overall one year actuarial survival for the PCD® Epicardial System (88.6%) [p=0.004]. This improvement in overall survival is primarily due to the marked improvement in perioperative mortality, the PCD® Transvene™ System having a 0.7% perioperative mortality versus the a perioperative mortality of 5.3% in the PCD® Epicardial System. This improvement in perioperative mortality is primarily due to the elimination of the need for a thoracotomy and its associated morbidity and mortality.

Comparison of the clinical performance and survival outcome of the PCD® Transvene™ System versus both the PCD® Epicardial and Ventak-P Epicardial Systems indicates that the PCD® Transvene™ Systems performs similarly while providing important patient benefit. The PCD® Transvene™ System eliminates the need for a thoracotomy for the implantation of defibrillation lead systems. This directly improves the overall patient survival by decreasing the perioperative patient morbidity and mortality when compared to the PCD® Epicardial System and Ventak-P Epicardial System. This is added benefit however is not gained at the expense the PCD® Transvene™ System efficacy in treating spontaneous VT/VF episodes when compared to the PCD® Epicardial System.

PCD® Transvene™ System Comparison of Patient Characteristics PCD® versus AICD		
	PCD®	Ventak-P
Number of Patients	757	292
Mean Follow-Up Time	11.7 months	6.8 months
% Males % Females	610 (81%) 147 (19%)	231 (79%) 61 (21%)
Mean Age	59.4 years	61.5 years
Primary Indication:* SCD VT SCD/VT	 281 (37%) 377 (50%) 99 (13%)	 49 (16%) 169 (59%) 73 (25%)
Coronary Artery Disease	561 (74%)	228 (78%)
Mean Ejection Fraction	35.6%	34%
Drug Therapy at Implant	42%	45.0%
Concomitant Surgery	0%	18.0%

* Statistically Significant ($p \leq 0.05$)

Table 2-1: Comparison of Patient Characteristics, PCD® versus Ventak-P 2/1/93

PCD® Transvene™ System Comparison of Implant Defibrillation Thresholds PCD® versus AICD		
	PCD®	AICD
Mean DFT	14.8J	13.4J

Table 2-2: Comparison of Implant DFT, PCD® versus Ventak-P -2/1/93

PCD® Transvene™ System Comparison of Incidence of Spontaneous VT/VF Episodes PCD® versus AICD		
	PCD®	AICD
Number of Patients with VT/VF Episode	458 (60.5%)	137 (46.9%)

Table 2-3: Comparison of Incidence of Spontaneous VT/VF Episodes: PCD® vs Ventak-P 2/1/93

PCD® Transvene™ System Comparison of Complication/Observation Rates PCD® versus AICD		
Category	PCD®%	AICD%
Fail to Cardiovert/Defibrillate	2.3%	4.1%
Inappropriate/Problematic VT/VF Therapy Delivery	9.6%*	20%
Pocket Infection (explant)	2.9%	2.2%
Erosion	0.8%	0.7%

* Includes Observations only; there were no Complications in this category.

Table 2-4: Comparison of Complication/Observation Rates: PCD® Transvene™ System vs AICD Epicardial System - 2/1/93

PCD® Transvene™ System Comparison of Patient Death Classifications PCD® versus AICD		
	PCD®	AICD
Sudden Cardiac	5	4
Non-Sudden Cardiac	30	8
Noncardiac	16	6
Unknown	-	1
TOTAL	51	19
Perioperative	5	8

Table 2-5: Comparison of Patient Death Classifications: PCD® versus AICD - 2/1/93

PCD® Transvene™ System Comparison of One Year Actuarial Survival PCD® versus AICD		
	PCD®	AICD
Sudden Cardiac Survival	99.7%	98.6%
Overall Survival*	94.2%	90.8%
Perioperative Mortality*	0.7%	2.7%

* Statistically Significant ($p \leq 0.05$)

Table 2-6: Comparison of Actuarial Survival: PCD® versus AICD - 2/1/93

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PCD® Transvene™ System Comparison of Patient Characteristics		
	PCD® Transvene™ System	PCD® Epicardial System
Number of Patients	757	742
Mean Follow-Up Time	11.7 months	16.3 months
% Males* % Females	610 80.6% 147 19.4%	637 85.8% 105 14.2%
Mean Age	59.4 years	59.6 years
Primary Indication* SCD VT SCD/VT	 281 37.1% 377 49.8% 99 13.2%	 214 28.8% 405 54.6% 123 16.6%
Cardiovascular History Coronary Artery Disease Cardiomyopathy	 561 74.1% 238 13.1%	 569 76.7% 222 29.9%
Mean Ejection Fraction	35.6%	34.0%
Number of Drugs Failed*	2.3	3.0

* Statistically Significant ($p \leq 0.05$)

Table 2-7: Comparison of Patient Characteristics, PCD® Transvene™ System versus PCD® Epicardial System - 2/1/93

PCD™ Transvene™ System Performance Comparison Implant Pace/Sense Parameters		
Parameter	**PCD® Transvene™ System**	**PCD® Epicardial System**
Pacing Threshold*	0.87 V (0.1-3.6V)	0.98 V (0.2-5.3 V)
R Wave Amplitude*	14.2 mV (1.3-32 mV)	13.5 mV (2.2-37.2 mV)
Slew Rate*	1.66 v/S (0.25-9.8 v/S)	1.38 v/S (0.15-7.2 v/S)
Resistance*	575 ohms (264-1381 ohms)	438 ohms (157-1206)

* Statistically Significant ($p \leq 0.05$)

Table 2-8: PCD® Transvene™ System: Comparison of Implant Pace/Sense Parameters - 2/1/93

PCD® Transvene™ System Performance Comparison Chronic Pace/Sense Parameters		
Parameter	**PCD® Transvene™ System**	**PCD® Epicardial System**
Electrogram Amplitude	10.0 mV (0.5 - 25 mV)	9.5 mV (0.5 - 40 mV)
Pulse Width Threshold	0.24 ms (0.03-1.59 ms)	0.24 ms (0.03-1.59 ms)

Table 2-9: PCD® Transvene™ System: Comparison of Chronic Pace/Sense Parameters - 2/1/93

PCD® Transvene™ System Performance Comparison Implant Defibrillation Thresholds	
System	**Mean DFT**
PCD™ Transvene™ System*	14.8J
PCD™ Epicardial System	9.8J

* Statistically Significant ($p \leq 0.05$)

Table 2-10: PCD® Transvene™ System: Comparison of Implant DFT - 2/1/93

PCD® Transvene™ System Performance Comparison Programmed Defibrillation Pathway		
Defibrillation Pathway	**PCD® Transvene™ System**	**PCD® Epicardial System**
Sequential	574 (75.3%)	251 (33.0%)
Simultaneous	178 (23.4%)	14 (1.8%)
Single	10 (1.3%)	496 (65.2%)

Table 2-11: PCD® Transvene™ System: Comparison of Programmed Defibrillation Pathway - 2/1/93

PCD® Transvene™ System Performance Comparison		
Spontaneous VT Episodes		
	PCD® Transvene™ System	**PCD® Epicardial System**
Mean Follow-Up	11.7 months	16.3 months
Number of Episodes	10,027	20,061
% Overall Efficacy	98.4%	98.3%
% Unsuccessful VT Termination	0.7%	1.0%
Spontaneous VF Episodes		
	PCD® Transvene™ System	**PCD® Epicardial System**
Mean Follow-Up	11.7 months	16.3 months
Number of Episodes	1982	2636
% Overall Efficacy	98.4%	98.7%
% Unsuccessful VF Termination	0.3%	0.5%

Table 2-12: PCD® Transvene™ System: Comparison of Spontaneous VT/VF Episode Efficacy - 2/1/93

PCD® Transvene™ System PCD® Transvene™ System versus PCD® Epicardial System Reported Complications		
Reported Complications	**PCD® Transvene™ System (N = 757)**	**PCD® Epicardial System (N = 742)**
Increased Defibrillation Requirements	1.2%	0.5%
Inappropriate Therapy	-	2.2%
Pace/Sense Related	0.8%	3.5%
Infection Related - Explant	2.9%	2.3%
Lead Related	15.1%	2.8%
Device Related	0.5%	0.9%

Table 2-13: Reported Complications: PCD® Transvene™ System versus PCD® Epicardial System - 2/1/93

PCD® Transvene™ System PCD® Transvene™ System versus PCD® Epicardial System Reported Observations		
Reported Observations	**PCD® Transvene™ System (N = 757)**	**PCD® Epicardial System (N = 742)**
Ineffective Therapy	1.1%	1.1%
Inappropriate Therapy	9.6%	13.6%
Pace/Sense Related	9.0%	14.0%
Infection Related	5.3%	2.5%
Lead Related	2.3%	1.2%
Device Related	-	-

Table 2-14: Reported Observations: PCD® Transvene™ System versus PCD® Epicardial System - 2/1/93

PCD® Transvene™ System Death Classifications PCD® Transvene™ System versus PCD® Epicardial System		
Death Classification	**PCD® Transvene™ System (N = 757)**	**PCD® Epicardial System (N = 742)**
Sudden Cardiac	5	24
Non-Sudden Cardiac	30	54
All Cardiac	35	78
Noncardiac	16	34
TOTAL	51	112
Perioperative Deaths	5	39

Table 2-15: Death Classifications: PCD® Transvene™ System versus PCD®Epicardial System - 2/1/93

PCD® Transvene™ System Comparison of Actuarial Survival PCD® Transvene™ System versus PCD® Epicardial System			
One Year Survival	**PCD® Transvene™ System**	**PCD® Epicardial System**	**P-Value**
Number of Patients	757	742	-
Sudden Cardiac	99.5%	98.9%	0.197
Non-Sudden Cardiac	96.2%	96.7%	0.542
All Cardiac	95.8%	95.7%	0.992
Noncardiac	98.1%	98.0%	0.820
Overall*	93.3%	88.6%	0.004
Perioperative Mortality*	0.7%	5.3%	0.001

* Statistically Significant ($p \leq 0.05$)

Table 2-16: Comparison of Actuarial Survival: PCD® Transvene™ System versus PCD® Epicardial System - 2/1/93

3. **An update of the PMA clinical study population must be provided. The update must include the data as presented in the PMA application, and must include the clinical experience in the use of the new anchoring sleeves, which are aimed at decreasing the incidence of dislodgement, and a summary of clinical experience (spontaneous treatment efficacy of ventricular tachycardia (VT) and ventricular fibrillation (VF), observations and complications, number of patient deaths and overall survival) of the patients followed for a year or more.**

RESPONSE:

A. The update of the PMA clinical study population is attached. This population consists of 757 patients entered into the Clinical Trial as of 6-24-92 and followed through 2-1-93 with a mean implant duration of 11.7 months.

B. Clinical Experience of Patients with Two Anchoring Sleeves

Analysis has been completed on 234 patients implanted with the Transvene system using leads that are packaged with two anchoring sleeves. **(NOTE: These 234 patients were enrolled in the Clinical Trial after 6-24-92 and are not included in the 757 patient population).** Table 3-1 contains a data summary for the 234 patients. This group of patients has similar characteristics to the 757 patient population in most areas with a slightly higher percentage of patients with VT reported as the primary indication for implant than the 757 group of patients (60.7% vs 49.8%).

PCD® Transvene™ System **Data Summary of Patients with Two Anchoring Sleeves**	
Number of Patients	234
Number, % Male Number, % Female	192 82.1% 42 17.9%
Mean Age	60.8 yrs
Primary Indication: SCD VT SCD/VT	 75 32.1% 142 60.7% 17 7.2%
Coronary Artery Disease	180 76.9%
Mean Ejection Fraction	33.1% (N=212)

Table 3-1: PCD® System Data Summary for Patients with Two Anchoring Sleeves

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Of these 234 patients, 186 have completed their 1 month follow-up and 49 have completed their 3 month follow-up. There has been one lead dislodgement in this group of patients.

Since the introduction of the dual anchoring sleeve the incidence of lead dislodgement has been dramatically reduced.

C. Clinical Experience of Patients Followed For Greater Than or Equal To One Year

Table 3-3 provides a data summary on the patients followed for a year or more. This table includes patient characteristics, defibrillation pathway configuration, mean LED and DFT, spontaneous VT and VF experience and efficacy. The characteristics of this subset of patients are similar to the original 757 patient population. Patients followed for a year or more had a slightly lower percentage of patients having a history of coronary artery disease (69.2% vs 74.1%) and a slightly higher mean ejection fraction (38% vs 35.6%). The differences are small and are not suspected to have an impact on implant duration or survival. Note that since by definition all patients have been followed for at least one year, the overall survival rate and the sudden cardiac survival rate is 100% at one year.

PCD™ Transvene™ System Data Summary	
	Patients with 12 months of Follow-up
Number of Patients	393
Device Months Follow-up	6454.6
Mean Follow-up Time	16.3 mo
Maximum Follow-up Time	37.4 mo
Number, % Male Number, % Female	310 78.9% 83 21.1%
Mean Age	58.8 yrs
Primary Indication: SCD VT SCD/VT	 150 38.2% 191 48.6% 52 13.2%
Coronary Artery Disease	272 69.2%
Mean Ejection Fraction	357 38.0%
Defibrillation Pathway: Sequential Simultaneous Single	 296 74.9% 93 23.6% 6 1.5%
Mean LED	15.6J (N=365)
Mean DFT	14.3J (N=184)
Spontaneous VT: Number of Patients Number of Episodes % Success	 186 6338 99.0% (6273/6338)
Spontaneous VF: Number of Patients Number of Episodes % Success	 176 1105 98.6% (1090/1105)

Table 3-3: PCD™ System Data Summary - Transvene™ Patients with 12 month Follow-up - 2/1/93

There have been a total of 7 patient deaths reported in this subset of patients. The deaths occurred greater than 12 months from the date of implant. Table 3-4 summarizes how these patient deaths have been classified.

PCD™ Transvene™ System Summary of Death Classifications in Patients followed for a Year or more	
Classifications	**Number of Deaths**
Sudden Cardiac	0
Non-Sudden Cardiac	4
Noncardiac	3
TOTAL	7

Table 3-4: PCD™ Transvene™ System - Summary of Death Classifications - 2/1/93

Complications and Observations in the patients followed for 1 year or more

The use of a multiprogrammable implantable cardioverter defibrillator (ICD) device allows the physician to resolve most relevant medical events by noninvasively changing programmed parameters thus, avoiding invasive procedures. However, there will continue to be certain relevant medical events which will require invasive procedures for resolution.

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following definitions:

COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

As of February 1, 1993, of the 393 patients with implant durations of greater than or equal to one year, there have been a total of 89 complications reported in 76 patients and 122

observations reported in 99 patients in the PCD™ Transvene™ System patient population. Thus, 19.3% (76/393) of the patients had a clinical event reported which was categorized as a complication vs 19.4% (147/757) in the overall population and 25.2% (99/393) of the patients had a clinical event reported which was categorized as an observation vs 23.8% (180/757) in the overall population.

Table 3-5 summarizes the reported PCD® Transvene™ System complications and observations by category. The reported complications and observations are recognized clinical events that may occur with **any** of the current ICD devices. These complications and observations are discussed in the PCD® device and Transvene™ manual. **None of the reported complications or observations have resulted in a patient death.**

PCD® Transvene System Reported Complications/Observations in Patients followed for 1 Year or more: By Category		
Category	**Complications**	**Observations**
	Num (% of Pts)	Num (% of Pts)
Increased Defibrillation Requirements	3 (0.8%)	2 (0.5%)
Inappropriate VF Therapy Delivery	-	10 (2.5%)
Inappropriate VT Therapy Delivery	-	40 (10.2%)
Loss of Capture	2 (0.5%)	6 (1.5%)
Oversensing	-	29 (7.4%)
Undersensing	-	-
Skin Erosion	2 (0.5%)	1 (0.3%)
Pocket Infection	5 (1.3%)	7 (1.8%)
Seroma	1 (0.3%)	9 (2.3%)
Hematoma	1 (0.3%)	7 (1.8%)
Pneumothorax	2 (0.5%)	1 (0.3%)
Pacemaker Syndrome	-	1 (0.3%)
Perforation	1 (0.3%)	-
Subclavian Vein Thrombosis	-	1 (0.3%)
Lead Fracture	6 (1.5%)	-
Subcutaneous Patch Crinkling	5 (1.3%)	3 (0.8%)
Early Device Explant	3 (0.8%)	-
Total Lead Dislodgement	56 (14.2%)	6 (1.5%)
Total	**89**	**122**

Table 3-5: PCD Transvene System: Reported Complications and Observations - 2/1/93

Table 3-6 contains a description of the lead dislodgements that have occurred in less than 30 days and in greater than 30 days.

PCD® Transvene System Reported Complications/Observations in Patients followed ≥1 Year Lead Dislodgements <30 days and >30 days N=393			
Complications		Observations	
<30 days	>30 days	<30 days	>30 days
27 (6.9%)	29 (7.4%)	0 (0)	6 (1.5%)

Table 3-6: PCD Transvene System: Lead Dislodgements occurring <30/>30 days in patients followed for greater than or equal to one year as of 2/1/93

There have been a total of 29 lead dislodgements reported in patients at greater than 30 days. None of the lead dislodgements resulted in an ineffective therapy for a spontaneous VT or VF episode or patient death. Lead dislodgements were documented by fluoroscopic examination during electrophysiologic evaluation, chest x-ray obtained during routine follow-up, or during pacing/sensing threshold evaluation during routine follow-up. In all 29 cases, reoperation was required to reposition the lead and reestablish an effective defibrillation lead system.

Lead dislodgements are not specific to the PCD® Transvene™ System and have been reported with dual chamber pacemakers and the current market released implantable cardioverter defibrillator (ICD) system. The early history of dual chamber pacemakers witnessed a high lead dislodgement rate of at least 20% (Smyth, PND, et al. Permanent perivenous atrial sensing and pacing with a new J-shaped lead. J Thoracic Cardiovascular Surgery. 1976;72:565-570). Winkle, et al reported that the incidence of dislodgement of the superior vena cava spring leads with the current market release ICD system to be 6.3%. (Winkle, et al. Automatic Implantable Cardioverter-Defibrillator: Efficacy, Complications, and Survival in Patients with Malignant Ventricular Arrhythmias. JACC. June 1988; Vol.11, No.6:1278-86).

In summary, this group represents the majority of the overall population and characteristics of the 393 patients with implant durations of greater than or equal to one year were similar to the overall population.

4. **Please provide a clear description of how you identified the "patient who did not meet the implant criteria." Please discuss your implant criteria and how implant testing attempted to satisfy protocol requirements.**

RESPONSE:

For purposes of the PCD® Transvene™ and Epicardial Systems, the implant criteria was defined as successful VF termination at least 3 times in 4 attempts with the final lead configuration with an output energy of 18 Joules or less.

"Patients who did not meet implant criteria" were defined as:

- Patients who had less than 3 successful VF terminations at 18 Joules or less;
- Patients in whom the lowest energy of success was greater than 18 Joules;
- Patients in whom either 1 or 2 successful VF terminations with the final lead configuration were obtained at 18 Joules or less; and,
- Patients in whom ventricular tachycardia or ventricular flutter was induced at the time of implant.

The PCD® Transvene™ and Epicardial Systems were evaluated through successive inductions and treatment of ventricular tachyarrhythmias according to study protocol. The protocol asked for a minimum of 3 inductions of VF in order to demonstrate reliable defibrillation efficacy at 18 Joules. If the first lead system evaluated successfully defibrillated the patient three consecutive times at 18 Joules or less, the implant criteria would have been satisfied and the implant could be completed. Additional inductions were required if the first lead system was not efficacious at 18 Joules. Performing additional inductions to obtain a defibrillation threshold was **not** a protocol requirement. The attached figure represents the recommended Defibrillation Efficacy Protocol used in lead evaluation testing for the PCD® Transvene™ and Epicardial Systems.

There is a class of patients who cannot tolerate the thoracotomy required for the utilization of the epicardial patch lead defibrillation lead system and are at high risk of sudden cardiac death. Because of the surgical risks and postsurgical complications associated with the implant of an epicardial lead system, implantation in the following patient groups may not be desirable or possible:

(1) Patients in whom there is no indication for concomitant cardiovascular surgery at the time of ICD implant;

(2) Patients with severe pulmonary disease who cannot tolerate prolonged anesthesia or an open chest procedure;

(3) Patients with severe congestive heart failure (ejection fraction < 40%) who are at increased risk for perioperative mortality post a thoracotomy procedure;

(4) Patients who may eventually require open chest procedures of treatment of their coronary artery disease or cardiac transplant.

For these patients, the PCD® Transvene™ System is the only therapy available. The PCD® Transvene™ System simplifies and greatly reduces the risk associated with lead introduction, making therapy available to these patient groups. Because there is no need to open the chest of these patients, options for future therapy remain available; e.g. CABG is associated with decreased morbidity and mortality if there has been no prior open chest procedure.

The investigators felt that for these patients a 10 Joule safety margin between the lowest energy of success (24J) and the maximum output (34J) of the PCD® Device provided adequate defibrillation efficacy evaluation. The investigators used this 10 Joule safety margin as a benchmark based on the clinical experience discussed in the article, Troup, et al. The Implanted Defibrillator: Relation of Defibrillating Configuration and Clinical Variables to Defibrillation Threshold. Journal of American College of Cardiology, 1985; 6:1315-1321. The investigators felt that for these patients the risk associated with not meeting the recommended implant criteria was outweighed by the benefit of not having to undergo an epicardial system implant with a thoracotomy approach and its associated morbidity and mortality.

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To determine whether a patient can be defibrillated reliably with a particular lead system, VF must be induced and successfully terminated at least 3 times in 4 attempts with a stored output energy of 18 Joules or less. The following protocol should be followed in assessing defibrillation efficacy:

Defibrillation Efficacy Protocol
(b) (4)
(b)(4)

Lead system testing will be accomplished using an External Cardioverter/Defibrillator (ECVD), Model 2394 or Model 5355.

NOTE: The following precautions should be observed when initiating and treating episodes of ventricular tachyarrhythmias with the Model 2394 External Cardioverter/ Defibrillator:

5. **Of the 214 patients who did not meet the implant criteria and yet were implanted with the device, 170 patients had successful defibrillation with 24 Joules (J). Please provide an update of the clinical experience on these patients, as described in item 3 above. Also, please discuss how your proposed labeling will address this protocol deviation. Will implant criteria be changed?**

RESPONSE:

Table 5-1 provides the patient characteristics for 170 patients who did not meet the implant criteria but had successful defibrillation at 24 joules and received the PCD™ Transvene™ System.

PCD™ Transvene™ System
Patients Meeting Implant Criteria vs 170 Patients with Successful Defibrillation at 24J

Patient Characteristics		
Number of Patients	170	543
Mean Follow-Up	9.6 months	12.3 months
Male*	151 (88.8%)	422 (77.7%)
Female	19 (11.2%)	121 (22.3%)
Mean Age	59.8 yrs	59.4 yrs
Indication*		
SCD	63 (37.1%)	209 (38.5%)
VT	77 (45.3%)	78 (51.2%)
SCD/VT	30 (17.6%)	56 (10.3%)
Cardiovascular History		
CAD	137 (77.7%)	396 (72.9%) 173
Cardiomyopathy	58 (34.1%)	(31.9%)
Mean EF*	32.7%	36.3%
NYHA Class		
I	45 (27.6%)	164 (30.9%)
II	90 (55.2%)	278 (52.4%)
III	24 (14.7%)	82 (15.4%)
IV	4 (2.5%)	7 (1.3%)

* Statistically Significant ($p \leq 0.05$)

Table 5-1: PCD™ Transvene™ System: Patients Meeting Implant Criteria N = 170 Patient Characteristics - 2/1/93

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There was a statistically significant difference in the number of males ($p=0.002$), the number of patients with the primary indication of VT ($p=0.032$), and the mean EF ($p=0.007$) between the groups above however these differences are not clinically significant.

In order to determine if the patient's not meeting implant criteria had higher risk for morbidity and mortality, a comparison of their clinical outcome was made with those patients who did meet the implant criteria. This comparison is provided in Table 5-2. There were no statistical or clinically significant differences in outcome as observed below.

PCD™ Transvene™ System Patients Not Meeting Implant Criteria 170 Patients with Successful Defibrillation at 24J		
Implant Data		
Number of Patients	170	543
Spontaneous VT Episode Efficacy	98.5%	98.7%
Spontaneous VF Episode Efficacy	99.4%	98.7%
Number of Patient Deaths	11	37
Perioperative Mortality	0.6%	0.7%
One Year Survival		
Sudden Cardiac	99.4%	99.5%
Non-Sudden Cardiac	98.6%	95.8%
All Cardiac	98.0%	95.4%
Noncardiac	96.3%	98.5%
Overall	93.8%	93.2%

Table 5-2: PCD™ Transvene™ System: Patients Not Meeting Implant Criteria N=170 - Clinical Outcome - 2/1/93

Complications and Observations: Patients Not Meeting Implant Criteria N = 170

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following definitions:

COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

Of the 170 patients with successful defibrillation at 24 Joules, as of February 1, 1993, there have been a total of 41 complications reported in 33 patients and 34 observations reported in 31 patients in the PCD™ Transvene™ System patient population. Thus, 19.4% (33/170) of the patients had a clinical event reported which was categorized as a complication and 18.2% (31/170) of the patients had a clinical event reported which was categorized as an observation. The percent of patients with complications reported in the overall population of 757 patients was 19.4% (147/757), the same percentage as in this subgroup of 170. There were 23.8% (180/757) of the patients in the overall population with reported observations, a slightly higher percentage than in this subgroup of 170. Table 5-3 summarizes the reported PCD® Transvene™ System complications and observations by category. The reported complications and observations are recognized clinical events that may occur with **any** of the current ICD devices. These complications and observations are discussed in the PCD® device and Transvene™ manual. **None of the reported complications or observations have resulted in a patient death.**

PCD® Transvene System Reported Complications/Observations Patients Not Meeting Implant Criteria 170 Patients with Successful Defibrillation at 24J		
Category	Complications	Observations
	Num (% of Pts)	Num (% of Pts)
Increased Defibrillation Requirements	5 (2.9%)	-
Inappropriate VF Therapy Delivery	-	-
Inappropriate VT Therapy Delivery	-	10 (5.9%)
Loss of Capture	-	5 (2.9%)
Oversensing	-	7 (4.1%)
Undersensing	-	-
Skin Erosion	-	-
Pocket Infection	3 (1.8%)	2 (1.2%)
Seroma	2 (1.2%)	3 (1.8%)
Hematoma	1 (0.6%)	2 (1.2%)
Pneumothorax	-	-
Pacemaker Syndrome	-	-
Perforation	1 (0.6%)	-
Subclavian Vein Thrombosis	1 (0.6%)	1 (0.6%)
Lead Fracture	2 (1.2%)	-
Subcutaneous Patch Crinkling	2 (1.2%)	1 (0.6%)
Early Device Explant	1 (0.6%)	-
Total Lead Dislodgement	23 (13.5%)	3 (1.8%)
Total	41	34

Table 5-3: PCD Transvene System: Reported Complications and Observations - 2/1/93

Table 5-4 contains a description of the lead dislodgements that have occurred in less than 30 days and in greater than 30 days in the 170 patients.

PCD® Transvene System Reported Complications/Observations Lead Dislodgements <30 days and >30 days Patients Not Meeting Implant Criteria 170 Patients with Successful Defibrillation at 24J			
Complications		Observations	
Num (% of Pts)		Num (% of Pts)	
<30 days	>30 days	<30 days	>30 days
9 (5.3%)	14 (8.2%)	1 (0.6)	2 (1.2%)

Table 5-4: PCD Transvene System: Lead Dislodgements <30/>30 days - 2/1/93

There have been a total of 14 lead dislodgements reported in patients at greater than 30 days. None of the lead dislodgements resulted in an ineffective therapy for a spontaneous VT of VF episode or patient death. Lead dislodgements were documented by fluoroscopic examination during electrophysiologic evaluation, chest x-ray obtained during routine follow-up, or during pacing/sensing threshold evaluation during routine follow-up. In the overall patients population of 757, lead dislodgement was reported in 6.5% of the patients implanted for >30 days which is slightly lower than in this subset of patients, 8.2%, which are included in the analysis of the overall population. In all 14 cases, reoperation was required to reposition the lead and reestablish an effective defibrillation lead system.

Lead dislodgements are not specific to the PCD® Transvene™ System and have been reported with dual chamber pacemakers and the current market released implantable cardioverter defibrillator (ICD) system. The early history of dual chamber pacemakers witnessed a high lead dislodgement rate of at least 20% (Smyth, PND, et al. Permanent perivenous atrial sensing and pacing with a new J-shaped lead. J Thoracic Cardiovascular Surgery. 1976;72:565-570). Winkle, et al reported that the incidence of dislodgement of the superior vena cava spring leads with the current market release ICD system to be 6.3%. (Winkle, et al. Automatic Implantable Cardioverter-Defibrillator: Efficacy, Complications, and Survival in Patients with Malignant Ventricular Arrhythmias. JACC. June 1988; Vol.11, No.6:1278-86).

In summary, there are no clinically significant differences in the characteristics and/or most importantly in outcome of the 170 patients

that did not meet implant criteria but were successfully defibrillated with 24 joules and those meeting implant criteria. Based on these data, the recommended defibrillation efficacy implant requirements will be revised to the following:

Two consecutive successful defibrillations with the final lead configuration with a stored output energy of 24 Joules or less; or

Three successful defibrillations in four attempts with the final configuration at a stored output energy of 24 Joules or less.

6. **There were 20 patients among the 214 who did not meet the implant criteria and were implanted without the 10 J safety margin. An update of the spontaneous episode experience in the treatment of VT and VF in these patients and the overall survival must be provided.**

RESPONSE:

There were 20 patients in whom the implant procedure was terminated due to poor patient condition. These patients received a PCD® Transvene™ System without at least a 10 Joule defibrillation safety margin. The mean ejection fraction of this group was 26.9%, indicating a more severe underlying cardiovascular disease, and may have contributed to the physicians decision to terminate the implant procedure prior to meeting the recommended defibrillation implant criteria.

Of these 20 patients, VT or VF has been induced at chronic follow-up visits in 16 patients (80%) and in all cases successful defibrillation with the implanted PCD® Transvene™ System was documented.

The overall spontaneous VT episode efficacy for the patient group was 98.9%. While the overall spontaneous VF episode efficacy for the patient group was 96.0%. Examination of the spontaneous VF episodes indicated that one patient experienced atrial fibrillation that was detected as VF and in whom all four programmed VF therapies were ineffective. This patient's antiarrhythmic drug therapy was modified and there were no further reports of ineffective therapies.

There have been no patients in this patient population who have experienced an actual spontaneous VF episode where all four programmed VF therapies failed to terminate the episode.

There have been two reported patient deaths, both of which were classified as non-sudden cardiac secondary to end stage heart failure. The one year sudden cardiac death survival in this patient population is 100% while the overall one year survival was 85.5%. This lower overall one year survival may be due to the lower mean ejection fraction and poorer cardiac status of this group.

The clinical outcome (which is summarized in the Table 4-1) of these twenty patients was not adversely affected by not meeting the recommended defibrillation implant criteria since there were no reports of failure to terminate a spontaneous VF episode and the overall one year sudden cardiac death survival was 100%.

PCD® Transvene™ System Patients Not Meeting Implant Criteria Due to Patient Condition	
Number of Patients	20
Mean EF	26.9%
# Patients with Induced VT/VF	16 (80%)
Spontaneous VT Episode Efficacy	98.9%
Spontaneous VF Episode Efficacy	96.0%
One Year Sudden Cardiac Death Survival	100%
One Year Overall Survival	85.5%

Table 4-1: PCD® Transvene™ System: Patients Not Meeting Implant Criteria Due to Poor Patient Condition

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7. **Table IK-4, page 151, compares the patients meeting the implant criteria to those who did not meet the criteria. However, many of the percentages were presented without numerical support. Please provide the appropriate numbers.**

RESPONSE:

The spontaneous VT and VF episode efficacy and perioperative mortality presented in table IK-4 are percentages, but the survival calculations are probabilities. The survival probabilities are calculated using a life-table survival analysis. For verification of survival probabilities, the data necessary to do calculations is available upon request. The following table is IK-4 with a June 24, 1992 data cutoff, providing you the additional numerical support for percentages where appropriate.

PCD® Transvene™ System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Implant Data		
Data	Meeting Criteria	Not Meeting Criteria
Number of Patients	543	214
Number of Successful VT Episodes Number of VT Episodes	3619 3657	1743 1773
Spontaneous VT Episode Efficacy	99.0%	98.4%
Number of Successful VF Episodes Number of VF Episodes	708 715	258 260
Spontaneous VF Episode Efficacy	99.0%	99.2%
Number of Patient Deaths	18	4
Perioperative Mortality	4 0.7%	1 0.5%
One Year Actuarial Survival		
Sudden Cardiac	100.0%	99.3%
Non-Sudden Cardiac	96.4%	98.6%
All Cardiac	96.4%	97.9%
Noncardiac	99.2%	100.0%
Overall	94.9%	97.4%

Table IK-4: PCD® Transvene™ System: Patients Not Meeting Implant Criteria versus Patients Meeting Implant Criteria - Comparison of Clinical Outcome - 6/24/92

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8. **Please provide an update on the patients who are implanted with the Transvene™ System and were not counted in the PMA population. The update must include a summary of the clinical experience as reference in item 3 above.**

RESPONSE:

Overview of Clinical Experience for Transvene Population of 1330 Patients

This response covers a total of 1335 implants in 1330 patients of the PCD™ Device with the Transvene™ Defibrillation Lead System. The patients included in this report includes the 757 patients described in the original PMA application and an additional 573 patients that have been implanted in the U.S. from 6/25/92 to 2/1/93. The first implant occurred internationally on October 20, 1989, and the first implant in the U.S. occurred on October 16, 1990.

The mean implant duration for this patient population is 8.0 months and ranges from implant to 37.4 months. The cumulative implant duration is 10,653.7 months.

The patient population (N=1330) enrolled in the clinical trial was predominately male (81.6%) with a mean age of 60.4 years. In half of the patients (54.5%), the primary indication for implant was recurrent, sustained ventricular tachycardia without an episode of sudden cardiac death. Sudden Cardiac Death was the primary indication for 34.7% of the patients and SCD in combination with recurrent, sustained VT was the primary indication in 10.8%. Coronary artery disease was the primary heart disease in 76.2% of the patient population with a mean reported ejection fraction of 34.3% Table 8-1 provides a data summary on these patients. Although there is a slightly higher percentage of patients with the primary indication of VT, 54.5% vs 49.8% (PMA patient population), there are no substantial differences or trends noted from the original PMA population.

PCD™ Transvene™ System Data Summary of Updated Population N = 1330	
Number of Patients	1330
Device Months Follow-up	10,653.7 mo
Mean Follow-up Time	8.0 mo
Maximum Follow-up Time	37.4 mo
Number, % Male Number, % Female	1085 81.6% 245 18.4%
Mean Age	60.4 yrs
Primary Indication: SCD VT SCD/VT	 462 34.7% 725 54.5% 145 10.8%
Coronary Artery Disease	1014 73.4%
Mean Ejection Fraction	1194 34.3%
Defibrillation Pathway: Sequential Simultaneous Single	 980 73.4% 341 25.5% 14 1.1%
Mean LED	16.4J (N = 1236)
Mean DFT	15.4J (N = 496)
Spontaneous VT: Number of Patients Number of Episodes % Success	 424 11577 98.1%
Spontaneous VF: Number of Patients Number of Episodes % Success	 427 2453 98.6%
One Year SCD Survival	99.3%
Overall Survival	93.0%

Table 8-1: PCD™ Transvene System: Data Summary - Updated Pts. (1330) - 2/1/93

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Complications and Observations

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following definitions:

COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

Of the 1330 patients, as of February 1, 1993, there have been a total of 225 complications reported in 195 patients and 275 observations reported in 228 patients in the PCD™ Transvene™ System patient population. Thus, 14.7% (195/1330) of the patients had a clinical event which was categorized as a complication and 17.1% (228/1330) of the patients had a clinical event which was categorized as an observation.

Table 8-2 summarizes the reported PCD® Transvene™ System complications and observations by category. In almost all categories, the percentage of patients in which a complication or observation was reported has decreased compared to the original PMA patient population of 757. The percentage of patients with lead dislodgements reported has substantially decreased from 12% with a complication to 8.8% and 1.6% with an observation to 0.9%. No new categories of complications or observations were reported. The reported complications and observations are recognized clinical events that may occur with **any** of the current ICD devices. These complications and observations are discussed in the PCD® device and Transvene™ manual. **None of the reported complications or observations have resulted in a patient death.**

PCD® Transvene System Reported Complications/Observations By Category N = 1330		
Category	Complications	Observations
	Num (% of Pts)	Num (% of Pts)
Increased Defibrillation Requirements	14 (1.1%)	8 (0.7%)
Inappropriate VF Therapy Delivery	-	17 (1.3%)
Inappropriate VT Therapy Delivery	-	68 (5.1%)
Loss of Capture	6 (0.5%)	16 (1.2%)
Oversensing	1 (0.1%)	83 (6.2%)
Undersensing	-	-
Skin Erosion	5 (0.4%)	1 (0.1%)
Pocket Infection	30 (2.3%)	12 (0.9%)
Seroma	10 (0.8%)	20 (1.5%)
Hematoma	12 (0.9%)	23 (1.7%)
Pneumothorax	2 (0.2%)	1 (0.1%)
Pacemaker Syndrome	-	2 (0.2%)
Perforation	7 (0.5%)	-
Subclavian Vein Thrombosis	1 (0.1%)	6 (0.5%)
Lead Fracture	9 (0.7%)	-
Subcutaneous Patch Crinkling	7 (0.5%)	5 (0.4%)
Early Device Explant	4 (0.3%)	-
Total Lead Dislodgement (n = 1330)	117 (8.8%)	12 (0.9%)
Total	225	275

Table 8-2: PCD Transvene System: Reported Complications/ Observations (n = 1330) - 2/1/93

117
91
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Table 8-3 contains a description of the lead dislodgements that have occurred in less than 30 days and in greater than 30 days. As noted earlier, the percentage of patients in which a complication or observation regarding lead dislodgement was reported has decreased from the original PMA patient population of 757.

PCD® Transvene System Reported Complications/Observations Lead Dislodgements <30 and >30 days (N=1330)				
Category	Complications		Observations	
	Num (% of Pts)		Num (% of Pts)	
	<30 days	>30 days	<30 days	>30 days
RV Lead Dislodgement n=1314	19 (1.4%)	13 (1.0%)	0 (0)	1 (0.1%)
CS Lead Dislodgement n= 387	19 (4.9%)	11 (2.8%)	2 (0.5%)	2 (0.5%)
SVC Lead Dislodgement n=989	16 (1.9%)	36 (3.6%)	1 (0.1%)	6 (0.6%)
Total Dislodgement n=1330	57 (4.3%)	60 (4.5%)	3 (0.2%)	9 (0.7%)

Table 8-3: PCD Transvene System: Lead Dislodgements <30/>30 days (n=1330) - 2/1/93

There have been a total of 60 lead dislodgements reported in patients at greater than 30 days. None of the lead dislodgements resulted in an ineffective therapy for a spontaneous VT of VF episode or patient death. Lead dislodgements were documented by fluoroscopic examination during electrophysiologic evaluation, chest x-ray obtained during routine follow-up, or during pacing/sensing threshold evaluation during routine follow-up. In all 60 cases, reoperation was required to reposition the lead and reestablish an effective defibrillation lead system.

Lead dislodgements are not specific to the PCD® Transvene™ System and have been reported with dual chamber pacemakers and the current market released implantable cardioverter defibrillator (ICD) system. The early history of dual chamber pacemakers witnessed a high lead dislodgement rate of at least 20% (Smyth, PND, et al. Permanent perivenous atrial sensing and pacing with a new J-shaped lead. J Thoracic Cardiovascular Surgery. 1976;72:565-570). Winkle, et al reported that the incidence of dislodgement of the superior vena cava spring leads with the current market release ICD system to be 6.3%. (Winkle, et al. Automatic Implantable Cardioverter-Defibrillator: Efficacy, Complications, and Survival in Patients with Malignant Ventricular Arrhythmias. JACC. June 1988; Vol.11, No.6:1278-86).

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Patient Deaths

The positive impact of implantable cardioverter defibrillator (ICD) therapy on sudden cardiac death mortality has been well documented in the medical literature. The use of device therapy for the treatment of recurrent ventricular arrhythmias has become an accepted and important clinical tool. An analysis of the sudden cardiac death survival in the PCD™ Transvene™ System patient population was performed.

For purposes of the clinical study, each of the patient deaths was categorized using the following definitions:

Non-Cardiac:	Deaths that occurred where the primary cause of death was determined to be non cardiac in nature, e.g. stroke, cancer, etc.
Cardiac:	Deaths that occurred where the primary cause of death was determined to be cardiac in nature.
Non-Sudden:	Deaths that occur greater than one hour after the onset of symptoms.
Sudden:	Deaths that occur within one hour of the onset of symptoms or where the death is unwitnessed. Sudden cardiac deaths were also categorized as being **Witnessed** or **Unwitnessed.**
Perioperative:	Deaths that occur within thirty days of implant.
System Related:	A death which results from a malfunction (operation not according to design specification) of a PCD™ System component, or as a result of a device induced arrhythmia, or an interaction between a PCD™ System component and the patient.
Procedure Related:	A death which occurs as a result of a procedure required to implant, follow or test a PCD™ System.

All deaths and significant complications have been and will continue to be reviewed by a committee comprised of PCD™ Transvene™ System investigators and other physicians. Two committees (Clinical Event Review Committees) have been formed, one to review North American deaths and complications, and the other to review European clinical events. The primary purpose of these reviews was to determine whether

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the PCD™ System was related to the deaths or significant complications that have occurred and, if so, what changes may be required to prevent such events in the future.

There have been a total of 68 patient deaths reported in the PCD™ Transvene™ System patient population. Table 8-4 summarizes how these patient deaths have been classified.

PCD™ Transvene™ System Summary of Death Classifications (n = 1330)	
Classifications	**Number of Deaths**
Sudden Cardiac	10
Non-Sudden Cardiac	37
Noncardiac	21
TOTAL	68

Table 8-4: PCD™ Transvene™ System - Summary of Death Classifications (n = 1330) - 2/1/93

None of the patient deaths were attributed to a malfunction of the PCD™ Transvene™ System.

Actuarial survival analysis on the PCD™ Transvene™ System was done on all patients who were either evaluated for implantation or in whom the device was implanted. Thus, the analysis is done from the perspective of **intention to treat.** Those patients in whom the PCD™ Device was OFF at the time of death or in whom no device was implanted <u>are</u> included in the survival analysis. Those patients that were screened for a PCD™ Transvene™ System but failed to receive a Transvene™ system are not included in this analysis.

Projected one year survival calculations for the various death classifications are provided in Table 8-5. **The actuarial projections include perioperative deaths only in the calculation of one year survival from death due to all causes (shown in the row labelled Overall).** The perioperative death rate defined as deaths which occurred within thirty days of implant was 0.8% (10/1330) which is considerably less than the perioperative mortality for the PCD™ System with Epicardial leads (5.3% - 39/742).

PCD™ Transvene™ System One Year Actuarial Survival	
Sudden Cardiac Death	99.3%
Non-Sudden Cardiac	96.3%
All Cardiac	95.6%
Noncardiac	98.1%
Perioperative	0.8%
Overall	93.0%

Table 8-5: PCD™ Transvene™ System - One Year Actuarial Survival - 2/1/93

The positive impact of the PCD™ Transvene™ System on patient mortality is clearly obvious from this analysis. The sudden cardiac death survival rate the total patient group (n = 1330) is 99.3%. This is a marked improvement when compared with the reported survival of similar patient groups treated with drug therapy alone of between 34% and 73% at one year.

In conclusion, the data above for the 1330 patients implanted and followed through 2-1-93 is similar to the 757 PMA patient population as expected. Although lead dislodgement is not an unexpected complication and patients are routinely evaluated during follow-up procedures at follow-up visits, in order to minimize the incidence of lead dislodgement, the dual anchoring sleeve has been introduced and the incidence of lead dislodgement has drastically decreased. The one year actuarial survival results continue to be stable, above 99% for SCD and efficacy rates continue at greater than 98%.

IPD

9. **Based on your study protocol, please differentiate between defibrillation threshold (DFT) testing and lowest energy to defibrillate (LED) testing. Based on the individual patient report forms of the 757 patients, how many patients underwent what is described as DFT testing and how many had LED testing? Samples of the patient report forms showing the scheme of testing which was categorized as DFT and LED testing must be provided. Please discuss how the DFT and LED data were reported and presented in the PMA application.**

RESPONSE:

The study protocol asks the investigator to determine the efficacy of the implanted lead system with the external test device prior to connecting the leads to the implantable PCD® device. The minimum amount of testing required to demonstrate lead system efficacy is 3 of 4 successful defibrillations at 18 Joules. The protocol asks that investigators go beyond this minimal level and perform testing using a step down procedure. Investigators attempt defibrillation at energy levels lower than 18 Joules in order to establish a defibrillation threshold. In order to make defibrillation testing uniform among the investigators, the protocol asks that testing be done using a common step down protocol. This protocol is as follows:

(b) (4)

(b)(4)

All investigators were asked to perform this step down testing, but the investigator was allowed to stop the step down testing, or waive it completely, if, in the investigators opinion, the patient could not tolerate

additional VF inductions. Since testing did not always follow this step down protocol, two terms were developed to accurately report defibrillation efficacy, Lowest Energy of Defibrillation (LED) and Defibrillation Threshold (DFT). They are defined as follows:

Lowest Energy of Defibrillation (LED):
LED is defined as the lowest programmed energy that successfully defibrillated the heart with the implanted lead system.

Defibrillation Threshold (DFT):
DFT is defined as the lowest programmed energy which successfully defibrillated the heart provided there is a failure at an energy below the lowest success or a success at $\leq$ 5J.

Based on these definitions all patients with a DFT also have an LED but not every patient with an LED has a DFT.

Several examples of the type of data used in this analysis is presented below. The first example shows successful completion of the step-down protocol with the first lead system tested. By having a success at 5 Joules this patient has both a DFT and LED of 5 Joules. This example also shows the various codes used in this section of the data forms.

5. Lead Evaluation Log **DFT and LED = 5 Joules**

Lead System Number	Episode Number	Therapy Number	Induced Rhythm	Therapy Data*	Post Therapy Rhythm	
(b) (4)						

(b)(4)

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The next example shows a failure at 5 Joules. This patient, therefore, has a DFT and LED of 10 Joules.

5. Lead Evaluation Log DFT and LED = 10 Joules

Lead System Number	Episode Number	Therapy Number	Induced Rhythm	Therapy Data*	Post Therapy Rhythm	
(b) (4)						

(b)(4)

The next example is one where the investigator decided to stop lead evaluation before reaching an energy low enough to demonstrate failure to defibrillate. The implant criteria was met since there was three successes at 18 Joules or less. Since a failure was never demonstrated, we are unable to calculate a DFT, only an LED. The LED in this example is 10 Joules.

5. Lead Evaluation Log LED = 10 Joules

Lead System Number	Episode Number	Therapy Number	Induced Rhythm	Therapy Data*	Post Therapy Rhythm	
(b) (4)						

(b)(4)

Typically, more than one lead system is evaluated. The lead systems are described on the previous page of the "Lead System Evaluation Data Form" and identified by number. Every induction and therapy delivered into the lead system is recorded on the "Lead Evaluation Log". This is an example of a difficult patient that required two modifications to the lead system before an efficacious system was found. This patient had an LED of 18 Joules and no DFT. Since defibrillation testing was not performed at an energy less than 18 Joules, a failure level was not established.

MEDTRONIC CONFIDENTIAL

5. Lead Evaluation Log LED = 18 Joules						
Lead System Number	Episode Number	Therapy Number	Induced Rhythm	Therapy Data*	Post Therapy Rhythm	
(b)(4)						

(b)(4)

Table VID-8 on page 213 of the PMA clinical report shows the LED for the lead configurations tested at implant. Below is an updated Table VID-8 based on 757 patients.

PCD™ Transvene™ System Lowest Energy of Defibrillation	
All Lead Systems: N	703
Mean	16.0
Std. Dev.	5.1
Maximum	34
Minimum	0.6
RV-SVC-SQ: N	456
Mean	16.7
Std. Dev.	4.8
Maximum	34
Minimum	3
RV-CS-SQ: N	210
Mean	14.6
Std. Dev.	5.6
Maximum	34
Minimum	0.6
RV-CS-SVC: N	37
Mean	15.2
Std. Dev.	4.9
Maximum	34
Minimum	10

Table VID-8: PCD™ Transvene™ System - Lowest Energy of Defibrillation - 6/24/92

Seven-hundred-three (703) patients had at least one successful defibrillation with the lead system implanted during lead system testing. During the remaining 59 implant procedures (762-703=59) the patient either could not be induced into VF during implant lead testing, only V-Flutter or VT, or testing of the final lead system was waived due to patient condition.

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A subset of patients were evaluated with the step-down protocol and either had a defibrillation failure at an energy below 18 Joules or was successful at 5 Joules. A defibrillation threshold (DFT) was calculated in this group of patients. This calculation was performed by Medtronic's statisticians from the information recorded on the study data forms. DFT is defined as the lowest programmed energy which successfully defibrillated the heart provided there is a failure at an energy below the lowest success or a success at $\leq$ 5J. There was no requirement to find the lowest DFT possible in a particular patient.

DFT's were obtained during 316 of the 762 implant procedures presented in this report. Table VID-9 on page 215 of the PMA clinical report contains the DFT's obtained during implant testing.

PCD™ Transvene™ System Defibrillation Threshold (DFT)	
All Lead Systems: N	316
Mean	14.8
Std. Dev.	5.2
Maximum	30
Minimum	0.6
RV-SVC-SQ: N	187
Mean	15.8
Std. Dev.	4.7
Maximum	30
Minimum	3
RV-CS-SQ: N	110
Mean	12.8
Std. Dev.	5.9
Maximum	24
Minimum	0.6
RV-CS-SVC: N	19
Mean	16.0
Std. Dev.	3.7
Maximum	24
Minimum	10

Table VID-9: PCD™ Transvene™ System - Defibrillation Threshold - 6/24/92

In summary the Lowest Energy of Defibrillation (LED) is defined as the lowest programmed energy that successfully defibrillated the patient with the implanted lead system. Defibrillation Threshold (DFT) is defined as the lowest programmed energy which successfully defibrillated the heart provided there is a failure at an energy below the lowest success or a success at $\leq$ 5J. An LED was determined during 703 of the 762 implant procedures included in the September 18, 1992 clinical update. In 316 of these implant procedures we were also able to calculate a DFT. Three-hundred-eighty-seven (387) (703-316=387) implant procedures had only an LED determined, since a failure level was never established.

10. **There is a statistically significant difference between the mean DFT obtained with the RV-CS-SQ lead configuration and the mean DFT obtained with the other lead configurations. How do you account for this difference? Was the DFT as reported and discussed for all lead configurations obtained using an identical or similar scheme? Please discuss. You must document that there were no significant differences between the scheme for performing DFT and LED testing between the Transvene™ and PCD® Epicardial patient populations, if that is the case.**

RESPONSE:

There was a statistically significant difference between the mean DFT obtained with the RV-CS-SQ lead configuration and the mean DFT obtained with the other lead configurations. Since there were no differences in the patient population implanted with any of the 3 lead configurations, this may be a configuration that results in lower DFTs than the other configurations. In theory, this may be due to better defibrillation current distribution throughout the myocardium. There is no intent to show that a lower DFT results in a better patient outcome. The premise of the PCD® Epicardial and Transvene™ studies was to demonstrate that if a patient was evaluated at implant and shown to meet implant criteria, that they would be reliably defibrillated over time, and therefore, have a high probability of survival from SCD regardless of which lead system or defibrillation pathway was chosen. We have shown that freedom from SCD at one year is at least equivalent to that afforded by the commercially available AICD for patients who meet the implant criteria regardless of lead system. As was described in Deficiency Response No. 5. Our data demonstrates that there is no difference in outcome between patients who met our 18J implant criteria (3/4 at $\leq$ 18J) or those with a 10J safety margin (at least one success at 24J). The DFT as reported for all Transvene™ and all Epicardial Systems was obtained using the same testing scheme. Please see Deficiency Response Number 9 for a thorough discussion of DFT and LED testing.

As previously discussed in the response to Deficiency #4, implanted defibrillation lead systems were evaluated through successive inductions and treatment of ventricular tachyarrhythmias according to study protocol. The protocol asked for a minimum of (b)(4) in order to demonstrate defibrillation efficacy. The attached table represents the recommended Defibrillation Efficacy Protocol that was used to evaluate all lead configurations.

The recommended implant criteria and Defibrillation Efficacy Protocol was identical for both the PCD® Transvene™ and Epicardial Systems. References from the investigational plan (provided in IDE submissions for both systems) for the PCD® Transvene™ and Epicardial Systems are attached.

To determine whether a patient can be defibrillated reliably with a particular lead system, VF must be induced and successfully terminated at least 3 times in 4 attempts with a stored output energy of 18 Joules or less. The following protocol should be followed in assessing defibrillation efficacy:

Defibrillation Efficacy Protocol
(b)(4)

(b)(4)

Lead system testing will be accomplished using an External Cardioverter/Defibrillator (ECVD), Model 2394 or Model 5355.

NOTE: The following precautions should be observed when initiating and treating episodes of ventricular tachyarrhythmias with the Model 2394 External Cardioverter/ Defibrillator:

08/10/92
UPDATE-
NTL

INVESTIGATIONAL PLAN

MODEL 7217B PCD
PACER-CARDIOVERTER-DEFIBRILLATOR WITH NON-THORACOTOMY LEAD SYSTEMS

A. STUDY PURPOSE

1. Name and Intended Use of System

The Model 7217B PCD System consists of several components, including a pulse generator; various transvenous, subcutaneous, and epicardial leads; and a dedicated software cartridge used with an existing programmer system.

The Model 7217B PCD (Pacer-Cardioverter-Defibrillator) is an implantable, multiprogrammable, automatic tachyarrhythmia control device designed to detect and treat episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF) using either low energy pacing therapies or higher energy cardioversion or defibrillation therapies.

Criteria for detection of episodes of ventricular tachycardia are independent of detection criteria for ventricular fibrillation. Up to four independently programmable VT therapies may be chosen and automatically delivered from among two overdrive pacing modes, burst and ramp, and synchronous cardioversion. Likewise, up to four programmable VF therapies, all defibrillation pulses, may be automatically delivered after VF detection. Pacing, cardioversion, and defibrillation therapies may also be delivered manually by the physician via the programmer.

The Model 7217B will be used with two basic types of lead systems -

a. an epicardial system OR

b. a transvenous or combination transvenous/ subcutaneous system.

To determine whether a patient can be defibrillated reliably with a particular lead system, VF must be induced and successfully terminated at least 3 times in 4 attempts with a stored output energy of 18 Joules or less. The following protocol should be followed in assessing defibrillation efficacy:

Defibrillation Efficacy Protocol

(b) (4)

(b)(4)

Lead system testing will be accomplished using an External Cardioverter/Defibrillator (ECVD), Model 2394 or Model 5355.

NOTE: The following precautions should be observed when initiating and treating episodes of ventricular tachyarrhythmias with the Model 2394 External Cardioverter/ Defibrillator:

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4/6/92
PVE

INVESTIGATIONAL PLAN

MODEL 7217B PCD
PACER-CARDIOVERTER-DEFIBRILLATOR SYSTEM
WITH EPICARDIAL PATCH LEADS

A. STUDY PURPOSE

1. Name and Intended Use of System

The Model 7217B PCD System consists of several components, including a pulse generator; various epicardial leads; adapters required to connect the leads to the pulse generator; and a dedicated software cartridge used with an existing programmer system.

The Model 7217B PCD (Pacer-Cardioverter-Defibrillator) is an implantable, multiprogrammable, automatic tachyarrhythmia control device designed to detect and treat episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF) using either low energy pacing therapies or higher energy, synchronized cardioversion for VT or defibrillation therapies for VF.

Criteria for detection of episodes of ventricular tachycardia are independent of detection criteria for ventricular fibrillation. Up to four independently programmable VT therapies may be chosen and automatically delivered from among two overdrive pacing modes, burst and ramp, and synchronous cardioversion. Likewise, up to four programmable VF therapies, all defibrillation pulses, may be automatically delivered after VF detection. Pacing, cardioversion, and defibrillation therapies may also be delivered manually by the physician via the programmer.

For both bradycardia (VVI) and tachycardia pacing, therapies are accomplished using a bipolar electrode configuration consisting of a standard, commercially-available myocardial pacing electrode and one of the cardioversion/defibrillation electrodes. For the **Model 7217B PCD Device**, sensing occurs between two myocardial pacing electrodes.

For patients with previously implanted CPI epicardial patch electrodes the following additional configurations may be tested:

3) SVC-Epicardial Patch
Single Pulse

4) SVC-Epicardial Patches
Sequential Pulse

The following flow diagrams summarize the recommended order of evaluation of the lead systems and the method for assessing the defibrillation safety margin (Defibrillation Efficacy Protocol - DEP) of a given configuration during implant testing.

To determine whether a patient can be defibrillated reliably with a particular lead system, VF must be induced and successfully terminated at least 3 times in 4 attempts with an output energy of 18 Joules or less. The following protocol should be generally followed in assessing defibrillation efficacy:

DEFIBRILLATION EFFICACY PROTOCOL

(b) (4)

(b)(4)

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11. Please elaborate on how the comparison of DFTs obtained from the PCD® Epicardial Lead study and the Transvene™ study can be considered as a valid comparison in that the majority of the patients (574 (75.3 percent)) in the Transvene™ study were programmed with the sequential pathway and 178 (23.4 percent) were programmed via the simultaneous pathway. The majority of the patients (496 (65.2 percent)) in the PCD® Epicardial study were programmed with the single pathway. Based on your PCD® Epicardial study, please discuss the DFTs or energy requirements obtained with the use of the single defibrillation pathway versus the sequential and simultaneous pathways.

RESPONSE:

The premise of the PCD® Epicardial and Transvene™ studies was to demonstrate that if a patient was evaluated at implant and shown to meet implant criteria, that they would be reliably defibrillated over time, and therefore, have a high probability of survival from SCD regardless of which lead system or defibrillation pathway was chosen. The Epicardial System is a valid comparison since the same PCD® was used in both systems, the same indications were used, the same implant criteria, the same protocol and data requirements and the studies were performed concurrently at the same centers. There is no other system that is currently market released that is a better, or more applicable control. We have shown for both studies that freedom from SCD at one year is at least equivalent to that afforded by the commercially available AICD for patients who meet the implant criteria regardless of lead system. All of the transvenous defibrillation systems that are available are currently under investigation and as such, limited or no data exists with which to compare our performance. A discussion of DFTs or energy requirements obtained with the use of the single defibrillation pathway versus the sequential and simultaneous pathways is found in the PCD® Epicardial IDE [(b) (4) (b)(4)]. In Section VII, Page 25 of the Clinical Summary report, it was shown that the DFTs were similar. A copy of that page is provided here for your convenience. The two patch (single pathway) DFT mean was 10.5J. The three patch (sequential/simultaneous) DFT mean was 8.8J. There was no difference in the outcome of patients with either of the systems.

Table VII-7 illustrates the lowest energy of defibrillation (LED) and defibrillation threshold (DFT) for the implanted lead systems. As noted previously, the implant criteria for the PCD™ Device was 3 of 4 episodes of VF successfully terminated at 18 Joules or less with a given lead configuration. As the DFT and LED indicate, VF was reliably terminated at an energy below the maximum output (34 Joules) of the PCD Device.

PCD Epicardial System Defibrillation Efficacy by Lead System		
Implant Frequency	**LED**	**DFT**
All Lead Systems	[(B)(4)]	[(B)(4)]
2 Patch System	[(B)(4)]	[(B)(4)]
3 Patch System	[(B)(4)]	[(B)(4)]

Table VII-7: PCD Epicardial System Defibrillation Efficacy by Lead System - 5/14/92

Of the 742 patients screened for a PCD Epicardial System, 92 patients (12.4%) received the system despite not meeting the recommended defibrillation implant criteria. The investigators felt in every case that the testing performed at the time of implant, though it did not meet the recommended implant criteria, demonstrated adequate defibrillation efficacy for implantation of the PCD Epicardial System.

A safety margin of at least [(B)(4)] between the successful defibrillation energy [(B)(4)] and the maximum output of the PCD Device [(B)(4)] was provided in 90% of the patients. The investigators utilized this 10 Joule safety margin as a benchmark based on the clinical experience discussed in the article, Troup., et al. The Implanted Defibrillator: Relation of Defibrillating Lead Configuration and Clinical Variables to Defibrillation Threshold. Journal of American College of Cardiology 1985; 6:1315-1321.

It is important to note that there was no statistical difference in overall spontaneous VT/VF episode efficacy and one year sudden cardiac death survival in patients who did not meet the recommended defibrillation implant criteria versus those patients who did meet the recommended implant criteria.

12. Please discuss the time between detection and delivery of therapy of the Transvene™ System versus the PCD® Epicardial System.

RESPONSE:

The time between the start of detection and delivery of therapy is dependent on the programmable VT/VF detection and therapy parameters and not on the implanted defibrillation lead system.

A representative VT episode duration can be determined by using the most frequently programmed parameters for VT detection and therapy during the clinical trial. For both the PCD® Transvene™ and Epicardial System the most frequent VT detection and therapy parameters were as follows:

• VT Numbers of Intervals to Detect (NID)	16
• VT Tachycardia Detection Interval (TDI)	400 ms
• VT Therapy #1 Type	Ramp
• VT Therapy #1 Parameters	91% rate adaption 5 pulses, 3 sequences, 10 ms decrements
• VT Therapy #2 Type	Cardioversion
• VT Therapy #2 Parameters	5 Joules

For both the PCD® Transvene™ and Epicardial System, the majority (90%) of spontaneous VT episodes were terminated with VT Therapy #1. Using the above listed parameters a VT episode would last 8.4 seconds in patient receiving one sequence of antitachycardia pacing and 25.2 seconds in a patient requiring all three sequences for termination of the VT episode. Note, that after each delivery of a pacing sequence the PCD® Device needs to redetect ventricular tachycardia. If VT Therapy #2 (cardioversion) was required for termination of the episode, the episode duration would be 32.6 seconds.

A representative VF episode duration can be determined by using the most frequently programmed parameters for VF detection and therapy during the clinical trial. For both the PCD® Transvene™ and Epicardial System the most frequent VF detection and therapy parameters were as follows:

• VF Numbers of Intervals to Detect (NID)	18
• VF Tachycardia Detection Interval (TDI)	320 ms
• VF Therapy #1 Type/Parameter	Defibrillation/34J
• Charge Time for VF Therapy #1	6.0 seconds
• VF Therapy #2 Type/Parameter	Defibrillation/34J
• Charge Time for VF Therapy #2	3.0 seconds

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For both the PCD® Transvene™ and Epicardial System, the majority (90%) of spontaneous VF episodes were terminated with VF Therapy #1. Using the above listed parameters a VF episode would last [(B)(4) (B)(4)] in patient requiring VF Therapy #1 for successful reversion. If VF Therapy #2 was required for termination of the episode, the VF episode duration for both the PCD® Transvene™ and Epicardial System would be [(B)(4)]

Since both the PCD® Transvene™ and Epicardial System patients were programmed to similar VT/VF detection and therapy parameters as well as the majority of spontaneous VT/VF episodes being terminated with Therapy #1, there is no difference in the time between start of detection and delivery of therapy for the two systems.

13. **On page 125 of the application, please explain and/or discuss what is meant by "a 2:1 VF sensing margin", how it is determined, and if the patients met the criteria.**

RESPONSE:

As previously described in the PCD® Transvene™ System PMA application as well as responses to deficiencies on the PCD® Epicardial System (PMA P900061, Submission dated 10/30/91), analysis of appropriate sensing and detection of VF is performed at the time of implant as well as during the course of follow-up. The goal of this testing is to ensure appropriate VF sensing and detection on an acute and chronic basis.

During defibrillation testing, the Model 5355 ETCD is programmed to a sensitivity value of [(B)(4)] which is [(B)(4)] times the nominal sensitivity setting [(B)(4)] of the Model 7217B PCD® Device. During VF inductions, the VF electrogram and corresponding Marker Channels which are available from the Model 5355 ETCD and PCD® Device are monitored and the majority of the VF signals (>75%) should have an amplitude equal to or greater than [(B)(4)].

For the sensitivity parameter, the programming recommendations recommend a programmed value of [(B)(4)]. Using the described testing, this would provide a [(B)(4)] sensing margin. In other words, appropriate sensing of VF was documented at a value four times less sensitive than the programmed value and would provide a four step safety margin when the PCD® Device is programmed to [(B)(4)]. If the PCD® Device was programmed to a sensitivity value of [(B)(4)] the described testing would provide a [(B)(4)] sensing margin. In other words, appropriate VF sensing was documented at a value two times less sensitive than the programmed value and would provide a two step safety margin when the PCD® Device is programmed to [(B)(4)]. In both of these cases, implant testing and sensitivity value programming allows for changes in the VF electrogram amplitude without impacting appropriate VF sensing and detection.

All of the patients who received the PCD® Transvene™ System met the 2:1 VF sensing margin. At the last known follow-up, 76.6% of the patients were programmed to [(B)(4)] sensitivity (4:1 VF sensing margin) and 22.3% were programmed to [(B)(4)] (2:1 VF sensing margin). In addition, there have been no reports of undersensing during induced episodes of VF as well as no reported patient deaths due to lack of detection of a spontaneous VF episode.
This clinical experience indicates that the recommended VF sensing implant criteria has provided safe and effective evaluation of VF sensing at implant and ensured chronic appropriate VF sensing.

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14. **Of the 329 patients who were followed for 6 months, 130 patients had spontaneous episodes. What was the average number of VT and VF episodes per patient? Of the patients followed for a year, how many had spontaneous episodes of VT and VF and what was the mean number of episodes of VT and VF and what was the mean number of episodes per patient in this group?**

RESPONSE:

Using the June 24, 1992 data cutoff there were 329 patients followed for 6 months or longer. Of the 329 patients, 130 patients had a spontaneous VT episode with a mean of 28.9 (3752/130) episodes per patient and 120 patients had a spontaneous VF episode with a mean of 5.6 (667/120) episodes per patient. A total of 179 patients had either spontaneous VT or VF episodes with a mean of 24.7 (4419/179) episodes per patient.

4|24|93

Of the 115 patients followed for 12 months or longer, 60 patients had a spontaneous VT episode with a mean of 29.5 (1770/60) episodes per patient and 37 patients had a spontaneous VF episode with a mean of 6.7 (248/37) episodes per patient. A total of 67 patients had either spontaneous VT or VF episodes with a mean of 30.1 (2018/67) spontaneous episodes per patient.

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15. **On page 130, Table IF-4, you report that there were 5,362 episodes of VT successfully terminated. On page 131, paragraph 2, you state that 25 patients experienced 45 (0.8 percent) episodes of sinus tachycardia or atrial fibrillation. Are these patients included in the success or failure category? Nine hundred and sixty-four episodes of VF were reported, however, 75 episodes were not actual VF. You must clarify how the successful and ineffective therapies and failures are discerned and categorized. Please prepare a table which includes a category of ineffective therapies with actual patient numbers and percentages. In addition, what assurance is there that an episode of supraventricular tachycardia or atrial fibrillation is not misinterpreted as VT or VF by the physician and considered a successful therapy?**

RESPONSE:

For purposes of this clinical trial, spontaneous VT and VF episodes were defined as those episodes that **satisfied the programmed** VT and VF detection criteria. Specifically, all programmed VT and VF detection criteria must be fulfilled to detect an episode. Successful termination of the episode was defined as satisfying the VT/VF episode termination criteria. All spontaneous VT and VF episodes detected and treated by the PCD® Device are used in determining therapy efficacy. An ineffective episode is defined as VT or VF episode detected by the PCD® Device in which all four programmed therapies failed to successfully terminate the episode. Spontaneous episode efficacy is determined by the following ratio: **Number of TOTAL Episodes Successfully Terminated by PCD® Device/Number of TOTAL Episodes Detected by the PCD® Device.** The attached PCD® Device telemetry printouts provide examples of how spontaneous episode efficacy is determined.

For those episodes where all four programmed VT/VF therapies failed to terminate the episode, the clinical follow-up data form was reviewed for investigator's comments on the episode. The investigator reviewed the patient's symptoms at the time of the episode as well as the stored episode information provided by the PCD® Device and indicates on the clinical dataform whether the ineffective therapy was due to a nonventricular tachyarrhythmia such as sinus tachycardia or atrial fibrillation. If there is no such indication on the clinical dataform, it is assumed that the ineffective therapy was for a spontaneous VT or VF episode. It should be noted that for all current ICD Systems, the delivery of inappropriate therapy for atrial fibrillation or sinus tachycardia is a known risk of the therapy.

The Table 15-1 summarizes the spontaneous VT/VF episode experience on 757 patients with a cutoff date of February 1, 1993. The discussion that follows provides additional data on these episodes.

PCD® Transvene™ System Spontaneous VT and VF Episode Experience		
Spontaneous VT Experience		
Category	**# Episodes**	**# Patients**
Overall Experience	10,027	316
Successfully Terminated Experience	9864/10,027 (98.4%)	256
Ineffective Episode Experience	163/10,027 (1.6%)	60
Ineffective Episode Due to Atrial Fibrillation	33/10,027 (0.3%)	16
Ineffective Episode Due to Sinus Tachycardia	62/10,027 (0.6%)	23
Ineffective Episode Due to VT	68/10,027 (0.9%)	21
Spontaneous VF Episode Experience		
Category	**# Episodes**	**# Patients**
Overall Experience	1982	317
Successful Terminated Experience	1951/1982 (98.4%)	301
Ineffective Episode Experience	31/1982 (1.6%)	16
Ineffective Due to Atrial Fibrillation	11/1982 (0.55%)	4
Ineffective Due to Sinus Tachycardia	7/1982 (0.4%)	4
Ineffective Due to Afib and Sinus Tachycardia	4/1982 (0.2%)	1
Ineffective Due to Lead Performance	2/1982 (0.1%)	2
Ineffective at Monitored Death	2/9182 (0.1%)	1
Ineffective Episode Due to VF	5/1982 (0.25%)	4

Table 15-1: PCD® Transvene™ System Spontaneous Episode Experience - 2/1/93

Spontaneous VT Episode Experience

To date, 10,027 spontaneous episodes of VT have been detected by the PCD® Device in 316 patients. Most spontaneous VT episodes (90.7%) were successfully treated with VT Therapy #1 and 98.4% were successfully treated with one of the four programmable VT therapies.

Sixty patients experienced 163 episodes in which the PCD® Device was ineffective in terminating a spontaneous episode of VT despite delivery of all four programmed therapies. Sixteen (16) patients experienced 33 episodes of atrial fibrillation with a rapid ventricular response that was not "successfully treated" by the PCD® Device. Twenty-three (23)

patients experienced 62 episodes of sinus tachycardia that was not "successfully treated" by the PCD® Device. It should be noted, that the possibility of inappropriate VT therapy delivery due the detection of atrial fibrillation with rapid ventricular response or sinus tachycardia that meets the programmed VT detection criteria is a known risk for all current ICD Systems.

And finally, twenty-one patients experienced 68 episodes of spontaneous VT in which the programmed VT therapies were ineffective in terminating a spontaneous episode. No patient deaths occurred as a result of ineffective VT therapy. Reprogramming and pharmacologic intervention resolved these events. The table provided at the end of this response summarizes this experience.

Spontaneous VF Episode Experience

To date, 1982 spontaneous episode of VF have been detected by the PCD® device in 317 patients. Most (89.1%) spontaneous VF episodes were successfully treated with VF Therapy #1 and 98.4% were successfully treated with one of the four programmable VF therapies.

Sixteen (16) patients experienced 31 episodes in which the PCD® Device was ineffective in terminating a spontaneous VF episode of VF despite delivery of all four programmed VF therapies. Four (4) patients experienced 11 episodes of atrial fibrillation with a rapid ventricular response that was not "successfully treated" by the PCD® Device. Four (4) patients experienced 7 episodes of sinus tachycardia that was not "successfully treated" by the PCD® Device. One patient experienced 4 episodes of both atrial fibrillation and sinus tachycardia that was not "successfully treated" by the PCD® Device. It should be noted, that the possibility of inappropriate VT therapy delivery due the detection of atrial fibrillation with rapid ventricular response or sinus tachycardia that meets the programmed VT detection criteria is a known risk for all current ICD Systems.

In addition, there were three (3) patients who experienced ineffective therapy for a spontaneous VF episode due to lead performance or secondary to a terminal event. One patient experienced one episode of ineffective VF therapy due to lead dislodgement, a second patient experienced one episode of ineffective VF therapy due lead fracture which generated "noise" which was classified by the PCD® Device as "VF" and the third patient experienced two episodes of ineffective therapy at the time of his monitored death.

And finally, four patients experienced 5 episodes of spontaneous VF in which the programmed VF therapies were ineffective in terminating a

spontaneous VF episode. In three patients, these events were resolved with reprogramming or pharmacologic intervention and as of the last known follow-up these patients remain alive and have had no further ineffective VF therapies.

The last of the four patients experienced cardiac arrest at home and was found by the paramedics to be in sinus rhythm. While on monitor the patient developed VF and the PCD® Device appropriately detected and terminated the episode. However, the patient developed EMD and upon admission to the ER was pronounced dead on arrival.

The overall success rate of the PCD® Transvene™ System in terminating spontaneous episodes of either VT or VF was 98.4%. Table 15-2 provides as summary of spontaneous episode efficacy.

PCD® Transvene™ System Spontaneous VT/VF Episode Efficacy	
Spontaneous VT Episodes	
Number of Episodes	10,027
% Overall Efficacy	98.4% (9864/10,027)
% Unsuccessful Due to VT	0.7% (68/10,027)
% Unsuccessful Due to Non VT Arrhythmias	0.9% (95/10,027)
Spontaneous VF Episodes	
Number of Episodes	1982
% Overall Efficacy	98.4% (1951/1982)
% Unsuccessful Due to VF	0.3% (5/1982)
% Unsuccessful Due to Non VF Arrhythmias	1.3% (26/1982)

Table 15-2: PCD® Transvene™ System Spontaneous VT/VF Episode Efficacy

The physicians who are investigators in our study are all highly trained and are qualified by their education and experience to evaluate ICD performance. These physicians are the experts and leaders in their field and, as such, their interpretation of the data is considered the state of the art. Also, as the PCD is not designed nor intended to treat atrial arrhythmias, it is unlikely that the ventricular arrhythmia therapy from the PCD would terminate a ventricular arrhythmia. If an atrial arrhythmia was misinterpreted as a ventricular arrhythmia, the PCD therapy would likely be ineffective and this would, therefore, lower the reported percent success for PCD® therapies. atrial

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(b)(4)

(b)(4)

LAST EPISODE DETECTION SEQUENCE:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

VF EPISODE TELEMETRY

TELEMETRY

(b) (4)

(b)(4)

LAST EPISODE DETECTION SEQUENCE:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

16. **Table IM-6, page 173 must be modified to include a column on inappropriate therapy or therapies delivered as the device was programmed so that the percentages add up to 100 percent.**

RESPONSE:

Table IM-6 has been modified to include rows for episodes that were unsuccessfully terminated but classified as Atrial Fibrillation or Sinus Tachycardia. Unsuccessful termination of an episode was defined as episodes in which the PCD® Device was ineffective in terminating a spontaneous episode despite delivery of all four programmed therapies.

PCD® Transvene™ System Performance Comparison		
Spontaneous VT Episodes		
	PCD® Transvene™ System	**PCD® Epicardial System**
Mean Follow-Up	5.6 months	9.7 months
Number of Episodes	5,430	13,706
% Overall Efficacy	5,362/5,430 98.7%	13,449/13,706 98.1%
% Unsuccessful Termination (VT)	27/5,430 0.4%	116/13,706 0.9%
% Unsuccessful Termination (AF,ST)	45/5,430 0.9%	141/13,706 1.0%
Spontaneous VF Episodes		
	PCD® Transvene System	**PCD® Epicardial System**
Mean Follow-Up	5.6 months	9.7 months
Number of Episodes	973	1,694
% Overall Efficacy	964/973 99.1%	1,671/1,694 98.6%
% Unsuccessful Termination (VT) VF	1/973 0.1%	9/1,694 0.5%
% Unsuccessful Termination (AF,ST)	8/923 0.8%	14/1,694 0.9%

Table IM-6: PCD® Transvene™ System: Comparison of Spontaneous VT/VF Episode Efficacy - 6/24/92

of the 30 pts.

Thirty patients out of 757 in the Transvene™ population experienced 68 (68/5430 = 1.3%) episodes in which the PCD® Device was ineffective in terminating a spontaneous episode of VT despite delivery of all four programmed VT therapies. Twenty five patients experienced 45 (0.9%) episodes that were due to sinus tachycardia or atrial fibrillation/flutter (SVT) with a rapid ventricular response that had been detected as VT. These episodes were resolved with either modification of programmed parameters or of antiarrhythmic drug therapy. It should be noted that the PCD® Device responded appropriately based on the programmed detection parameters.

Seventy nine patients out of 742 in the Epicardial population experienced 257 (257/13,706 = 1.9%) episodes in which the PCD® was ineffective in terminating a spontaneous episode of VT despite delivery of all four programmed VT therapies. Of the ineffective episodes, 141 episodes (1.0%) were due to sinus tachycardia or atrial fibrillation with a rapid ventricular response that had been detected as VT. These episodes were resolved with either modification of programmed parameters or of antiarrhythmic drug therapy. It should be noted that the PCD® Device responded appropriately based on the programmed detection parameters.

Five patients in the Transvene™ population experienced 9 episodes (9/973 = 0.9%) in which the PCD® Device was ineffective in terminating a spontaneous episode of VF despite delivery of all four programmed VF therapies. Four patients had eight reported ineffective VF spontaneous episodes that were due to sinus tachycardia or atrial fibrillation with rapid ventricular response rather than VF. Reprogramming and pharmacologic intervention resolved these problems. It should be noted that the PCD® Device performance was appropriate based on the programmed detection parameters.

Thirteen patients in the Epicardial population experienced 23 episodes (23/1,694 = 1.4%) in which the PCD® Device was ineffective in terminating a spontaneous episode of VF despite delivery of all four programmed VF therapies. Fourteen of the ineffective episodes (0.9%) were due either to atrial fibrillation with a rapid ventricular response that had been detected as VF, sinus tachycardia or the device not being disabled at the time of explant allowing the PCD® Device to sense external noise as VF. The episodes due to atrial fibrillation and sinus tachycardia were resolved with either modification of antiarrhythmic drug therapy or programmed parameters. It should be noted that the PCD® Device performance was appropriate based on the programmed detection parameters.

17. **On page 162, Table IL-2 lists a category "Fail to Cardiovert/Defibrillate" as 0.8 percent. Please clarify. If a patient survives an episode of an inappropriate therapy, is it categorized as a success? Please discuss. The tables must include percentages with the representative numerical support.**

RESPONSE:

Table IL-2 references a side by side comparison of complication/ observation rates observed in the PCD® Transvene™ System and the AICD Epicardial System. The table is provided here for reference and the PCD® Transvene™ System reflects an update on the clinical experience with the 757 patients with a new cutoff date of 2/1/93. The incidence of "Fail to Cardiovert/Defibrillate" was 0.8% and is now 1.2% due to the increase in mean follow-up time from 5.6 months to 10.8 months.

PCD® Transvene™ System
Comparison of Complication/Observation Rates
PCD® versus AICD

Category	PCD%	AICD%
Fail to Cardiovert/Defibrillate	1.2% (9 pts)	4.1% (7 pts)
Inappropriate/Problematic VT/VF Therapy Delivery	9.6% (73 pts)	20% (55 pts)
Pocket Infection	2.9% (22 pts)	2.2% (6 pts)
Erosion	0.7% (5 pts)	0.7% (2 pts)

The AICD Epicardial System clinical experience data is from Winkle, et al. Long Term Outcome with Automatic Implantable Cardioverter-Defibrillator; JACC, May 1989; 13(6);135-161. This article was selected because it provides a detailed clinical complication experience on large patient population, 270 patients.

As described in the PCD® Transvene™ System PMA Application clinical experience report, Section X, Comparison to AICD System, the instances of failure to cardiovert and/or defibrillate in the PCD® Transvene™ System patient population were associated with increased defibrillation requirements during induced VF episodes, none of which resulted in patient death. The failures to cardiovert/defibrillate reported in Winkle et al, article were associated with patch dislodgement, patch crinkling, lead conductor fracture and elevated defibrillation thresholds due to changing patient conditions.

For purposes of this PCD® Transvene™ System clinical trial, spontaneous VT and VF episodes were defined as those episodes that **satisfied the programmed** VT and VF detection criteria. This includes all tachyarrhythmia episodes (i.e, VT, VF and supraventricular tachycardia) that meet the programmed detection criteria. It should be noted for all current ICD Systems, the possible delivery of inappropriate therapy for atrial fibrillation or sinus tachycardia is known risk of the therapy. There have been no patient deaths due to the delivery of inappropriate VT or VF therapy in the PCD® Transvene™ System population. Using the stored episode information available in the PCD® Device and evaluation of the patient's symptoms at the time of the episode, the physician can attempt to discern whether the therapy was delivered for spontaneous VT/VF episode or a nonventricular arrhythmia such as atrial fibrillation or sinus tachycardia.

18. **There were 38 inactive patients reported in Table IH-1, however, 34 patients were reported to be no longer active. Please clarify.**

RESPONSE:

The text accompanying Table IH-1: Inactive Patients, page 136 of the clinical summary provided in the September 18, 1992 amendment, contained an error. The text preceding the table should state "there are a total of 38 patients who had received a PCD system and are no longer active in the study as of 6/24/92." Note that the information in the table was correct.

As of 2/1/93 there are a total of 82 patients who had received a PCD system and are no longer active in the study. The distribution of these patients is presented below and also appears in the updated clinical summary report under "Inactive Patients."

Transvene Inactive Patients

Reason for inactivity	# of Patients
Patient deaths	51
Infection (explant)	22
Heart transplant	9
Total	82

19. Please discuss how the 1 year sudden cardiac death survival, as reported in Table IF-2, page 128, was calculated. The numbers and an explantation of patient classification must be included. Was every patient included who had a prior cardiac arrest regardless of the arrhythmia.

RESPONSE:

Sudden cardiac death is defined as a death that occurs within one hour of onset of symptoms or where the death is unwitnessed. The sudden cardiac death survival probability shown in Table IF-2 is calculated using a life-table survival analysis procedure. The life-table procedure estimates the probability of survival for an interval by looking at the number of patients entering the interval, number of patients censored during the interval, and the number of deaths occurring in that interval. The calculations were estimated using the commercial statistical software package SAS.

Presentation of the number of patients does not allow calculation of the survival probability. Therefore, a dataset will be available upon request if you desire to verify the survival probability.

The sudden cardiac death survival probability estimates the likelihood that a patient enrolled in the study will survive to one year without dying a sudden cardiac death. All patients in the Transvene™ clinical study are included in the analysis regardless of the indication (VT,SCD or SCD/VT), arrhythmia (VT or VF), or prior cardiac arrest status.

20. **On page 177, the number of patients must be provided so that the percentages and calculated p-values can be confirmed.**

RESPONSE:

The percentages in Table IM-10 page 177 are calculated using the life-table survival estimate procedure.

PCD® Transvene™ System Comparison of Actuarial Survival PCD® Transvene™ System versus PCD® Epicardial System			
One Year Survival	**PCD® Transvene™ System**	**PCD® Epicardial System**	**P-Value**
Number of Patients	757	742	-
Sudden Cardiac	99.8%	98.7%	0.144
Non-Sudden Cardiac	96.8%	95.7%	0.803
All Cardiac	96.6%	94.4%	0.656
Noncardiac*	99.4%	97.3%	0.022
Overall*	95.3%	87.2%	0.001

* Statistically Significant $p \leq 0.05$

Table IM-10: Comparison of Actuarial Survival: PCD® Transvene™ System versus PCD Epicardial System - 6/24/92

The life-table procedure estimates the probability of survival for intervals. All patients for each population enter the model for estimation and are censored at their last known follow-up or counted as an event at time of death. The calculations were estimated using the commercial statistical software package SAS. Therefore, providing a number of patients would not aid in verification of percentages and p-values. For verification of percentages and p-values datasets are available upon request.

B

21. Table IV-C, page 649 of the original submission shows a comparison of patient variables for the three lead systems and provides p-values for the variables tested, but the hypothesis was not clearly stated. Please state the hypothesis and discuss the p-values obtained when reporting by primary indication, and the chi-square test of the data set and how it was computed.

RESPONSE:

For Table IV-C, page 649 of the original submission the null hypothesis was: the patient characteristics are equivalent for the three lead configurations; RV/SVC/SQ, RV/CS/SQ, and RV/CS/SVC.

PCD® Transvene™ System RV/SVC/SQ vs RV/CS/SQ vs RV/CS/SVC					
CATEGORY	RV/SVC/SQ	RV/CS/SQ	RV/CS/SVC	Statistical Test	P-Value
Mean Age	57.9	60.7	56.3	Analysis of Variance	0.177
Number, % Male Number, % Female	170 82.9% 35 17.1%	71 83.5% 14 16.5%	19 70.4% 8 29.6%	Chi-Square Test	0.255
Mean Ejection Fraction	37.4%	35.5%	35.8%	Analysis of Variance	0.605
Primary Indication: SCD VT SCD & VT	 79 38.5% 92 44.9% 34 16.6%	 31 36.5% 41 48.2% 13 15.3%	 10 37.0% 12 44.5% 5 18.5%	Chi-Square Test	0.985
NYHA Classification: I/II III/IV	 163 81.1% 38 18.9%	 74 87.1% 11 12.9%	 23 85.2% 4 14.8%	Fisher's Exact Test	0.495
Coronary Artery Disease	73.2%	69.4%	74.1%	Chi-Square Test	0.789
Myocardial Infarction	68.3%	65.9%	66.7%	Chi-Square Test	0.919
Congestive Heart Failure	32.2%	25.9%	29.6%	Chi-Square Test	0.565
Cardiomyopathy	27 13.2%	14 16.5%	4 14.8%	Fisher's Exact Test	0.717

Table IVC: Summary of Variables Tested on Lead Configurations - 11/27/92

The Chi-Square test is used to test for association between variables. It is used for R x C (R Rows and C Columns) contingency tables. All calculations in Table IV-C were estimated using the commercial statistical software package SAS. For chi-square calculations the Pearson chi-square statistic was used. This statistic involves the

differences between the observed and expected frequencies (SAS Users's Guide: Statistics, Version 5 Edition, 1985, pp. 411-412).

There were no statistically significant differences at a 0.05 significance level in patient characteristics between the lead configurations. Therefore, we accept the null hypothesis that the patient populations are equivalent.

22. **For purposes of justification of data pooling and data analysis of Table IV-C, please discuss why the multiple statistical significant difference was not adjusted at a 0.05 significance level using a more widely accepted procedure such as the Hochberg procedure (Dunnett and Tarnhoue: A Step-up Multiple Test Procedure, Journal of the American Statistical Association, March, 1992, Vol 87: pp. 162-170).**

RESPONSE:

The Hochberg procedure was not used to adjust for multiple inference in table IV-C of the original submission because the Dunnett and Tarnhoue article was not published and not known by us until the same month that the original submission was submitted, March 1992. Also procedures that adjust for multiple inference are used to adjust the p-value below 0.05 to correct for a type I error (rejecting the hypothesis of no difference between the populations when the hypothesis should be accepted). As shown in table IV-C below, none of the comparisons are significant at a 0.05 significance level so there is no reason to adjust the significance level below 0.05 to eliminate type I errors.

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PCD® Transvene™ System RV/SVC/SQ vs RV/CS/SQ vs RV/CS/SVC					
CATEGORY	RV/SVC/SQ	RV/CS/SQ	RV/CS/SVC	Statistical Test	P-Value
Mean Age	57.9	60.7	56.3	Analysis of Variance	0.177
Number, % Male Number, % Female	170 82.9% 35 17.1%	71 83.5% 14 16.5%	19 70.4% 8 29.6%	Chi-Square Test	0.255
Mean Ejection Fraction	37.4%	35.5%	35.8%	Analysis of Variance	0.605
Primary Indication: SCD VT SCD & VT	 79 38.5% 92 44.9% 34 16.6%	 31 36.5% 41 48.2% 13 15.3%	 10 37.0% 12 44.5% 5 18.5%	Chi-Square Test	0.985
NYHA Classification: I/II III/IV	 163 81.1% 38 18.9%	 74 87.1% 11 12.9%	 23 85.2% 4 14.8%	Fisher's Exact Test	0.495
Coronary Artery Disease	73.2%	69.4%	74.1%	Chi-Square Test	0.789
Myocardial Infarction	68.3%	65.9%	66.7%	Chi-Square Test	0.919
Congestive Heart Failure	32.2%	25.9%	29.6%	Chi-Square Test	0.565
Cardiomyopathy	27 13.2%	14 16.5%	4 14.8%	Fisher's Exact Test	0.717

Table IV-C: Summary of Variables Tested on Lead Configurations - 11/27/92

23. You claim that confidence interval analysis was performed to compare the overall mortality of the PCD® and AICD™ populations. What was the confidence interval?

RESPONSE:

The survival probability at one year for the Transvene™ population was 95.3%. From the analysis run, using the commercially available statistical software package SAS, the survival standard error was also calculated. The confidence interval was calculated by taking the survival probability +/- the 1.96(survival standard error). The survival standard error was 1.1, therefore the confidence interval for Transvene™ survival at 1 year is 95.3 +/- 2.2 or [93.1,97.5]. The overall survival probability reported for the Ventak-P was 90.8%. We do not have the data necessary to calculate the confidence interval around 90.8% for the Ventak-P. This probability is outside the lower range of the confidence interval for the Transvene™ survival probability at one year, therefore by using the best available information we conclude that there is a statistically significant difference between the survival probabilities.

24. Please clarify and/or discuss the following regarding Table XB-1, page 378, Volume 2:

a. the total number of patients in the Ventak P population (292) versus those reported by primary indication (291); and

RESPONSE:

b. a chi-square test of primary indication, using the StatXact computer software, yields a p-value of nearly 0. This is statistically significant, indicating the PCD® and Ventak P populations are significantly different.

RESPONSE:

As noted in the PCD® Transvene™ System PMA Application, for purposes of comparison the Ventak-P Epicardial System described in the Summary of Safety and Effectiveness Data (PMA Application Number P890061) dated May 2, 1991 was used. Therefore only that data which was presented in this summary is available via the Freedom of Information Act. The primary indication for one patient was not available in the Ventak P Epicardial System summary.

Analysis performed by Medtronic indicated that there was a statistical a difference in the category of patient indication between the two patient population groups. There were more patients that had Sudden Cardiac Death as their primary indication in the PCD® Transvene™ System population than the AICD Epicardial System population ($p = 0.001$).

Cox regression analysis was performed to see what effect gender, primary indication and system implanted (PCD® Transvene™ or PCD® Epicardial) had on survival outcome.

This analysis showed that for overall survival at one year the system implanted had an influence on the probability of survival but gender and primary indication had no influence.

Thus, since there is no impact on survival outcome based on primary indication, the PCD® Transvene™ System and AICD Epicardial System can be compared. There was a statistical difference (Confidence Interval Analysis) in one year overall survival between the PCD® Transvene™ (95.6%) and AICD Epicardial System (90.8%). This difference is due to the implanted defibrillation lead system.

25. **Please discuss the incidence of inappropriate therapies reported as observations in the Transvene™ study. It appears as if there has only been a slight improvement over the PCD® Epicardial study as it relates to programming and patient management (drug therapy). Please discuss the experience of both studies and how the labeling supports effective programming of the device parameters and the use of the Onset and Stability algorithms. How many patients in the Transvene™ study have the Onset and Stability algorithms programmed ON? At what interval during the study were the majority of patients programmed with the algorithms? Your experience in the treatment of induced and spontaneous episodes with use of the algorithms must be discussed.**

RESPONSE:

a. Inappropriate Therapies

Inappropriate therapy delivery is defined as the delivery of either VT or VF therapy for reasons other than a spontaneous VT or VF episode. This includes atrial fibrillation with a rapid ventricular response or sinus tachycardia that overlaps with the programmed detection criteria. Delivery of therapy for rhythms other than VT and VF is a known risk of ICD therapy which is clearly discussed in the device labeling.

Physicians initially program the PCD® based on the known cardiac arrhythmias and tend to program the device toward greatest sensitivity for VT and VF detection. When patients go home and recover from the implant procedure they will generally become more active and may experience increases in their sinus rate. If these increased sinus rates overlap the programmed VT detection rate criteria, the patient may experience an inappropriate VT therapy. Similarly atrial arrhythmias may develop as the patient's heart disease progresses. The philosophy behind Medtronic's labeling recommendations and the practice of PCD® investigators is to accept some overdetection of non-VT/VF rather than risk underdetection of a life threatening tachycardia. If the patient experiences inappropriate therapies due to either ventricular response to atrial fib/flutter or sinus tachycardia, the investigator will evaluate both device programming and other medical/surgical therapeutic options. Because of these patient management practices the incidence of inappropriate therapy delivery will never be zero. Physicians will likely always wait until inappropriate therapy delivery occurs before programming supplementary detection criteria.

The incidence of inappropriate/problematic VT/VF therapy delivery was lower in the PCD® clinical experience than the published experience with the AICD (Winkle, et al. Long-Term Outcome With the Automatic Implantable Cardioverter-Defibrillator; JACC, May, 1989; 13(6); 135-161.). Table XII F-2 on page 253 Transvene™ clinical update dated 9/18/92 shows 10.6% (N=742) of patients with the PCD® epicardial system and 8.2% (N=757) of patients with the Transvene™ system experienced inappropriate VT or VF therapies. The Winkle article reports a 20% rate of delivery of inappropriate therapies. The reduction in inappropriate therapies can be attributed to the incorporation of independently programmable detection algorithms for VT and VF.

The circumstances reported in the Winkle, et al article were nonsustained VT, recurrent stable VT, sinus tachycardia, atrial fibrillation with rapid ventricular response and pacemaker interaction. The patients with VT complained of receiving multiple shocks with limited or no symptoms. The incorporation of antitachycardia pacing in the PCD Device decreases the need for delivery of cardioversion shocks for the termination of stable VT and increases patient acceptance of ICD therapy.

The slight reduction of inappropriate therapies between the epicardial and the Transvene™ systems is likely due to the difference in the incidence of atrial fibrillation between the two systems. Atrial fibrillation, with a risk of inappropriate shocks and the potential need for concomitant antiarrhythmic drug therapy, is a recognized medical event in patients receiving an ICD System utilizing an epicardial defibrillation lead system. The occurrence of atrial fibrillation in these patients may be related to the thoracotomy procedure required for implant, manipulation of the atrium during the implant procedure or the positioning of the epicardial patch leads near or on the atrium resulting in irritation and induction of atrial fibrillation. The incidence of inappropriate therapy for atrial fibrillation in the PCD Epicardial System was 6.1% while that for that the PCD Transvene System was 4.9%. An decreased incidence of inappropriate therapy results in a decreased potential risk for acceleration on non VT/VF rhythms as well as increased patient acceptance of ICD therapy. Though the introduction of a transvenous lead system has not totally removed the risk of inappropriate therapy for atrial fibrillation, from this clinical experience it appears that the incidence has been decreased.

The Transvene™ clinical update dated September 18, 1992 reported forty nine patients with inappropriate VT therapy which

were all classified as observations and discussed this experience in detail. Inappropriate VT therapy was delivered for atrial fibrillation with a rapid ventricular response in 28 patients and due to sinus tachycardia in 21 patients. This observation was resolved by reprogramming of the VT detection parameters in 21 patients, with modification of drug therapy in 26 patients and no action was required in one patient. One patient with atrial fibrillation underwent successful AV Node ablation. Post this procedure, appropriate PCD Device function was documented.

In two patients in whom inappropriate VT therapy was delivered for sinus tachycardia, the ONSET algorithm was enabled to improve discrimination between VT and sinus tachycardia. The use of this algorithm resulted in no further delivery of inappropriate therapy for sinus tachycardia.

In three patients in whom inappropriate VT therapy was delivered for atrial fibrillation, the STABILITY algorithm was enabled to improve discrimination between VT and atrial fibrillation. The use of this algorithm resulted in no further delivery of inappropriate therapy for atrial fibrillation.

The Transvene™ clinical update also reported thirteen patients who experienced an episode of inappropriate VF therapy, all of which were classified as observations. In nine cases, inappropriate VF therapy was delivered for atrial fibrillation that had a rapid ventricular response that met the programmed VF detection criteria. In two cases, inappropriate VF therapy was delivered secondary to sinus tachycardia that was detected as ventricular fibrillation. Modification of the programmed VF detection criteria or the patient's antiarrhythmic drug therapy corrected these two clinical observations.

One patient received inappropriate VF therapy secondary to the sensing of T waves during sinus rhythm with the PCD device programmed to a sensitivity of 0.3 mV. This was resolved with reprogramming of the sensitivity to 1.2 mV. Appropriate VF sensing was documented at this programmed setting.

The final patient received inappropriate VF therapy secondary to nonsustained ventricular tachycardia. In the PCD Device, once "VF" is detected the device is committed to the delivery of defibrillation therapy. This observation was resolved by reprogramming of the FDI and VF NID.

b. Labeling

The PCD® technical manual contains specific recommendations for programming both VT and VF detection. For VT detection, specific statements are made for programming the Tachycardia Detection Interval (TDI), the Number of Intervals to Detect (VT NID), as well as the Onset and Stability Criteria. For VF detection recommendations are made for Sensitivity, Fibrillation Detection Interval (FDI) and Number of Intervals to Detect (VF NID).

The recommendations specify initial programming recommendations for each parameter as well as appropriate warnings for potential programming problems.

The programming recommendations for the Onset Criterion in the PCD® technical manual are:

> Onset Criterion is indicated if inappropriate detection of sinus tachycardia resulting in inappropriate VT therapy delivery has occurred. Treadmill testing, beginning at 81% Onset, is suggested to evaluate the appropriate function of this algorithm.
>
> This algorithm was used safely in 8.5% of 434 patients in the clinical study. Its use has demonstrated its safety and effectiveness.
>
> If the Onset Criterion is ON and is not met at the beginning of a spontaneous ventricular tachycardia, the VT episode could remain "undetected", such as with an exercise-induced VT. If VT Detection uses the Onset Criterion and detection is enabled after the start of a VT, the VT may not be detected.
>
> A low programmed onset percentage value will increase the specificity of the Onset Criterion to detect the targeted tachycardia, but will also decrease the sensitivity of the overall VT detection algorithm.

The programming recommendations for the Stability Criterion in the PCD® technical manual are:

> Stability Criterion is indicated if atrial fibrillation or atrial flutter with a rapid ventricular response has caused inappropriate detection and therapy delivery. A stability value of 60ms is suggested initially.
>
> This algorithm was used safely in 17.9% of 434 patients in the clinical study. Its use has demonstrated its safety and effectiveness.
>
> Decreasing the programmed interval stability value increases the specificity of the Interval Stability Criterion to detect the targeted stable tachycardia, but may also decrease the sensitivity of the detection algorithm.

The labeling directed at programming these two algorithms is necessary and appropriate in that it clearly states that while specificity for VT detection is enhanced, sensitivity for VT detection is reduced. For this reason the recommendations clearly state that these supplementary detection criteria should be used after the need for this increase in specificity has been clearly demonstrated, that is, inappropriate therapies form either sinus tachycardia or atrial fib/flutter have occurred.

The values recommended for initial programming of both of these features was made through analysis of the clinical data base. In both cases the values chosen were the most widely used values.

c. Transvene™ Experience

As of February 1, 1993 thirty-three (33) of the 757 Transvene™ patients in the clinical report had the Onset Criterion enabled and 55 patients had the Stability Criterion enabled. Eleven of these patients had both the Onset and the Stability Criteria programmed ON. The most widely used programmed value for the Onset Criterion was 81% (54.5% of patients with Onset programmed ON). The most widely used programmed value for the Stability Criterion was 60ms (45.4% of patients with Stability programmed ON).

Table 25c-1 shows a distribution of the time from implant to the first programming of the Onset and the Stability Criteria. Almost half (48.5% 16/33) of the patients with the Onset Criterion programmed ON did so within the first 30 days following implant. The greatest time from implant to the first programming of the Onset Criterion is 345 days. More than half (63.6% 35/55) of the patients with the Stability Criterion programmed ON did so within the first 30 days. Like the Onset Criterion many patients had the Stability Criterion programmed on for the first time very late in the follow-up period, the greatest being 622 days.

PCD® Transvene™ System Time to Program Onset and Stability Criterions ON		
Days Post Implant	Onset Criterion (# of Patients Programmed ON)	Stability Criterion (# of Patients Programmed ON)
0 - 10 days	13	29
10 - 30 days	3	6
30 - 100 days	7	9
101 - 200 days	3	3
201 - 300 days	4	4
301 - 400 days	3	1
401 + days	0	3
Total	33	55

Table 25c-1: Time to Program Onset and Stability Criterions ON

While most of the patients requiring these supplementary detection algorithms do so relatively early following implant, some patients require this feature much later. This is an example of the dynamic nature of patient's underlying heart disease and the need to have these programmable features available for use long after implant, as the patient's cardiac condition changes.

At the time of programming either of these supplementary VT detection criteria ON, many patients had arrhythmias induced to assure appropriate detection of VT/VF. Table 25c-2 shows the number of episodes of VT and VF induced during the follow-up evaluation where the criterion was programmed ON. Fifty percent (11/22) of the patients with the Onset Criterion only programmed ON were induced into a tachyarrhythmia at the follow-up evaluation where the programming occurred. Over half (61.3% 27/44) of the patients with the Stability Criterion only programmed ON and 72.7% (8/11) of those patients with both supplementary criteria programmed ON were induced at the follow-up where the programming occurred. In all cases the PCD® system performed appropriately.

PCD® Transvene™ System Induced Episodes When Onset or Stability Were Programmed ON			
	VT	V-Flutter	VF
Onset Only ON (11 of 22 Patients)	18 Episodes 10 Patients	-- --	14 Episodes 8 Patients
Stability Only ON (27 of 44 Patients)	78 Episodes 19 Patients	4 Episodes 2 Patients	41 Episodes 21 Patients
Both ON (8 of 11 Patients)	31 Episodes 6 Patients	-- --	18 Episodes 5 Patients

Table 25c-2: Induced Episodes When Onset or Stability Were Programmed ON

Table 25c-3 shows the spontaneous episode experience in the patients with these two detection criteria programmed ON. Three-hundred-nine (309) episodes occurred in 30 of the patients with the Stability Criterion programmed ON. Two-hundred-ninety-three (293) were successfully terminated by the PCD® Transvene™ system. The remaining episodes were due to ventricular response to atrial fib/flutter that met the programmed Stability Criterion value. Twelve (12) of the "Failed" episodes were in one patient who was hospitalized for titration of medical therapies. Eleven patients with the Onset Criterion experienced 493 VT episodes which were terminated with an efficacy of 99.2%. Ventricular fibrillation was terminated 100% of the time in this patient group.

PCD® Transvene™ System Spontaneous Episodes When Onset or Stability Were Programmed ON		
	VT	VF
Stability Criterion Only		
# Patients	30	18
# Episodes	309	125
Efficacy	94.8%	100.0%
Onset Criterion Only		
# Patients	11	7
# Episodes	493	17
Efficacy	99.2%	100.0%
Both Criteria		
# Patients	10	4
# Episodes	364	39
Efficacy	97.0%	100.0%

Table 25c-3: Spontaneous Episodes When Onset or Stability Were Programmed ON

d. Conclusion

The Onset and the Stability Criteria for VT detection are the same algorithms that were demonstrated to be safe and effective with the market released PCD® Epicardial System. They remain a useful tool in a subset of patients requiring discrimination between ventricular tachycardia and the rapid ventricular response to atrial fib/flutter or sinus tachycardia in the PCD® Transvene™ System.

26. Please discuss the "device related" complications reported for the Transvene™ and the PCD® Epicardial System.

RESPONSE:

As described in the PCD® Transvene™ System PMA Application, "Device Related" complications includes patients in whom the device was explanted for reasons other than patient death, infection or transplant.

In the case of the PCD® Transvene™ System, these patients were discussed in detail in the Clinical Experience Report, Section XII, Complications and Observations and detailed information on each patient was provided in Volume 3, Clinical Appendices, Appendix C. There were four patients (0.5%) in whom the PCD® Device was explanted due to reasons other than death, infection or heart transplant. Reasons for explant included, **(1)** lower than expected battery voltage for time in service due to leakage at the input to one of the integrated circuits (1 unit), **(2)** failure to appropriately synchronize and deliver cardioversion therapy for an induced VT episode (1 unit); **(3)** Power on Reset (POR) condition that was not related to the delivery of external defibrillation or cautery (1 unit); and, **(4)** inappropriate delivery of VF therapy during a manual capacitor charge time (1 unit). In all cases, the devices were safely replaced with no adverse patient consequences. The attached information from the PCD® Transvene™ System Application provides a summary of these patients.

In the case of the PCD® Epicardial System, there were seven patients (0.9%) in whom the PCD® Device was explanted due to reasons other than death, infection or heart transplant. The reason for explant for all seven devices was lower than expected battery voltage for time in service. The identified causes for low battery voltage were (1) failure in an integrated circuit which increases the current drain and results in reduced battery longevity (3 units); (2) leakage at the input of one of the integrated circuits where voltage measurement is taken (1 unit); and (3) leakage at tantalum capacitors (3 units). Information on these identified causes for low battery voltage have been previously provided the agency. In all cases, the devices were safely replaced with no adverse patient consequences.

Early Device Explant

There were four patients in whom the PCD Device was explanted due to reasons other than death, infection or heart transplant. In all cases these medical events were classified as complications.

In the first patient the PCD Device was explanted for lower than expected battery voltage measurement for time in service. Analysis indicated the decreased battery voltage measurement was due to leakage at the input to one of the integrated circuits. This lead to a voltage drop across a resistor where the voltage measurement was taken. Analysis indicated the battery to be performing to specifications and the leakage to be a random event.

The second patient received inappropriate VF therapy during reformation of the device capacitors. Analysis of the explanted unit indicated that arcing occurred between the conductors in the high power hybrid. As a result, high voltage was momentarily applied to the low power circuitry, including the low power hybrid. This low power hybrid lost function including the capability to pace and transmit telemetry due to the excessive voltage applied.

Since this is the only device that exhibited this type of failure in the field and the hybrid manufacturing process has demonstrated that it will screen out infant mortality, this was determined to be a random component failure.

In the third patient, during the pre-hospital discharge electrophysiology study, VT was induced and cardioversion therapy failed to appropriately synchronize and deliver therapy for this induced episode. The PCD Device was explanted and the patient received a second device without difficulties. Analysis of the explanted PCD Device indicated a random device failure in the microprocessor and low power hybrid. The manufacturing process was modified to incorporate a screening process to identify any further devices which may exhibit this behavior.

In the final patient, the PCD Device exhibited a Power On Reset (POR) condition that could not be related to use of electrocautery or external defibrillation. The device was explanted and returned to Medtronic for analysis. Final results on the analysis are not available at the time of this submission but will be submitted to the FDA when they are available.

27. **Please describe in detail the complications reported in the patients followed for a year.**

RESPONSE:

Complications and Observations in the patients followed for 1 year or more

The use of a multiprogrammable implantable cardioverter defibrillator (ICD) device allows the physician to resolve most relevant medical events by noninvasively changing programmed parameters thus, avoiding invasive procedures. However, there will continue to be certain relevant medical events which will require invasive procedures for resolution.

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following definitions:

COMPLICATION:	A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.
OBSERVATION:	A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

As of February 1, 1993, of the 393 patients with implant durations of greater than or equal to one year, there have been a total of 89 complications reported in 76 patients and 122 observations reported in 99 patients in the PCD™ Transvene™ System patient population. Thus, 19.3% (76/393) of the patients had a clinical event which was categorized as a complication and 25.2% (99/393) of the patients had a clinical event which was categorized as an observation. These percentages are consistent with the percentages of patients with complications, 19.4% (147/157) and observations 23.8% (180/757) in the original PMA patient population.

Table 27-1 summarizes the reported PCD® Transvene™ System complications and observations by category. The reported complications and observations are recognized clinical events that may occur with **any** of the current ICD devices. These complications and observations are discussed in the PCD® device and Transvene™ manual. **None of the reported complications or observations have resulted in a patient death.**

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PCD® Transvene System Reported Complications/Observations in Patients followed for 1 Year or more : By Category (n=393)		
Category	**Complications**	**Observations**
	Num (% of Pts)	Num (% of Pts)
Increased Defibrillation Requirements	3 (0.8%)	2 (0.5%)
Inappropriate VF Therapy Delivery	-	10 (2.5%)
Inappropriate VT Therapy Delivery	-	40 (10.2%)
Loss of Capture	2 (0.5%)	6 (1.5%)
Oversensing	-	29 (7.4%)
Undersensing	-	-
Skin Erosion	2 (0.5%)	1 (0.3%)
Pocket Infection	5 (1.3%)	7 (1.8%)
Seroma	1 (0.3%)	9 (2.3%)
Hematoma	1 (0.3%)	7 (1.8%)
Pneumothorax	2 (0.5%)	1 (0.3%)
Pacemaker Syndrome	-	1 (0.3%)
Perforation	1 (0.3%)	-
Subclavian Vein Thrombosis	-	1 (0.3%)
Lead Fracture	6 (1.5%)	-
Subcutaneous Patch Crinkling	5 (1.3%)	3 (0.8%)
Early Device Explant	3 (0.8%)	-
Total Lead Dislodgement	56 (14.2%)	6 (1.5%)
Total	**89**	**122**

Table 27-1: PCD Transvene System: Reported Complications and Observations - 2/1/93

Table 27-2 contains a description of the lead dislodgements that have occurred in less than 30 days and in greater than 30 days.

PCD® Transvene System Reported Complications/Observations in Patients followed ≥1 Year Lead Dislodgements <30 days and >30 days (N=393)			
Complications		Observations	
Num (% of Pts)		Num (% of Pts)	
<30 days	>30 days	<30 days	>30 days
27 (6.9%)	29 (7.4%)	0 (0)	6 (1.5%)

Table 27-2: PCD Transvene System: Lead Dislodgements <30/>30 days - 2/1/93

There have been a total of 29 lead dislodgements reported in patients at greater than 30 days. None of the lead dislodgements resulted in an ineffective therapy for a spontaneous VT of VF episode or patient death. Lead dislodgements were documented by fluoroscopic examination during electrophysiologic evaluation, chest x-ray obtained during routine follow-up, or during pacing/sensing threshold evaluation during routine follow-up. In all 29 cases, reoperation was required to reposition the lead and reestablish an effective defibrillation lead system.

Lead dislodgements are not specific to the PCD® Transvene™ System and have been reported with dual chamber pacemakers and the current market released implantable cardioverter defibrillator (ICD) system. The early history of dual chamber pacemakers witnessed a high lead dislodgement rate of at least 20% (Smyth, PND, et al. Permanent perivenous atrial sensing and pacing with a new J-shaped lead. J Thoracic Cardiovascular Surgery. 1976;72:565-570). Winkle, et al reported that the incidence of dislodgement of the superior vena cava spring leads with the current market release ICD system to be 6.3%. (Winkle, et al. Automatic Implantable Cardioverter-Defibrillator: Efficacy, Complications, and Survival in Patients with Malignant Ventricular Arrhythmias. JACC. June 1988; Vol.11, No.6:1278-86).

28. **There was a substantial increase in the number of infections reported in the Transvene™ study. Even though you discussed why there was an increase, based on your experience, how will your labeling address the procedures for reduction in the number if infections? Please validate these procedures.**

RESPONSE:

In the current update of our database, we report in Table IM-7 (a copy is attached for your convenience) that there is a 2.9% incidence of infection leading to explant of the PCD® in the 757 Transvene™ patients and 2.3% for the 742 Epicardial patients. These two rates are not substantially different nor are they different from the 2.4% rate reported in the Ventak-P Summary of Safety and Effectiveness Data, PMA Application P890061, May 2, 1991. Therefore, it is our assertion that there is not a substantial increase in infections and the current labeling is appropriate.

29. A discussion of your experience in the use of the different entry sites for the placement of the Transvene™ leads, and how your labeling assists in the selection of an entry site, must be provided.

RESPONSE:

Transvene leads are placed via several approaches; either through the subclavian, cephalic or jugular veins. The specific site is determined by the implanting physician. Analysis of Transvene data shows that the left subclavian vein is the most frequently used entry site regardless of the type of lead or intended lead location, i.e., RV or CS/SVC lead. A presentation of entry sites is presented below. The total number of RV lead entry sites is greater than the total number of patients included in this report because of patients with multiple lead evaluation sessions. This information was also presented in the clinical experience report provided in the September 1992 PMA amendment.

PCD™ Transvene™ System Venous Entry Site			
	RV Leads Model 6884/6966/SP2100	CS/SVC Leads Model 6881/6963	All Transvene™ Leads
Left Subclavian	483	583	1066
Right Subclavian	40	47	87
Left Cephalic	213	180	393
Right Cephalic	8	7	15
Left Internal Jugular	7	9	16
Right Internal Jugular	11	9	20
Other	5	4	9
Total	767	839	2097

Venous Entry Site - 6/24/92

There have been two reports of fractures of the Model 6884 right ventricular lead associated with clamping of the lead body between the clavicle and first rib. Both of these leads were placed via a right subclavian approach. These patients are discussed in detail in the complications section of the clinical summary. There were no reports of ineffective therapy for a spontaneous VT/VF episode due to a right ventricular lead fracture.

Technical manuals for both the Model 6966 RV lead and Model 6963 CS/SVC lead provide a detailed discussion of selection of a lead entry site. This is addressed under, "Suggested Implantation Procedure" in each of the technical manuals. Copies of the applicable pages of the technical manual for each lead are provided following this response. Note that this information was also provided in the original Transvene PMA application dated March 31, 1992.

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TECHNICAL MANUAL

TRANSVENE™-SVC Unipolar, Endocardial, Coronary Sinus or Superior Vena Cava Lead for Cardioversion and Defibrillation

MODEL 6963

CAUTION: Investigational Device. Limited by U.S. Law to Investigational Use.

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POTENTIAL COMPLICATIONS

The potential complications related to the use of transvenous leads include, but are not limited to, the following patient-related conditions that can occur during and following lead insertion: fibrillation or other arrhythmias, conduction disturbances, loss of contractility, air embolism, cardiac perforation, heart wall rupture, cardiac tamponade, infection, and tissue necrosis.

Other potential complications related to the lead include, but are not limited to, the following: lead dislodgement, lead conductor fracture, and insulation failure.

ENSURING PRODUCT INTEGRITY

Carefully inspect the package before opening. It is not recommended that you use the product after its expiration date.

If the integrity of the package has been compromised prior to the product expiration date, place the contents in a gas-permeable bag and resterilize it with ethylene oxide as described below.

CAUTION: Use ethylene oxide only.

The process should not exceed temperatures of 55° C (125° F). Allow proper aeration of ethylene oxide residues prior to implantation. Use some acceptable method to determine sterilizer effectiveness, such as a biological indicator.

Due to the variability between sterilizers, precise sterilization instructions cannot be provided. Contact your sterilizer manufacturer for more information regarding sterilization procedures.

SUGGESTED IMPLANTATION PROCEDURE

General Instructions

The implantation procedure generally includes using a stylet guide, stylets, and vein lifter; selecting an insertion site; positioning the lead; taking electrical and defibrillation efficacy measurements; anchoring the lead; and connecting the lead to the pulse generator.

Some implantation techniques vary according to physician preference and the patient's anatomy or physical condition. The techniques for selecting an insertion site, using a stylet guide or a stylet, positioning a lead, and anchoring a lead,

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described below suggest one or two possible versions, while more may exist.

Opening the Package

While lifting the lead out of the package, make sure that the anchoring sleeve does not slide off the distal end of the lead.

Using the Stylet Guide and Stylets

The lead is packaged with the stylet guide attached to the connector pin and a stylet already inserted. If the stylet guide has been removed, replace it by gently pushing it as far as possible onto the connector pin (Figure 1).

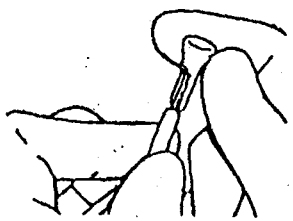

Figure 1. Stylet guide attachment.

A stylet provides additional stiffness and controlled flexibility for maneuvering the lead into position. Stylets vary in stiffness for different lead and stylet flexibility. Each stylet knob is etched with the stylet diameter and length.

If a stylet is not already in the lead, insert a stylet through the stylet guide and into the lead body. If a slight curve is needed for the stylet, refer to instructions in the section titled "Positioning a Lead in the Coronary Sinus or Superior Vena Cava."

CAUTION: To avoid damage to the lead or body tissue, do not use excessive force or surgical instruments to insert a stylet into the lead. When handling a stylet, avoid overbending, kinking, or blood contact.

CAUTION: Repeated insertions of a stylet increase the chance that blood may accumulate on it, which may cause difficulty in passing the stylet through the lead and may cause damage to the lead.

Selecting an Insertion Site

The lead may be inserted by venotomy through several different venous routes, including the right or left cephalic vein or the external or internal jugular vein. In general, a left venous entry site will aid in maneuvering the lead into the coronary sinus orifice.

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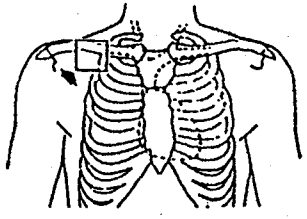
CAUTION: If insertion is done via a subclavian approach, the lead should be positined far laterally to avoid clamping the lead body between the clavicle and the first rib. Clamping the lead may eventually cause the conductor to fracture, may cause damage to the insulation, or may cause other damage to the lead. This may result in complications such as loss of detection, loss of pacing therapies, or loss of cardioversion./defibrillation therapy. Certain anatomical abnormalities, such as thoracic outlet syndrome, may also precipitate pinching andf subsequent fracture of the lead. If significant resistance is encountered during a subclavian stick implant procedure, do not force the lead by adjusting patient's posture (i.e., raising the arm or putting a towel behind the person's back) to facilitate the passage of the lead. In such cases it is recommended that an alternate venous entry site be used.

Use fluoroscopy to facilitate accurate lead placement.



Using a Vein Lifter

A vein lifter facilitates lead introduction. Insert its tapered end into the incised vein and gently push the lead tip underneath and into the vein (Figure 2). During insertion of the lead into the vein, make sure the anchoring sleeve does not slide off the distal end of the lead.

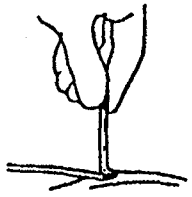


Figure 2. Using the vein lifter.

CAUTION: Avoid placing the lead under extreme tension or angulation to prevent lead dislodgement and possible lead fracture. **Do not grip the lead with surgical instruments.**

Positioning a Lead in the Coronary Sinus or Superior Vena Cava

For added control in maneuvering the lead tip, the distal end of the lead may be slightly curved by inserting a gently curved stylet as shown in Figure 3. A possible angle of curvature is illustrated in Figures 4 and 5.

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TECHNICAL MANUAL

The TRANSVENE™-RV Tripolar, Endocardial, Screw-in Lead for Ventricular Pacing, Sensing, Cardioversion and Defibrillation

MODEL 6966

CAUTION: Investigational Device. Limited by U.S. Law to Investigational Use.

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ENSURING PRODUCT INTEGRITY

Carefully inspect the package before opening. It is not recommended that you use the product after its expiration date.

If the integrity of the package has been compromised prior to the product expiration date, place the contents in a gas-permeable package and resterilize it with ethylene oxide as described below.

CAUTION: Use ethylene oxide only.

The process should not exceed temperatures of 55° C (125° F). Allow proper aeration of ethylene oxide residues prior to implantation. Use some acceptable method to determine sterilizer effectiveness, such as a biological indicator.

Due to the variability between sterilizers, precise sterilization instructions cannot be provided. Contact your sterilizer manufacturer for more information regarding sterilization procedures.

SUGGESTED IMPLANTATION PROCEDURE

The implantation procedure generally includes checking the mechanical functioning of the lead electrode before it is inserted; using a stylet guide, stylets, and vein lifter; selecting an insertion site; positioning the lead; securing the lead; taking electrical and defibrillation efficacy measurements; anchoring the lead; and connecting the lead to the pulse generator.

Some implantation techniques vary according to physician preference and the patient's anatomy or physical condition. As described below, the techniques for selecting an insertion site, using a stylet guide or a stylet, positioning a lead, and anchoring a lead suggest one or two possible versions, while more may exist.

Verifying the Mechanical Functioning of the Helix Electrode

Before implantation, verify the mechanical functioning of the electrode, as described below.

1. Within the sterile field, remove the lead and the accompanying stylets from the sterile packaging. The lead is packaged with a stylet guide attached and a stylet already inserted. The connector pin that accepts the stylet controls the helix mechanism.

2. To attach the fixation tool, first remove the stylet guide. Press both legs of the fixation tool together and place the most distal hole of the fixation tool on the connector pin that accepts the stylet (Figure 2).

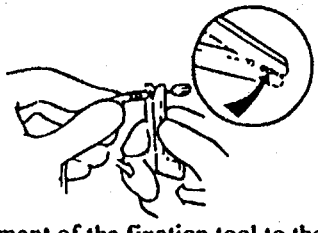

Figure 2. Attachment of the fixation tool to the connector pin.

3. Rotate the tool clockwise until the coiled electrode is completely exposed (Figure 3). Maximum electrode exposure reveals 2 coils.

Figure 3. Rotating the fixation tool.

The maximum number of revolutions of the fixation tool needed to extend or retract the helix is 20.

CAUTION: Exceeding the maximum number of revolutions may damage the lead.

4. Disconnect the fixation tool from the connector pin and release the proximal end of the lead body. Allow several seconds for the lead and its conductor coil to unwind.
5. After allowing the lead and its conductor coil to unwind, reattach the fixation tool and turn it counterclockwise until the helix tip is retracted in the sheath.

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Using the Stylet Guide and Stylets

The lead is packaged with a stylet guide attached and a stylet already inserted. The connector pin with the stylet in it controls the helix mechanism. Use of the stylet guide is optional. An attached stylet guide may be removed by gently pulling it off. To attach a stylet guide, gently push it as far as possible onto the connector pin that accepts the stylet (Figure 4).

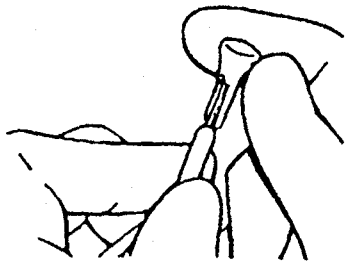

Figure 4. Stylet guide attachment.

A stylet provides additional stiffness and controlled flexibility for maneuvering the lead into position. Stylets vary in stiffness to accommodate a physician's preference for lead and stylet flexibility.

CAUTION: To avoid damage to the lead or body tissue, do not use excessive force or surgical instruments to insert a stylet into the lead. When handling a stylet, avoid overbending, kinking, or blood contact.

CAUTION: Repeated insertions of a stylet increase the chance that blood may accumulate on it, which may cause difficulty in passing the stylet through the lead and may cause damage to the lead.

After the stylet is inserted, gently remove the stylet guide so that it rests alongside the stylet knob.

Selecting an Insertion Site

The lead may be inserted by venotomy through several different venous routes, including the right or left cephalic vein or the external or internal jugular vein.

CAUTION: If insertion is done via a subclavian approach, the lead should be positioned far laterally to avoid clamping the lead body between the clavicle and the first rib. Clamping the lead may eventually cause the conductor to fractur, may cause damage to the insulation, or may cause other damage to the lead. This may result in complications such as loss of detection, loss of pacing therapies, or loss of cardioversion/defibrillation therapy. Certain anatomical abnormalities, such as thoracic outlet syndrome, may also precipitate pinching and subsequent fracture of the lead. If significant resis-

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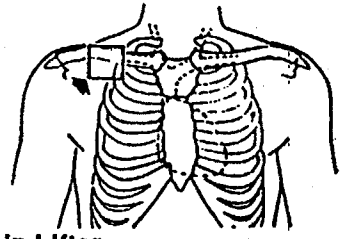
tance is encountered during a subclavian stick implant procedure, do not force the lead by adjucting patient's posture (i.e., raising the arm or putting a towel behind the person's back) to facilitate the passage of the lead. In such cases it is recommended that an alternate venous entry site be used.

Use fluoroscopy to facilitate accurate lead placement.



Using the Vein Lifter

A vein lifter facilitates lead introduction. Insert its tapered end into the incised vein and gently push the lead tip underneath and into the vein (Figure 5).

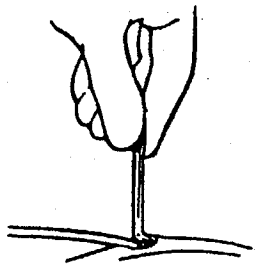


Figure 5. Using the vein lifter.

CAUTION: Avoid placing the lead under extreme tension or angulation to prevent lead dislodgement and possible lead fracture. **Do not grip the lead with surgical instruments.**

Positioning a Ventricular Lead

Advance the lead into the right atrium. For added control in maneuvering the lead tip through the tricuspid valve, the distal end of the lead may be slightly curved by inserting a gently curved stylet (Figure 6). After the lead tip is passed into the ventricle, the curved stylet may be replaced with a straight stylet. Then the lead tip may be advanced to the right ventricular apex while taking care to avoid perforation of the ventricular wall.

CAUTION: To avoid damage to the stylet, do not use a sharp object to impart a curve to the distal end (Figure 6).

30. **Of the 22 deaths, 15 systems were explanted and returned for analysis. The results of the analyses (PCD® and Transvene™ leads) must be provided. What did device interrogation reveal? How many of the 41 Transvene™ lead systems which were explanted were returned and analyzed? How long were the leads implanted? A description of the protocol for analysis and the results of the analyses on all leads and devices must be provided. The PMA application must document how your study has addressed the need for the return and analysis of all Transvene™ leads and the PCD®.**

RESPONSE:

In the 762 implants in 757 patients, a total of 41 units (5.4%) were explanted secondary to patient deaths, infection, heart transplant, low battery voltage measurement and PCD® Device performance issues. This information was provided in the PCD® Transvene™ System PMA Application, Clinical Experience Report, Section IX, System Performance. For convenience, Table 30-1 provides an overview of the units explanted, and returned to Medtronic for analysis and reason for explant.

PCD® Transvene™ System Reasons for PCD® Device Explant	
Reason	All Models
Number of Implants	762
Patient Death	15
Infection	17
Cardiac Transplant	5
Low Battery Voltage Measurement	1
PCD® Device Performance Issues	3
Total	41

Table 30-1: Reasons for PCD® Device Explant

There were 22 reported patient deaths and 15 devices were explanted and returned to Medtronic for analysis. In the remaining 7 deaths, either the family refused to allow the PCD® Transvene™ System to be explanted or the patient expired and was buried prior to notification of the primary investigator.

Of the fifteen devices which were explanted due to patient death, ten (10) have been analyzed and found to be performing within normal specifications. The remaining five (5) PCD® Devices are pending final analysis, however, none of the deaths were classified as being PCD® Transvene™ System related, and initial analysis has not indicated that these devices were performing outside normal specifications. Results of analysis performed on the 41 explanted devices is presented in Table 30-2.

PCD® Transvene™ System Final Analysis on Explanted PCD® Devices (N = 762)	
Within Normal Specifications	20
Hermetic Leakage at IC	1
Random Component Failure	2
Shorted on Pulse 2 Output	1
Analysis Pending	17
Total	41

Table 30-2: Final Analysis on Explanted PCD® Devices

Of the 41 devices explanted, final analysis on 19 units indicated that the devices were functioning within normal specifications. Final analysis is not available on 17 units which have been explanted. The reason for explant in these units includes patient death (5), infection (10) and cardiac transplant (2). It should be noted that none of these devices were explanted secondary to concern over the function of the implanted PCD® Transvene™ System.

Four PCD® Devices were explanted for the following device performance issues:

- explanted due to a Power On Reset (POR) condition that was not related to the delivery of external defibrillation or cautery (N = 1);
- explanted for lower than expected battery voltage for time in service (N = 1);
- explanted secondary to failure to appropriately synchronize and deliver cardioversion therapy for an induced VT episode (N = 1); and
- explanted post inappropriate delivery of VF therapy during a manual capacitor charge time (N = 1).

Of the 41 lead systems previously discussed, 21 lead systems, or portions of systems, were returned. Of those 21 only one 6966 lead was damaged, specifically, the helix. The remaining leads were found to be within specification.

The investigational plan requests that if the PCD® Transvene™ System is explanted during the course for any reason (i.e., patient death, infection, cardiac transplant or PCD® Device performance issues) that the PCD® device be returned to Medtronic for analysis. In addition, the patient informed consent also indicates that the patient allows permission of explant of the PCD® Transvene™ System at the possible time of his/her death.

The PCD® Transvene™ System clinical dataform specifically requests information on whether the system has been explanted and justification for not explanting the system.

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A description of the protocol for PCD device and Transvene lead analysis is presented below.

Failure Analysis Procedure: PCD Device and Transvene Leads

Failure investigation of implantable pacing products returned to Rice Creek for failure analysis is the responsibility of the Rice Creek Product Analysis Laboratory. The Supervisor of the Product Analysis Lab reports directly to the Director of Product/Configuration Assurance.

Any device that is returned to Medtronic is tested/analyzed for performance to specifications. Any device found to be out of specification is analyzed to determine the cause of the failure. Detailed procedures guide every step of the process from the receipt of the returned device through the implementation of any corrective action. Routine and specialized testing are described in procedures to ensure adequate testing of every device.

PCD Device

Failure investigation of a PCD device includes:

1. [(B)(4)]
2. [(B)(4)]
3. [(B)(4)]
4. [(B)(4)]
5. [(B)(4)]

Specialized testing may include:

1. [(B)(4)]
2. [(B)(4)]
3. [(B)(4)]
4. [(B)(4)]
5. [(B)(4)]

Destructive testing may include:

1. (B)(4)
2. (B)(4)
3. (B)(4)
4. (B)(4)
5. (B)(4)
6. (B)(4)
7. (B)(4)
8. (B)(4)

Specialized battery depletion testing may include:

1. (B)(4)
2. (B)(4)
3. (B)(4)

Transvene Leads

Failure investigation of a returned Transvene lead includes:

1. (B)(4)
2. (B)(4)
3. (B)(4)
4. (B)(4)
5. (B)(4)

Specialized testing may include:

1. (B)(4)
2. (B)(4)
3. (B)(4)
4. (B)(4)

[

(B)(4)

]

PD

M.4 Incidence of Complications/Observations

A comparison of the reported complications and observations was made between the PCD™ Transvene™ System and the PCD™ Epicardial System. The PCD™ Epicardial System patient population used for comparison included clinical experience as of January 5, 1992 with 742 patients and a mean implant duration of 16.3 months. These two patient groups are similar in the patient demographics and indication for implant of the PCD™ System. In the PCD™ Transvene™ System patient population, 19.4% of the patients experienced a clinical complication and 23.8% of the patients experienced a clinical observation. In the PCD™ Epicardial System, 14.2% of the patients experienced a clinical complication and 32.9% of the patients experienced a clinical observation.

Table IM-7 and IM-8 provide a comparison of the reported complications/observations and their incidence in the two patient populations.

PCD™ Transvene System
PCD™ Transvene System versus PCD™ Epicardial System
Reported Complications

Reported Complications	PCD™ Transvene™ System (N=757)	PCD™ Epicardial System (N=742)
Increased Defibrillation Requirements	1.2%	0.5%
Inappropriate Therapy	-	2.2%
Pace/Sense Related	0.8%	3.5%
Infection Related - Explant	2.9%	2.3%
Lead Related	9.5%	2.8%
Device Related	0.5%	0.9%

Table IM-7: Reported Complications: PCD™ Transvene™ System versus PCD™ Epicardial System - 2/1/93

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31. Please discuss the circumstances surrounding the death of the patient who died 22.5 months post implant. What did interrogation of the device reveal?

RESPONSE:

The circumstances of this patient death (Patient ID 96097) were provided in PMA Amendment (9/18/92), Volume 3 page 543-545. A copy of the patient death summary is provided here for convenience.

In summary, the patient had been admitted for worsening symptoms of congestive heart failure, renal decompensation and increased frequency of spontaneous VT and VF episodes. In addition the patient had digitalis toxicity. The patient's condition worsened and the family members elected not to use heroic measures in the treatment of the patient. The patient eventually expired secondary to progressive cardiac failure due to left ventricular pump dysfunction. The patient death was classified as non-sudden cardiac and not related to the PCD® Transvene™ System. Final interrogation of the PCD® Device, at the time of explant, indicated normal battery voltage and charge time and the patient had experienced no new episodes of VT or VF since the last follow-up visit. The PCD® Device was explanted and analysis found the device to be performing within specifications.

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Patient 96097

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PCD Serial Number: (b)(4) B6
Date of Implant: (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

This patient was 77 year old male with history of recurrent ventricular tachycardia associated with a sudden cardiac death episode. In the six months prior to implant of the PCD Transvene System, the patient experienced [(b)(6)], and greater than 20 episodes of [(b)(6)] The patient's cardiovascular history included [(b)(6)] with an ejection fraction of 15% and a NYHA Classification of Class III. The patient's antiarrhythmic drug therapy at the time of implant included (b)(6)

The patient received a PCD Transvene System which consisted of RV/SVC/SQ. The implant defibrillation threshold was 10 Joules with a programmed defibrillation pathway of simultaneous. A total of seven inductions were performed and one lead configuration was evaluated. The mean duration of each of the episodes was 10 seconds.

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The patient did not undergo a pre-hospital discharge electrophysiology study. The PCD Device programmed status was as follows: 116

Parameter	Value
Sensitivity	0.3 mV
TDI	440 ms
VT NID	12
VT Rx #1	Burst
VT Rx #2	CV/10J/SIM
VT Rx #3	CV/20J/SIM
VT Rx #4	CV/34J/SIM
FDI	330 ms
VF NID	18
VF Rx #1	34J/SIM
VF Rx #2	34J/SIM
VF Rx #3	34J/SIM
VF Rx #4	34J/SIM

At the one month follow-up, a chest x-ray documented that the SVC lead had dislodged. Reoperation was required and the lead was repositioned. In addition, the patient had experienced a total of 154 spontaneous VT episodes that had all been successfully reverted by VT Therapy #1 (Ramp). In order to control the frequency of spontaneous VT episodes, the patient's antiarrhythmic drug therapy was modified to quinidine and pindolol.

At the three month follow-up visit, VF was induced and successfully reverted by VF Therapy #1 (18J). The patient had experienced no spontaneous episodes of VT or VF since the last visit.

Six months post implant of the PCD Transvene System, the patient was admitted for an increase in frequency of spontaneous VT episodes as well as symptoms of congestive heart failure. During this hospitalization, the patient experienced a total of 194 episodes of ventricular tachycardia. All of these episodes were

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successfully reverted by VT Therapy #1. However, VT Therapy #1 had been programmed to Ramp which in the case of two VT episodes accelerated the rhythm to ventricular fibrillation which were successfully reverted by VF Therapy #1 (34J). In order to control the episodes of ventricular tachycardia, the patient's previous antiarrhythmic drug therapy of quinidine and pindolol was discontinued and [redacted] therapy was restarted.

Approximately one week prior to his death, the patient was admitted for symptoms of congestive heart failure, renal decompensation and increased frequency of spontaneous VT/VF episodes. In addition, the patient had digitalis toxicity. Early in his admission, the patient experienced five episodes of VT, all of which were effectively treated with VT Therapy #1 (Burst). The patient's cardiac failure initially improved however his condition eventually worsened and he was treated aggressively with vasodilator and inotropic agents with a marked improvement in his symptoms. Eventually, his cardiovascular status again worsened and his symptoms of congestive heart failure did not respond to aggressive medical therapy. The family elected not have the patient placed on a respirator. The patient's cardiac failure continued to worsen with associated hypotension and signs of central and peripheral failure. The patient eventually expired secondary to progressive cardiac failure due to left ventricular pump dysfunction.

The PCD Device was explanted and returned to Medtronic for analysis and found to be performing within specification.

The investigator classified this patient death as non-sudden cardiac and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

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32. Of the perioperative deaths, how many devices were programmed OFF? Please discuss the circumstances surrounding each death. The number of perioperative deaths must be reported in a table and be identified as sudden cardiac, non-sudden cardiac or non-cardiac. Were there other deaths when the device was programmed OFF? 118

RESPONSE:

As of February 1, 1993, there have been a total of 51 reported patients deaths in the 757 patients who received a PCD® Transvene™ System. There have been five (5) reported perioperative patient deaths with a resultant perioperative mortality of 0.7%. The patient death in which the PCD® Device was programmed OFF (Patient ID 95170) was classified as non-sudden cardiac and was not related to a ventricular tachyarrhythmia episode. Table 32-1 summarizes these perioperative patient deaths.

PCD® Transvene™ System Perioperative Patient Deaths	
Death Classification	**Number of Patients**
Sudden Cardiac	2
Non-Sudden Cardiac	2
Noncardiac	1
TOTAL	5 (0.7%)
PCD® Device OFF	1

Table 32-1: PCD® Transvene™ System Perioperative Death Classifications

The circumstances of these patient deaths were provided in PMA Amendment (9/18/92), Volume 3 page 503-580. A copy of the patient death summaries is provided here for convenience.

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In the total patient death group of 51 patients, there were seven (7) deaths were the device was programmed OFF. In none of these cases did the primary investigator indicate that the patient death was related to the implanted PCD® Transvene™ System. There was one sudden cardiac death in which the PCD® Device was programmed OFF. One month post implant of the PCD® Transvene™ System, this patient experienced fourteen (14) episodes of VF which were all successfully terminated by the PCD® Device. The patient was admitted for evaluation and during this hospitalization requested that the PCD® Device be programmed OFF. Approximately 30 minutes later the patient experienced an episode of ventricular tachycardia and expired. The death classifications for those patient deaths where the PCD® Device was programmed OFF are provided in Table 32-2.

PCD® Transvene™ System PCD® Device OFF Death Classification	
Death Classification	**Number of Patients**
Sudden Cardiac	1
Non-Sudden Cardiac	4
Noncardiac	2
TOTAL	7
Perioperative	1

Table 32-2: PCD® Transvene™ System - PCD® Device OFF Death Classifications

Patient 94207

PCD Serial Number: (b)(4), (b)(6)
Date of Implant: (b)(4), (b)(6)
Date of Death:
Death Classification: **Noncardiac**

This patient was a 63 year old male with a history of recurrent ventricular tachycardia. In the six months prior to the implant of the PCD Transvene System the patient had experienced greater than ten cardiac arrests. The patient's cardiovascular history included cardiomyopathy with an ejection fraction of 29% and NYHA Classification Class IV. The patient had undergone an [(b)(6)] approximately [(b)(6)] to the implant of the PCD Transvene System. At the time of implant the patient was on no antiarrhythmic drug therapy.

The patient received a PCD Transvene System consisting of RV/SVC/SQ. The implant LED was 18 Joules with a programmed defibrillation pathway of SEQUENTIAL. A total of four inductions and one lead configuration was tested. The total duration of VF for the implant procedure was 40 seconds with the mean duration of each episode being eight seconds.

The patient's post-operative course was complicated by recurrent ventricular tachyarrhythmia episodes. The patient experienced a total of seven VF episodes, six which were terminated by VF Therapy #1 (34J/SEQ) and one which required VF Therapy #2 (34J/SEQ). In order to control the recurrent VT/VF, the patient's antiarrhythmic drug therapy was modified to include [(b)(6)] and [(b)(6)]

At the prior to discharge EPS, VF was induced and successfully terminated with VF Therapy #1 (34J/SEQ). The investigator elected to continue the patient on Amiodarone therapy. The PCD Device programmed status was as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	450 ms
VT NID	20
VT Rx #1	CV/34J/SEQ
VT Rx #2	CV/34J/SEQ
VT Rx #3	CV/34J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	380 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

The patient was not discharged from the hospital after the prior to discharge EPS but was instead transferred to a nursing home for his continued recovery. The patient developed symptoms of infection and eventually expired due overwhelming staphylococcus sepsis. The investigator indicated that patient presumably had an [(B)(4)] of his [(B)(4)]. The patient death was not associated with any spontaneous VT/VF episodes. No autopsy was performed nor was the PCD Transvene System explanted prior to the patient's burial.

The investigator classified the patient death as perioperative, noncardiac and not related to the implanted PCD Transvene System. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

Patient 94244

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PCD Serial Number: (b)(4), (b)(6)
Date of Implant: (b)(4), (b)(6)
Date of Death:
Death Classification: **Sudden Cardiac**

This patient was a 72 year old male with a history of recurrent ventricular tachycardia. In the six months prior to the implant of the PCD Transvene System the patient had experienced 3 episodes of spontaneous ventricular tachycardia. The patient's cardiovascular history included coronary artery disease and congestive heart failure. The patient's ejection fraction was 20% with a NYHA Classification of Class III. The patient was on no antiarrhythmic drug therapy at the time of implant.

The patient received a PCD Transvene System that consisted of RV/CS/SQ. The implant DFT was 5 Joules with a programmed defibrillation pathway of SIMULTANEOUS. A total of 12 inductions were performed and with one lead configuration being evaluated. The total duration of VF for the implant procedure was 129 seconds with one episode last 45 seconds and requiring two transthoracic defibrillations for successful termination.

The patient's post-operative course was complicated by recurrent VT/VF episodes as well as the delivery of inappropriate VT therapy for atrial fibrillation with a rapid ventricular response. The patient experienced 13 episodes of VT that were successfully reverted by VT Therapy #1 (Burst) and two episodes of VF that were successfully reverted by VF Therapy #1 (18J/SIM). In addition, the patient experienced 7 episodes of atrial fibrillation that resulted in the delivery of inappropriate VT therapy. The PCD Device TDI was reprogrammed to manage this delivery of inappropriate VT therapy.

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At the prior to discharge EPS, VF was induced and successfully reverted with VF Therapy #1 (18J/SIM). In addition, VT was also induced and successfully terminated by the PCD Device. The PCD Device programmed status was as follows: 12

Parameter	Value
Sensitivity	0.3 mV
TDI	490 ms
VT NID	12
VT Rx #1	Burst
VT Rx #2	CV/5J/SIM
VT Rx #3	CV/34J/SIM
VT Rx #4	CV/34J/SIM
FDI	320 ms
VF NID	18
VF Rx #1	18J/SIM
VF Rx #2	34J/SIM
VF Rx #3	34J/SIM
VF Rx #4	34J/SIM

The patient's death was unwitnessed however an interrogation of the device was performed prior to explant and return to Medtronic for analysis. The results of this analysis are not available as of this submission but will be provided to the FDA.

Since discharge from the hospital the patient had experienced an additional 23 episodes of spontaneous VT and 1 episode of spontaneous VF. In the case of VT, 22 episodes were successfully treated by VT Therapy #1 (Burst) and one episode required VT Therapy #4 (CV/34J/SIM). The episode of VF was successfully reverted by VF Therapy #1 (34J/SIM).

The last episode detected by the PCD Device was VT and the cycle length of the episode was 480 ms. VT Therapy #1 (Burst) successfully terminated this episode however the cycle length of the 10 intervals post the delivery of therapy were 490 ms. There was no autopsy performed per the patient's family request.

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The investigator classified this patient death as perioperative and sudden cardiac. The relationship of the death to the implanted PCD Transvene System was classified as unknown. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification. 124

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Patient 94268

PCD Serial Number:	(b)(4), (b)(6)
Date of Implant:	(b)(4), (b)(6)
Date of Death:	
Death Classification:	**Sudden Cardiac**

This patient was a 56 year old female with a history of recurrent ventricular tachycardia. In the six months prior to the implant of PCD Transvene System, the patient experienced one episode of spontaneous VT and no episodes of cardiac arrest. The patient's cardiovascular history included cardiomyopathy and congestive heart failure. The patient's ejection fraction was 13% with a NYHA Classification of Class III. The patient was on no antiarrhythmic drug therapy at the time of implant.

The patient initially received a PCD Transvene System which consisted of RV/SVC/SQ. The implant DFT was 20 Joules with a programmed defibrillation pathway of SEQUENTIAL. A total of five inductions were performed and three lead configurations were evaluated. With the lead system connected to the PCD Device, VF was successfully terminated with 20 Joules.

The patient underwent her first post implant electrophysiology study two days post the implant procedure. Two inductions of VF were performed both indicating a increase in defibrillation requirements. In the first episode, VF Therapy #1 was programmed to 20J/SEQ however VF Therapy #4 (34J/SEQ) was required for successful reversion. In the second episode, VF Therapy #1 was reprogrammed to 34J and in this case VF Therapy #2 was required for successful reversion. There was no evidence of lead dislodgement. The patient was scheduled for a second EPS with possible modification to an PCD Epicardial System if successful defibrillation could not be demonstrated. After this procedure, VT and VF Detection and Therapies were both enabled.

The patient underwent her second post implant electrophysiology study four days post implant of the PCD Transvene System. The initial interrogation of the PCD Device indicated a Power On Reset with VT/VF Detection and Therapies disabled. There had been no history of electrocautery use near the PCD Device or the delivery of external defibrillation since the first EP study. The Power On Reset was cleared from the PCD Device memory, the device was

successfully reprogrammed and VF inductions were performed.

A total of two inductions were performed with the PCD Transvene System. In the first induction, VF was successfully reverted with VF Therapy #1 (20J/SEQ). In the second induction, with VF Therapy #1 still programmed to 20 Joules, VF Therapy #3 (34J/SEQ) was required for successful termination. Post delivery of this therapy, the patient's rhythm was atrial fibrillation with a wide complex QRS. Based on these results, the patient was scheduled for surgery that day and evaluation of a PCD Epicardial System.

In the second implant procedure, the PCD Transvene Systems lead configurations evaluated were unable to produce the original implant DFT of 20 Joules and the only effective energy was 34J/SEQ. The investigator elected to explant the PCD Transvene System and implant a (b)(6) The LED with the epicardial defibrillation lead system was 15 Joules. In the final induction with the lead system connected to the PCD Device, VF was successfully reverted with 18 Joules.

The patient underwent her third electrophysiology study 12 days post her initial implant procedure. In this case, the efficacy of the implanted epicardial defibrillation lead system was evaluated. A total of three VF inductions were performed. In the first induction, VF Therapy #1 was programmed to 18 Joules however VF Therapy #3 (34J/SINGLE) was required for successful reversion. In the second induction, VF Therapy #1 (34J/SINGLE) was successful. In the final induction, VF Therapy #1 was programmed to 28 Joules however VF Therapy #3 (34J/SINGLE) was required for successful reversion. Based on these results and the patient history, Medtronic was contacted. After review of the data, it was recommended that the PCD Device be explanted however the investigator elected to discharge the patient over concern about her psychological status. The PCD Device programmed status was as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	450 ms
VT NID	12
VT Rx #1	Ramp
VT Rx #2	CV/34J/SINGLE
VT Rx #3	CV/34J/SINGLE
VT Rx #4	CV/34J/SINGLE
FDI	300 ms
VF NID	12
VF Rx #1	34J/SINGLE
VF Rx #2	34J/SINGLE
VF Rx #3	34J/SINGLE
VF Rx #4	34J/SINGLE

Approximately one week post discharge from the hospital, the patient was at home and developed symptoms of chest pain and received several shocks from the PCD Device. Upon arrival of the EMT's, the patient was in a "[(b) (6)]" and was still conscious. Upon arrival to the emergency room, her heart rate was 150 beats per minute, she was pale, anxious and dyspneic. Her blood pressure gradually decreased and defibrillation by the emergency room personnel was unable to terminate her ventricular tachyarrhythmia. She underwent a lengthy code with multiple defibrillations, IV medications and CPR without success.

The PCD Device was explanted and returned to Medtronic for analysis. The analysis of the device indicated that the PCD Device was performing within normal specifications. However, due to the Power On Reset condition, the device is undergoing further analysis. No autopsy was performed per the patient's family request.

A final interrogation of the device was obtained. There was no evidence of Power on Reset, the battery voltage was 6.32 Volts and the Charge Time was 6.32 seconds. Since discharge the

patient had experienced a total of 15 VT episodes and 8 VF episodes. Eleven of the spontaneous VT episodes were not successfully terminated by the PCD Device and in fact the last VT episode was not effectively terminated. The remaining VT episodes had been successfully reverted by VT Therapy #1 (Ramp). 128

All eight episodes of VF were terminated, 7 being successfully reverted by VF Therapy #1 (34J/SINGLE) and one episode requiring VF Therapy #4 (34J/SINGLE). The last episode detected by the PCD Device was VF with intervals ranging from 130 - 760 ms. The events after the last therapy were a paced rhythm and VF Therapy #1 (34J/SINGLE) was successful.

The investigator classified this patient death as perioperative, sudden cardiac and not related to the implanted PCD Transvene System. The investigator felt that the patient's death was related to her severe left ventricular dysfunction. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

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Patient 95170

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

This patient was a 73 year old male with history of recurrent VT, coronary artery disease and dilated cardiomyopathy as well as severe chronic obstructive pulmonary disease that had been treated with steroid therapy. The patient's ejection fraction was 30% with a NYHA Classification of Class I. Prior to implant of the PCD system the patient had failed [(b)(6)] however the patient was on no antiarrhythmic drug therapy at the time of implant. Due to the patient's severe [(b)(6)], a [(b)(6)] was indicated in this patient.

The patient received a PCD Transvene System which consisted of RV/CS/SQ. The right ventricular lead (Model 6884) was positioned easily with two attempts necessary to screw the helix into the myocardium. The R wave amplitudes measured 4.0 mV in sinus rhythm. Only one lead configuration was tested with the Model 6884 lead serving at the COMMON electrode, the Model 6895 patch serving as PULSE 1 and the Model 6881 lead serving as PULSE 2. The defibrillation pathway evaluated was SEQUENTIAL.

A total of six inductions were performed utilizing the Model 5355 ETCD with 18, 15, 10, and 5 Joules being successful in terminating the induced ventricular fibrillation. During these inductions appropriate sensing and detection of VF was documented. The lead system was connected to the Model 7217B PCD and one final VF induction was performed. This episode was neither sensed or converted by two 34 Joule shocks delivered manually from the PCD device. Several external defibrillations and prolonged resuscitative measures restored sinus rhythm. After this episode it was determined that the pacing thresholds had increased to greater than 10 Volts and there were no identifiable ventricular electrogram from the RV lead. The investigator felt at this time that this suggested either RV lead dislodgement or perforation, lead malfunction or device malfunction. However, due to the patient's pulmonary status the procedure was terminated without performing any further procedures. The PCD device VT/VF detection and therapies were

deactivated for the immediate post-operative period. The investigator noted that the plan was to reevaluate the lead system post-operatively once the patient's status had stabilized. 13(

The patient's recovery was uneventful over the next 48 hours with no significant chest pains or cardiac rubs on physical exam. With the PCD device programmed to VVI mode with a rate of 30 ppm and sensitivity of 0.3 mV, asynchronous ventricular pacing with non capture was noted continuously post-operatively. Occasional episodes of nonsustained VT were noted, alternating with sinus rhythm but this was not significantly different from the patient's pre-implant rhythm. No significant ST-T changes were noted on ECG.

The patient then developed [(b)(6) (b)(6)]. Despite intubation and administration of fluids and pressors he had electro-mechanical dissociation followed by episodes of [(b)(6) tachycardia/fibrillation. The diagnosis of [(b)(6)] was made but due to the patient's [(b)(6)] and [(b)(6)] was not performed. The patient expired after prolonged resuscitative measures. It should be noted, that at the time of the patient's death VT/VF detection and therapies were programmed OFF.

The PCD device was explanted and an autopsy was performed. The autopsy identified a perforation of the right ventricle by the RV lead, accompanied by hemopericardium and presumed tamponade. No other potential causes of death could be identified.

The Model 7217B PCD device was explanted and returned for analysis and was found to be performing within specifications.

The investigator classified this patient death as periopertive, non-sudden cardiac and related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and felt that the death was related to the implant procedure and not the implanted PCD Transvene System.

Patient 95774

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PCD Serial Number: (b)(6), (b)(4)
Date of Implant:
Date of Death:
Death Classification: **Non-Sudden Cardiac**

This patient was a 71 year-old male with a history of recurrent ventricular tachycardia. His cardiovascular history included coronary artery disease and congestive heart failure. His ejection fraction was 10% with a NYHA Classification of Class III. In the six months prior to implant of the PCD Transvene System, the patient experienced three spontaneous VT episodes. At the time of implant the patient was on no antiarrhythmic drug therapy.

The patient received a PCD Transvene System consisting of RV/SVC/SQ. A total of four inductions were performed, one lead configuration was tested and the total time in VF was 53 seconds. The lowest energy of defibrillation was 18J.

The prior to hospital discharge electrophysiology study was done two days post implant of the PCD Transvene System with two inductions of VF. In the first episode, VF Therapy #1 was programmed to 34J/SEQ which successfully reverted the episode. In the second episode, VF Therapy #1 was programmed to 10J/SEQ which was unsuccessful but VF was successfully reverted by VF Therapy #2 (34J/SEQ). Based on the results of this study, the PCD device was programmed as follows:

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Parameter	Value
Sensitivity	0.3 mV
TDI	OFF
VT NID	OFF
VT Rx #1	OFF
VT Rx #2	OFF
VT Rx #3	OFF
VT Rx #4	OFF
FDI	320 ms
VF NID	24
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

The patient was not discharged at this time due to symptoms of congestive heart failure. Over the next two days the patient's condition worsened and aggressive therapy was started in attempt to improve the patient's condition. At the time of his death the patient was receiving [(b)(6)] therapy without improvement. Prior to his death the patient experienced an episode of VF that was successfully treated by the PCD Device VF Therapy #1 (34J/SEQ). After this episode, the patient also began receiving [(b)(6)] therapy. The patient eventually expired [(b)(6)] failure not associated with a VT/VF episode. The PCD device was explanted and was found to be within normal specifications.

The cause of death was reported as perioperative, non-sudden cardiac secondary to end stage heart failure by the investigator and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of the patient death and agreed with the investigator's classification.

33. You state that there have been no reported patient deaths in the group with a 1 year sudden cardiac death survival and overall actuarial survival of 100 percent. Does this include the perioperative deaths and the patients who have been followed out for a year?

RESPONSE:

This question refers to our response to Deficiency No. 17 from the 9/18/92 Transvene™ PMA update. A copy of that response is provided for your convenience. That deficiency asked us to discuss our clinical experience (treatment efficacy, lead orientation, complications and survival rates) of the patient who have been followed for 1 year and more.

The patients who were included in that group were those who had completed at least one year of follow-up. This included patients of all indications. Therefore, by definition all of these patients were alive at one year post implant so their survival from all causes of death (sudden, non-sudden cardiac, non-cardiac, perioperative) was 100%. Patients who died in the perioperative period are those who died in the first 30 days after implant, and therefore, cannot be followed for more than 30 days and are not a part of the patient group with one year follow-up.

17. Please discuss your clinical experience (treatment efficacy, lead orientation, complications and survival rates) of the patients who have been followed for 1 year and more.

RESPONSE:

A summary table of this experience and relevant discussion is provided below.

PCD™ Transvene™ System Data Summary		
	All Patients (3 Electrode Systems)	Patients with 12 months of Follow-up
Number of Patients	757	115
Device Months Follow-up	4246.4 mo	1835.5 mo
Mean Follow-up Time	5.6 mo	15.7 mo
Maximum Follow-up Time	28.6 mo	28.6 mo
Number, % Male Number, % Female	610 80.6% 147 19.4%	91 79.1% 24 20.9%
Mean Age	59.4 yrs	57.0 yrs
Primary Indication: SCD VT SCD/VT	 281 37.1% 377 49.8% 99 13.1%	 45 39.1% 56 48.7% 14 12.2%
Coronary Artery Disease	561 74.1%	85 73.9%
Mean Ejection Fraction	35.6% (n=688)	40.5% (n=104)
Lead Orientation: RV-CS-SQ RV-SQ-SVC RV-CS-SVC	 222 29.3% 496 65.5% 39 5.2%	 33 28.7% 73 63.5% 9 7.8%
Mean LED	16.0 (n=702)	15.2 (n=105)
Mean DFT	14.8 (n=316)	13.8 (n=62)
Spontaneous VT: Number of Patients Number of Episodes % Success	 226 5430 98.7%	 60 1770 98.9%
Spontaneous VF: Number of Patients Number of Episodes % Success	 198 973 99.1%	 37 248 98.8%
One Year Overall Survival One Year SCD Survival	95.3% 99.8%	100.0% 100.0%
Patients with complications	138 18.2%	24 20.9%

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The patients population (n=115) with 12 months or more of follow-up is predominantly male (79.1%) with a mean age of 57.0 years. In the majority of patients (48.7%), the primary indication for implant was recurrent, sustained ventricular tachycardia without an episode of sudden cardiac death. The treatment efficacy for this patient population was 98.9% for spontaneous VT episodes, and 98.8% for VF episodes, which is equivalent to the overall patient population with 98.7% and 99.1% respectively. Overall and sudden cardiac death one year survival for this patient population is 100.0% since all patients have been followed for one year or greater. In the patients followed for 12 months or more there has been one death which is classified as non-sudden cardiac. This death occurred 684 days (22.5 months) post implant. Twenty-four (20.9%) of the patients followed for 12 months had a complication.

Based on the data above, the PCD™ has performed safely and reliably for patients followed for 12 months or greater.

34. Please provide an engineering drawing of each Transvene™ lead model which identifies the segments of the lead and a description of the tests that each segment and the full lead body underwent. 136

RESPONSE:

The table below lists the tests which each Transvene™ lead underwent as indicated by the "x". The segments are labeled on the engineering drawings that follow. For consistency, each lead has been labeled as follows:

Segment A	Full Lead
Segment B	Electrode
Segment C	Lead Body
Segment D	Proximal

	Segment			
Test Method	**A**	**B**	**C**	**D**
Lead System Test[1]	x	x	x	
DC Resistance	x			
Leak Test[2]	x			
Lead Stiffness[3]			x	
Anchoring Sleeve Sliding			x	
Flex Testing[4]		x	x	
Tensile Strength	x			
Crimp/Weld Strength		x		x
Crush Test			x	
Biostability[5]	x	x	x	x
Biocompatibility	x			

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[1] The Lead System Test consists of four (4) tests that were repeated sequentially over a one (1) year period of time on forty-five (45) total leads. The tests are; 1) [(B)(4)]

[2] [(B)(4)] on the tripolar RV lead is the only lead that has more than one conductor where internal lead shorting could occur due to conductive fluid ingression.

[3] Lead Stiffness testing is done on [(B)(4)] only.

[4] In addition to the normal lead body flex testing, the [(B)(4)] and the [(B)(4)] were flexed to [(B)(4)] cycles without failure during the Lead System Test.

[5] [(B)(4)] testing is included in the Biostability test for the Model 6966 RV, a polyurethane lead.

Test Method	Safety Issue
Lead System Test	Lead reliability due to a combination of flex, soak and high energy pulsing.
DC Resistance	Lead Continuity
Leak Test	Conductive Fluid Leakage Between Conductors
	Conductor to Conductor Shorting
	Fluid leakage which could prevent helix extension during placement and repositioning.
Lead Stiffness	Heart Tissue Damage
Anchoring Sleeve Sliding	Stability of Lead Position
Flex Testing	Conductor Fracture
Tensile Strength	Normal Handling during Implantation
Crimp/Weld Strength	Reliable Mechanical/Electrical Connection
Crush Test	Lead to Lead Insulation Stability
Biostability	Material Disassociation in the Body
	MIO resistance for Polyurethane
Biocompatability	Mutagenic or Carcinogenic Activity

Test Description

Lead System Test

Initially each lead was inspected and tested for DC resistance. In the [(b)(4) (b)(4)] protocol, each lead went through the following sequence of tests eight (8) times:

Flex Testing at Room Temperature
Lead Body ([(b)(4)] cycles) Segment C
Defibrillation Electrode Body ([(b)(4)] cycles) Segment B
[(b)(4)] Fluid Soak [(b)(4)]
Submerge Entire Lead in solution : (BX4) Segment A
High Energy Pulsing
[(b)(4)] Volt Shock [(b)(4)] shocks) Segment A
[(b)(4)] Fluid Soak [(b)(4)]
Submerge Entire Lead in solution (BX4)) Segment A

By repeating the sequence of testing outlined above, each lead would receive:

Flex Testing
Lead Body (8 x [(b)(4)] cycles) Segment C
Defibrillation Electrode Body (8 x [(b)(4)] cycles) Segment B
[(b)(4)] Soak [(b)(4)]
Submerged Lead (8 x [(b)(4)] days) Segment A
High Energy Pulsing
[(b)(4)] Volt Shock (8 x [(b)(4)] shocks) Segment A
[(b)(4)] Soak [(b)(4)]
Submerged Lead (8 x [(b)(4)] days) Segment A

The lead body and the defibrillation electrode body were flexed at a [(b)(4)] inch radius. The Model 6999, unipolar, subcutaneous patch, received patch (defibrillation electrode) flexing in a fixture that is slightly different than the lead body flexing, because of the design of the subcutaneous patch. The patch is the region of the lead where the [(b)(4)] electrode coils are imbedded.

At the end of the Lead System Testing, each lead was visually reinspected, had the DC resistance measured and intermittency tested. In conclusion, all the leads met all test requirements without failure and therefore demonstrate an acceptable assurance of safety and reliability in lead design.

DC Resistance

Electrical resistance is measured from the[(BX4)] This test is performed on[(BX4)]of production devices.

Leak Test

[(BX4)]

Lead Stiffness

[(BX4)]

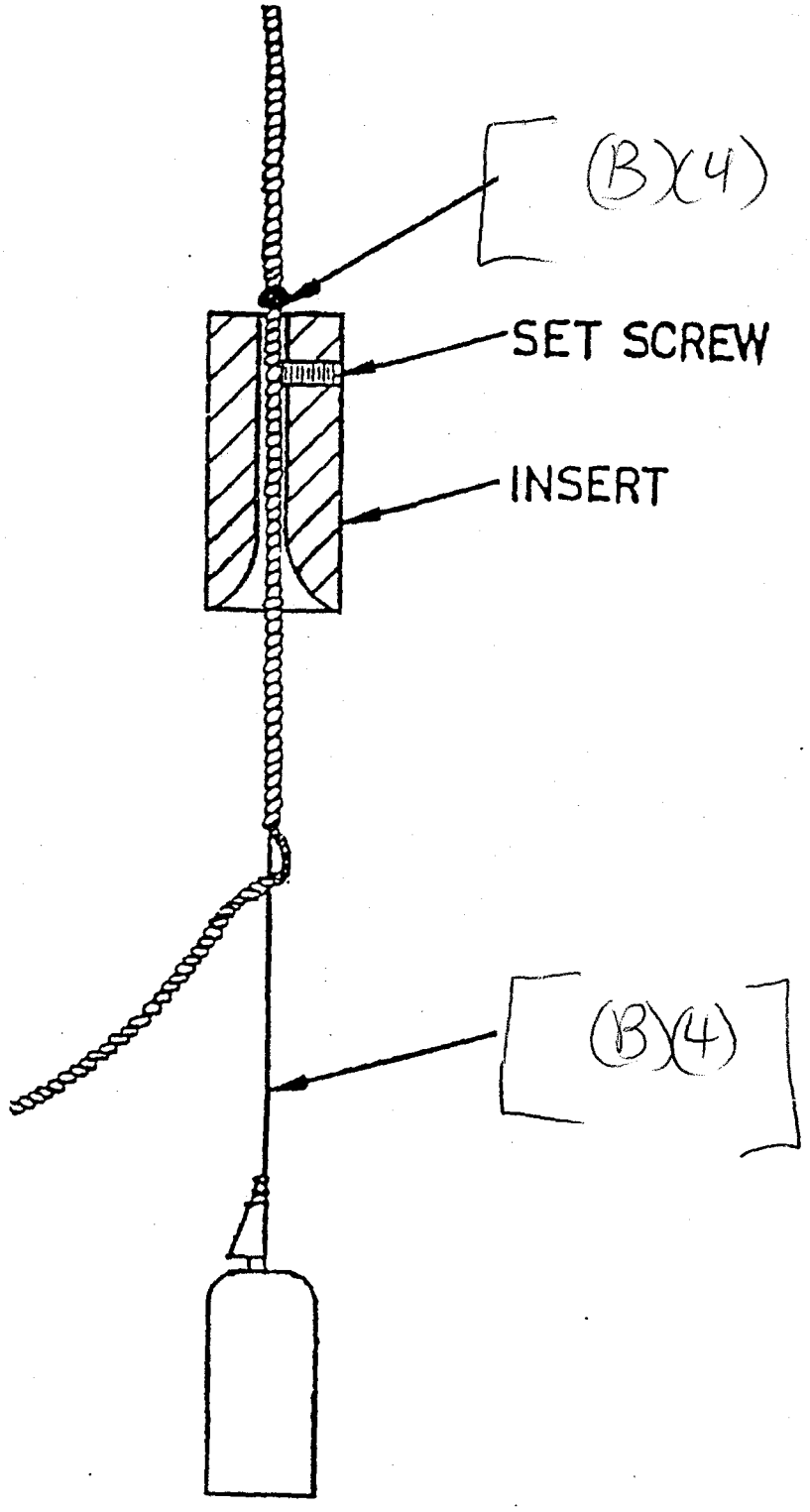
Anchor Sleeve Sliding

[(BX4)]

Flex Testing

[(B)(4)]

See figure below:



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See response to #35 for an illustration of the flex test fixture.

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[(B)(4)]

Tensile Strength

[(B)(4)]

Crimp/Weld Strength

[(B)(4)]

Crush Test

[(B)(4)]

Biostability

[(B)(4)]

[(B)(4)]

Biocompatibility

The biocompatability testing performed on both silicone and (b) (4) (b)(4) leads is in accordance with the Office of Device Evaluation, Division of Cardiovascular Devices, Implantable Pacemaker Lead Testing Guidance for the Submission of a 510(k) Notification, September 1989. Per this guidance, the following biocompatibility tests were performed; hemolysis, tissue culture, USP Pyrogen, USP Biological Test for Plastics Class V, 4-12 week Intramuscular Implant, Ames Mutagenicity, and GPMT.

Details on all nonclinical testing performed on the Transvene leads can be found in Appendix B.

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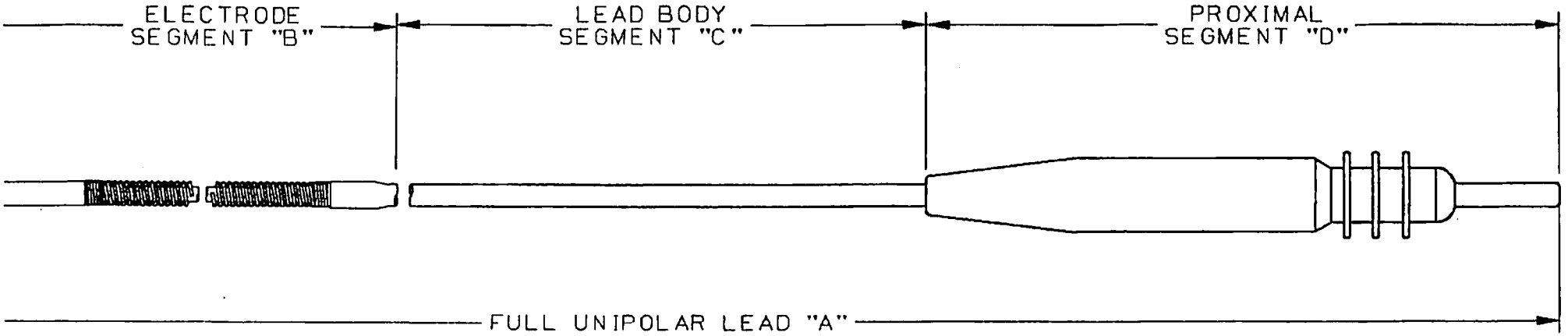
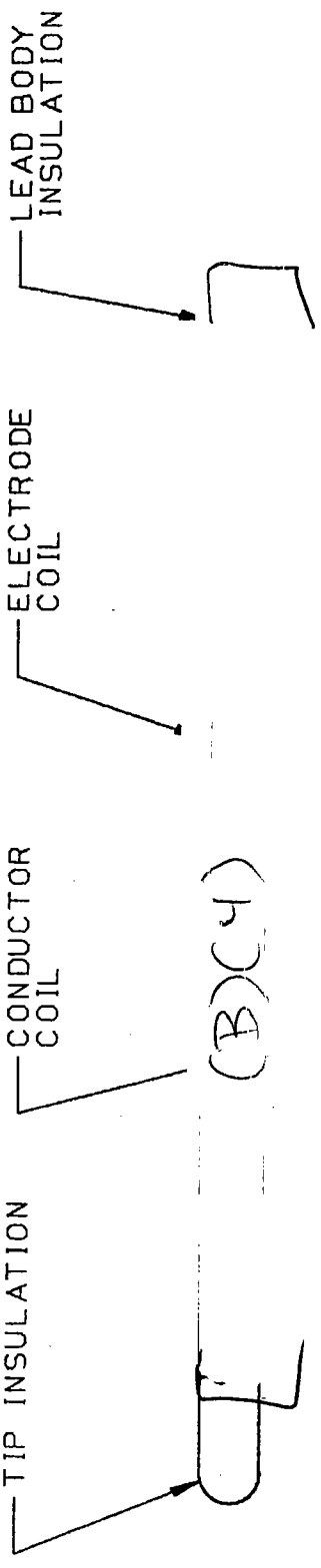


NOTE : ANCHORING SLEEVE REMOVED
FOR CLARITY.

MODEL 6963 CS / SVC LEAD

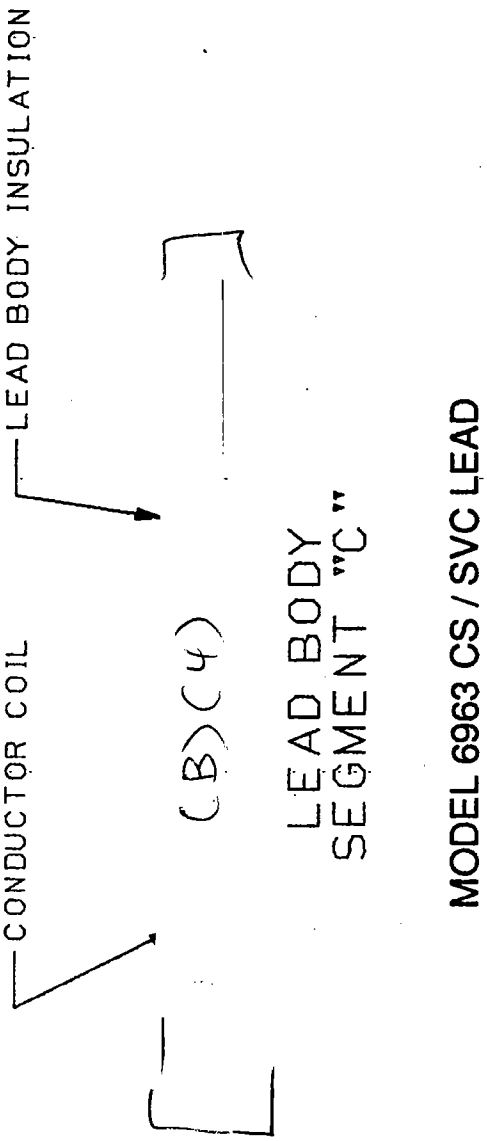
MEDTRONIC CONFIDENTIAL 14

A



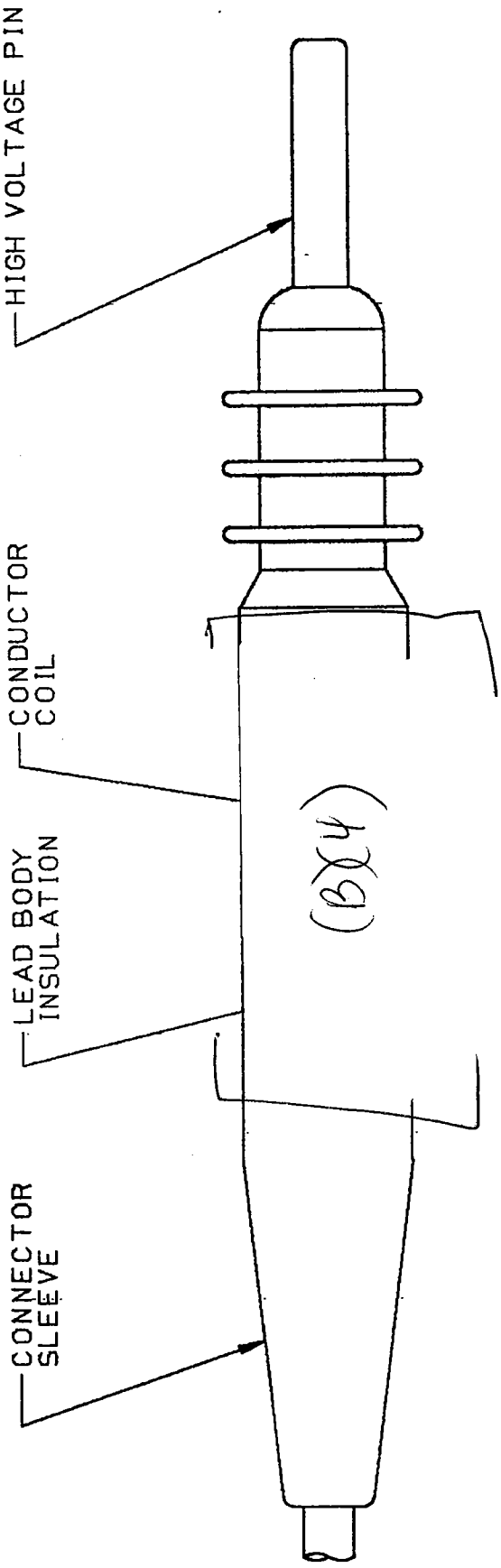
MODEL 6963 CS / SVC LEAD

27



MODEL 6963 CS / SVC LEAD

23



MODEL 6963 CS / SVC LEAD

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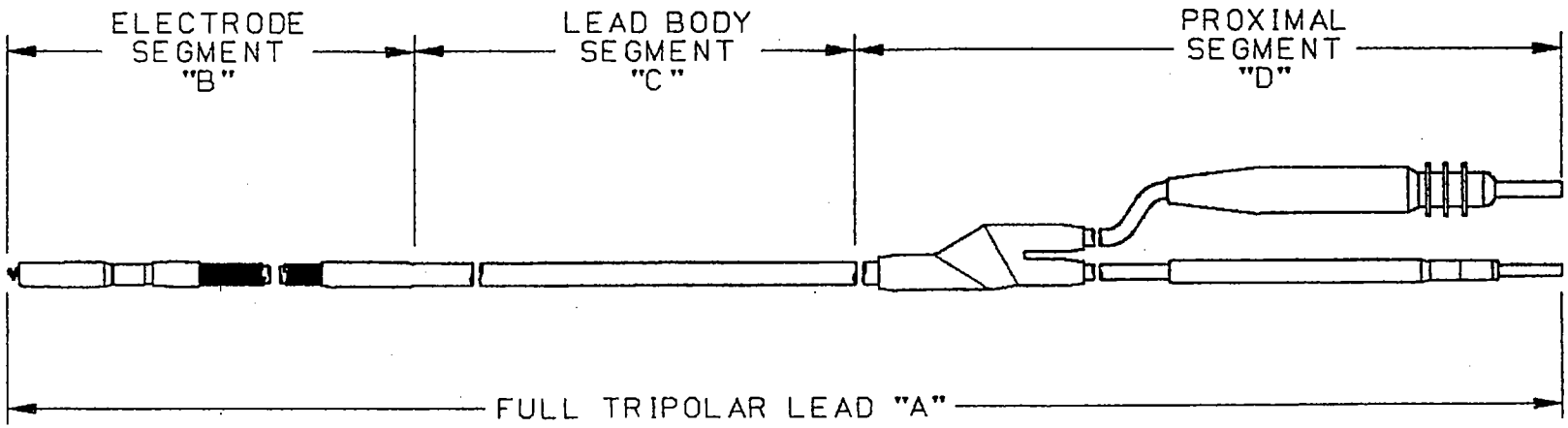
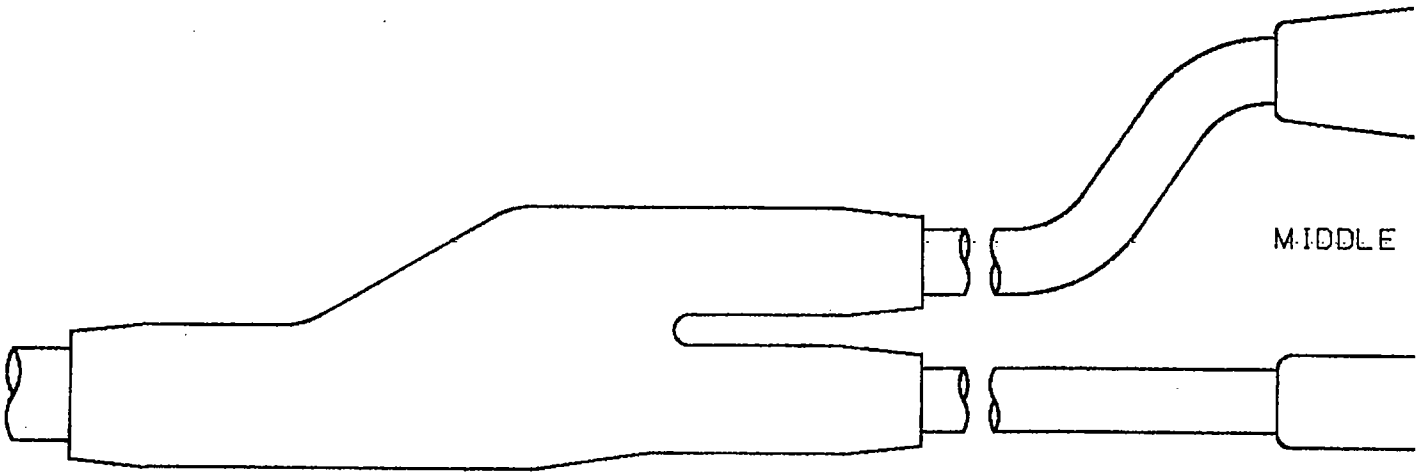
Part 1 - page 1446



ANCHORING SLEEVE(S) REMOVED FOR CLARITY

MODEL 6966 RIGHT VENTRICULAR LEAD

MEDTRONIC CONFIDENTIAL



M

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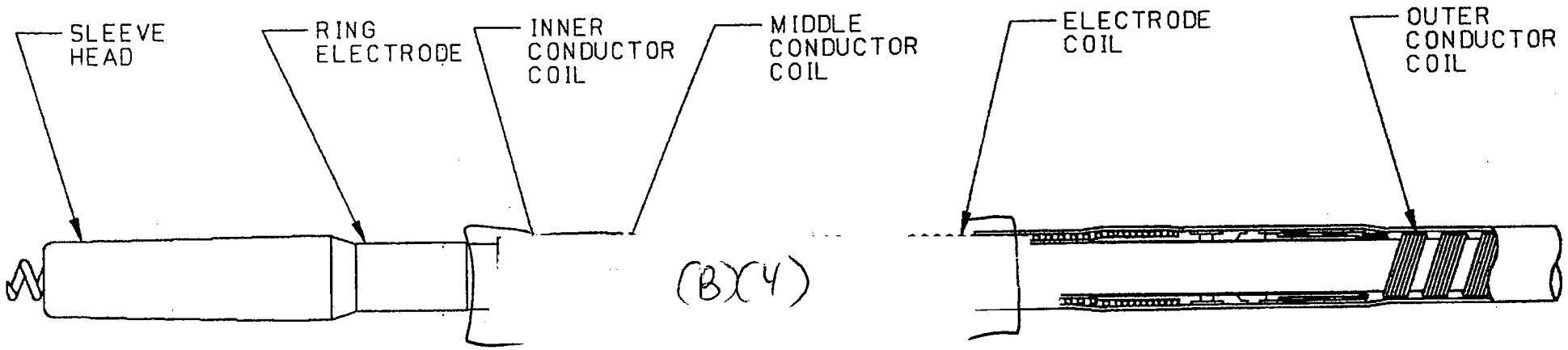
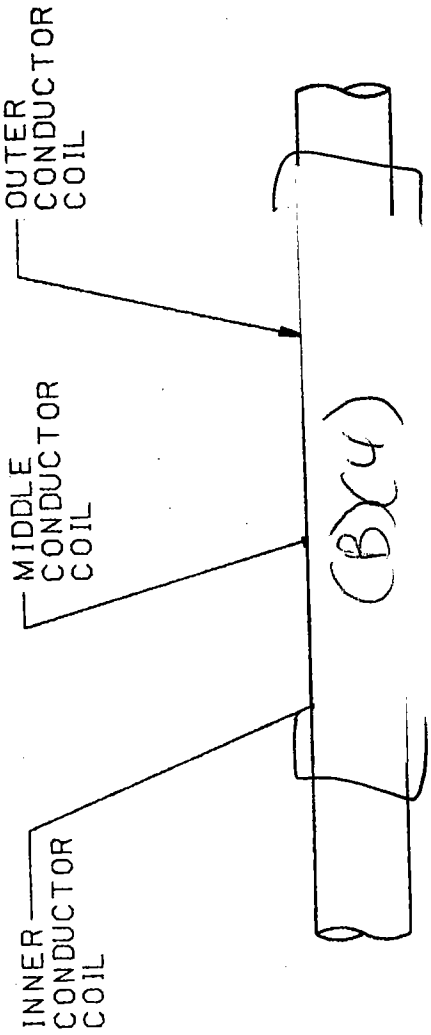


ELECTRODE SEGMENT "B"

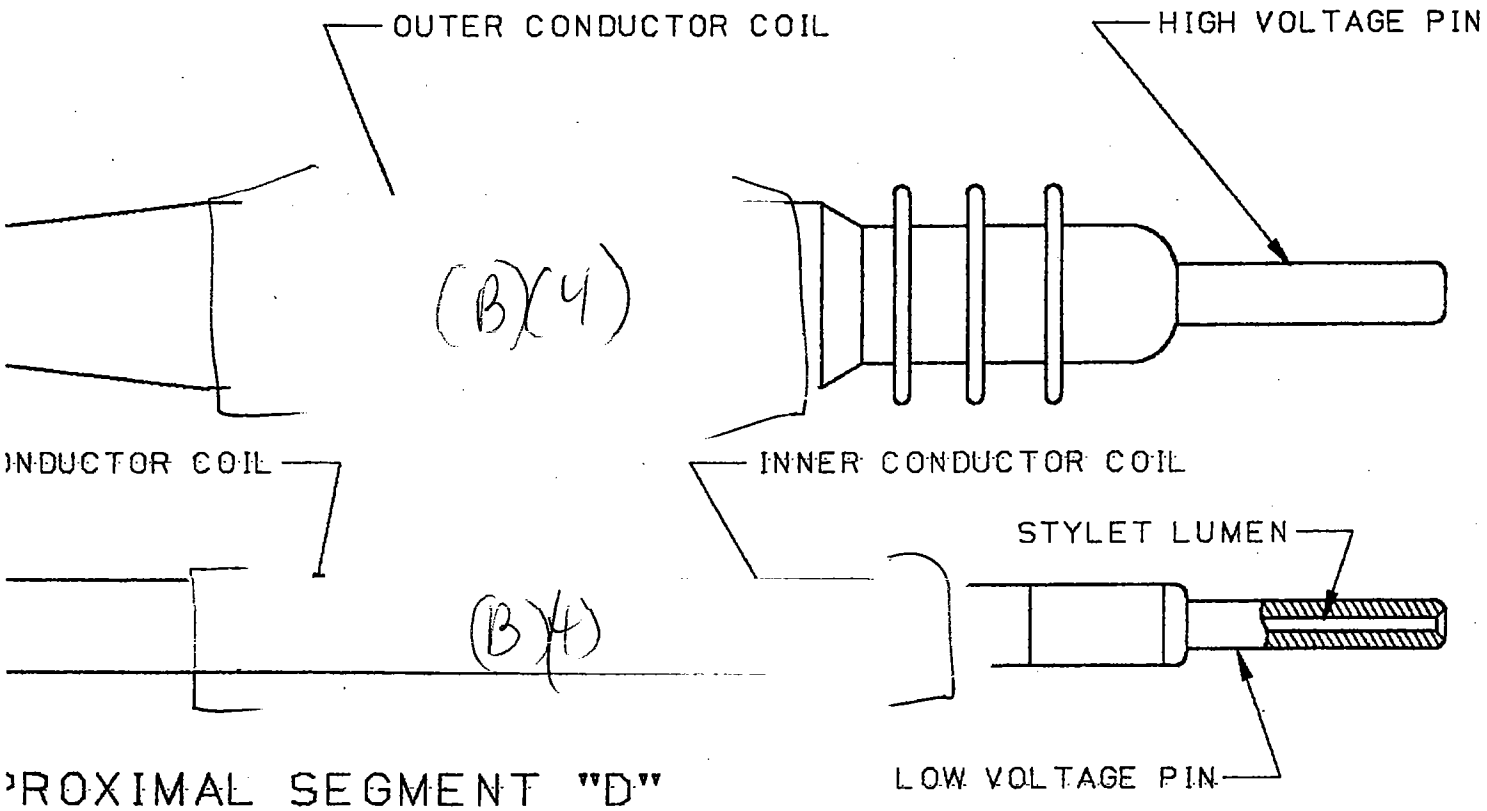
MODEL 6966 RIGHT VENTRICULAR LEAD

MEDTRONIC CONFIDENTIAL



LEAD BODY SEGMENT "C"

MODEL 6966 RIGHT VENTRICULAR LEAD



PROXIMAL SEGMENT "D"

DEL 6966 RIGHT VENTRICULAR LEAD

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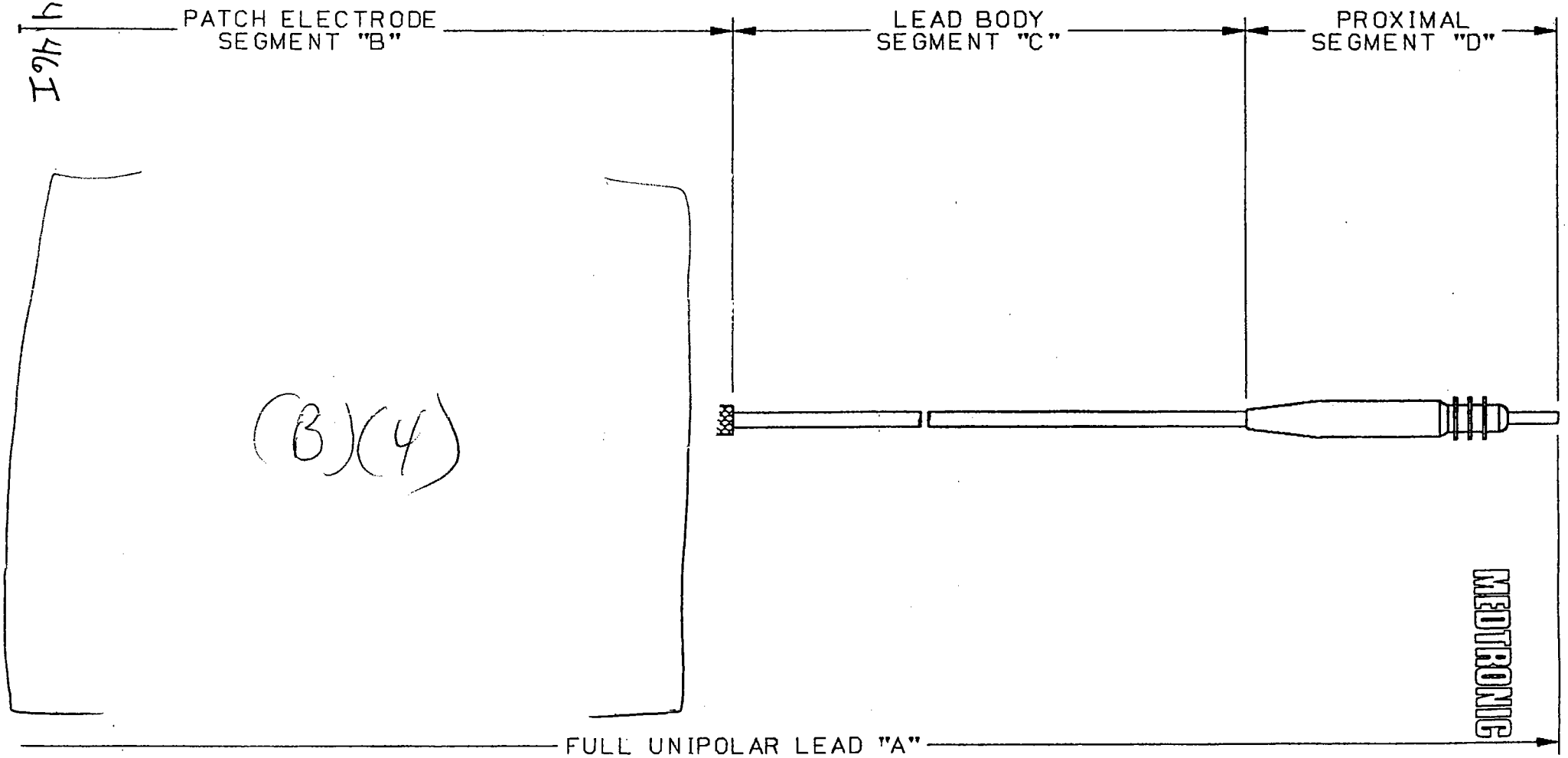
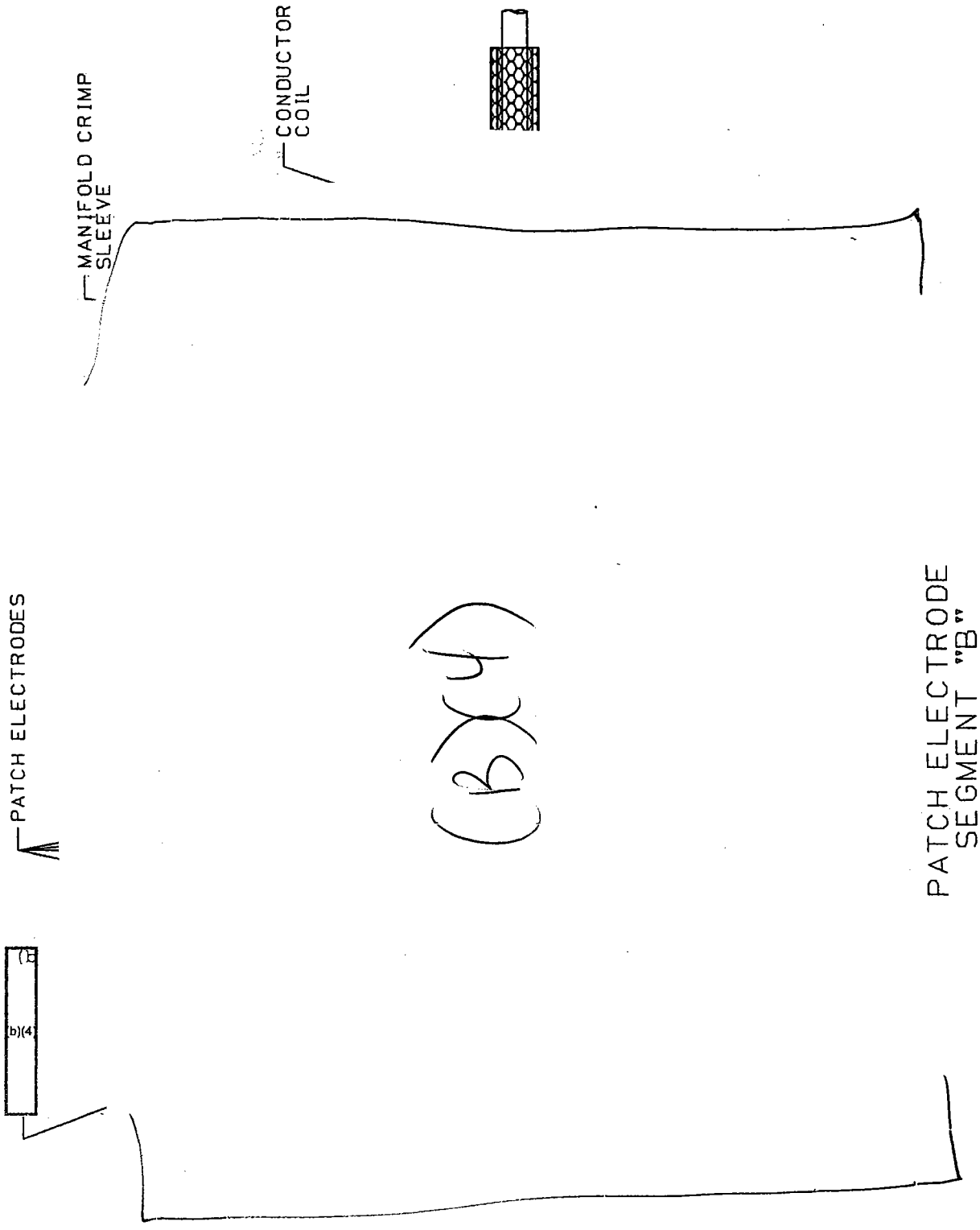


MODEL 6999 SUBCUTANEOUS PATCH LEAD

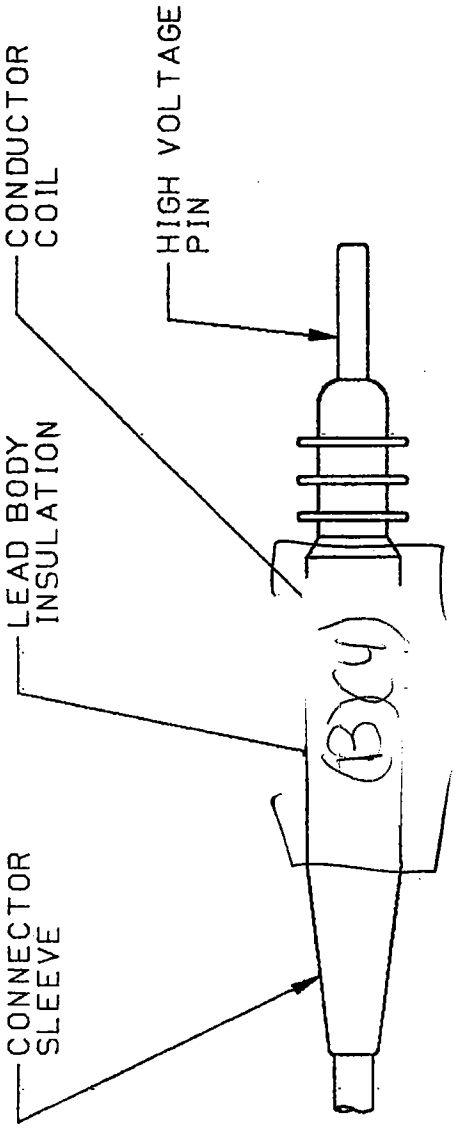
MEDTRONIC CONFIDENTIAL



MODEL 6999 SUBCUTANEOUS PATCH LEAD

(b)(4)

MODEL 6999 SUBCUTANEOUS PATCH LEAD



MODEL 6999 SUBCUTANEOUS PATCH LEAD

35. Since flex testing exerts a considerable amount of stress on the lead, and is essential to life testing, why was it considered that (b)(4) cycles at a bend radius of (b)(4) inch per lead model over a 12 month period would be sufficient? Describe how the full lead and different segments were flexed. Did you do a finite element stress analysis to validate the flex testing stress?

RESPONSE:

Flex testing is considered an important factor in assessing lead flex life longevity. The Medtronic flex standard minimum requirement is a B50 (median) of (b)(4) cycles at a (b)(4) inch radius. This flex standard was applied to the design of the one (1) year Lead System Test sequence. Initially each lead was inspected and tested for DC resistance. In the one (1) year test protocol, each lead went through the following sequence of tests eight (8) times:

Flex Testing at Room Temperature
Lead Body (b)(4) cycles)
Defibrillation Electrode Body (b)(4) cycles)
(b)(4) Fluid Soak (b)(4)
Submerge b(4) in solution b(4)
High Energy Pulsing
(b)(4) Volt Shock (b)(4) shocks)
(b)(4) Fluid Soak (b)(4)
Submerge Entire Lead in solution b(4)

By repeating the sequence of testing outlined above, each lead would receive:

Flex Testing
Lead Body (b)(4) cycles)
Defibrillation Electrode Body (b)(4) cycles)
(b)(4) Soak (b)(4)
Submerged Lead (b)(4)
High Energy Pulsing
(b)(4) Volt Shock (b)(4) shocks)
(b)(4) Soak (b)(4)
Submerged Lead (b)(4)

The lead body and the defibrillation electrode body were flexed at a (b)(4) inch radius. The Model 6999, unipolar, subcutaneous patch, received patch (defibrillation electrode) flexing in a fixture that is slightly different than the lead body flexing, because of the design of the subcutaneous patch. The patch is the region of the lead where the (b)(4) (b)(4) are imbedded.

At the end of the Lead System Testing, each lead was visually reinspected, had the DC resistance measured and intermittency tested. In conclusion, all the leads met all test requirements without failure and therefore demonstrate an acceptable assurance of safety and reliability in lead design.

Each lead had a section marked to identify were to flex the lead body. This was done to assure that each lead had the same section of the lead body flexed for each of [(B)(4)] test cycles. By assuring the same location, each lead body was subjected to a total of [(b)(4)] cycles of flexing. The marked section was in the same region identified as "Lead Body" in the answer to question 34 for each lead Model. The Lead Body flex test set-up is illustrated below:

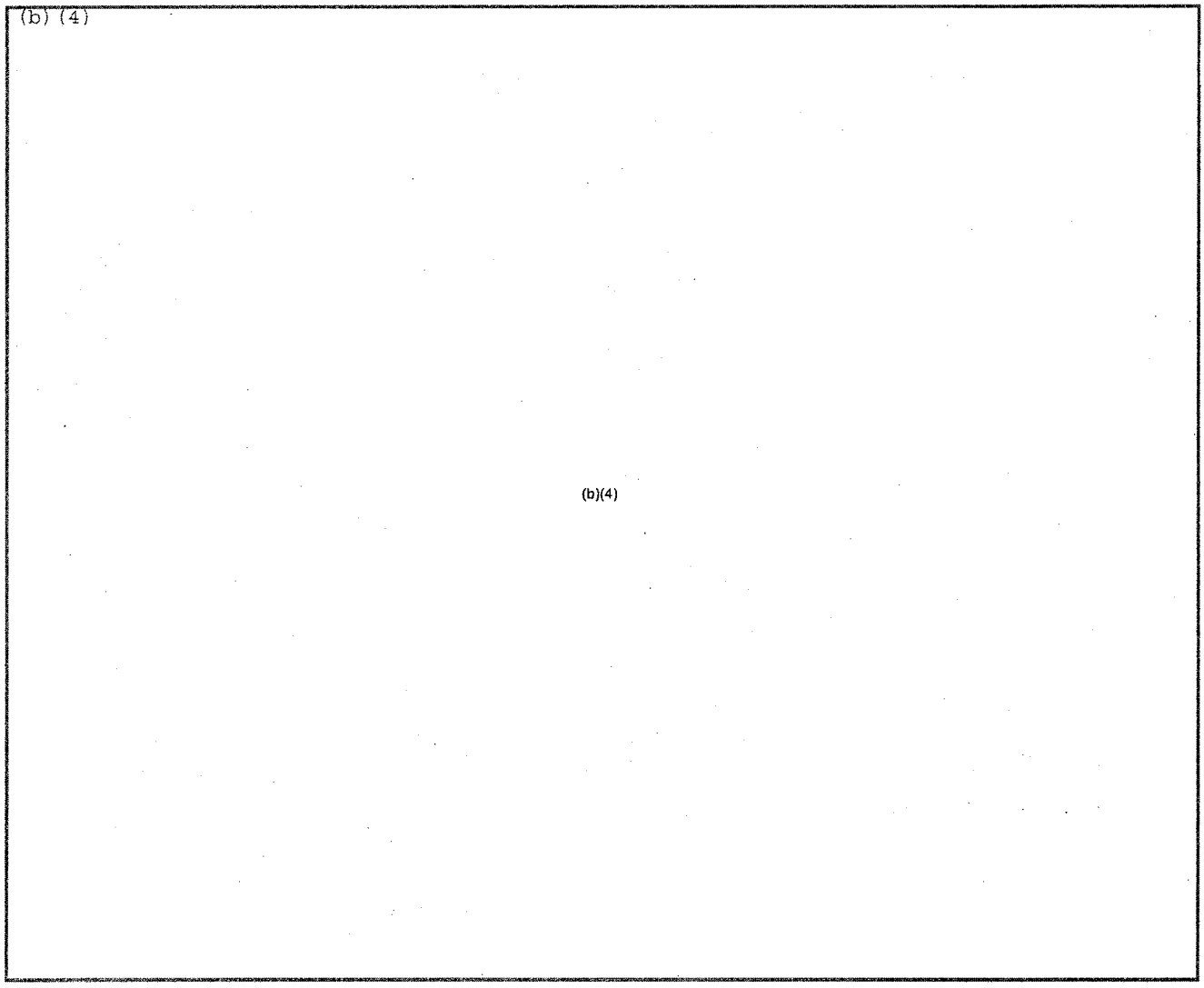
FLEX TEST FIXTURE

(b) (4)

(b)(4)

Each lead was flexed at the rate of (b)(4) cycles per minute over a radius of (b)(4) inch at room ambient temperature until reaching the required number of cycles per the Lead System Testing protocol.

The Model 6999, a unipolar, subcutaneous patch, was subjected to a flex test of the electrode region that could be a result of patient body motion. The patch flex set-up is illustrated below:



TEST FIXTURE FOR FLEX OF PATCH BODY

The design of the Lead System Testing protocol required that the leads remain intact throughout the entire test, therefore no leads were segmented during the test.

The flex testing stress (b)(4) (b)(4)

(b)(4)

(b)(4)

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36. In light of the failure of your platinum sputtered polyurethane bradycardia pacing leads, and since the Transvene™ lead Model 6966 is also a platinum sputtered polyurethane lead, please provide documentation regarding the failure mechanism of the pacing leads and all relevant information pertaining to these cases. How can we be assured that the failure may be restricted to the bradycardia pacing leads? Based on your testing to date regarding the pacing leads and the testing of the Model 6966 lead, discuss the potential and the probability of failure of the Model 6966 lead. A side by side comparison of the Model 6966 and the 4,000 series bradycardia pacing leads must be provided. The comparison must include material, design, dimensions, function, tests performed and a schematic drawing.

RESPONSE:

Background on Brady Pacing Lead Experiences

Medtronic utilizes two systems to monitor performance of its brady pacing leads. The analysis of returned product is used to identify lead failure mechanisms. However, it cannot be used to estimate clinical performance since all leads/lead segments are not explanted or returned. Clinical performance is monitored through our Chronic Lead Study (CLS), a multi-center study currently involving eleven representative U.S. Clinical centers and over 20,000 leads. Lead performance in the CLS is presented as actuarial survival from clinical complications resulting in lead explants or abandonment. Specific complication criteria have been established (reference Medtronic Product Performance Report, February 1993, in Appendix C). Since all leads are not explanted it is not always possible to relate a clinical complication to a specific failure mechanism and not all complications are associated with lead failure.

The primary failure mechanisms for brady pacing leads are conductor fracture and insulation failure. Conductor fractures are primarily associated with the widely accepted "Subclavian Stick" implant procedure using percutaneous lead introducers. Leads implanted by this procedure can be clamped and crushed between the first rib and clavicle, leading to fracture of the conductor, and sometimes, insulation failures as well. Bipolar leads are more susceptible to this failure mechanism than unipolar leads because of their larger lead body diameter. Crush fractures tend to occur primarily during the first two years post implant.

For leads with polyurethane insulation, the primary insulation failure mechanisms are Environmental Stress Cracking (ESC) and Metal Ion

Oxidation (MIO); both tend to occur starting about 2 years post implant. Bipolar leads tend to be more susceptible to insulation failure than unipolar leads.

ESC is associated with stress on the lead either induced during manufacture or via implant procedure. Newer generation Medtronic leads have greater ESC resistance due to improvements in design, manufacturing processes and materials.

MIO is an oxidative degradation of polyurethane insulation. The reaction is catalyzed by metal ions released by the corrosion of the conductor coils. To reduce the potential for MIO, newer Medtronic lead designs have applied a sputtered coating of platinum to the conductor coils. Also, (b)(4) polyurethane tends to be more resistant to MIO than (b)(4) Medtronic has used an accelerated oxidation environment, (b) (4)(b)(4) to evaluate MIO and potential factors that can minimize its occurrence.

A table depicting the frequency of these failure mechanisms (conductor fractures, MIO and ESC) for brady leads, Models 4004/M and 4058/M, follows this response. As shown, conductor fracture due to crush is the predominate failure mode. See table, Failure Mechanisms, following this response.

The Model 4004/M is a bipolar lead incorporating (b)(4) polyurethane and platinum coating. As of February 28, 1993, survival probability of the Models 4004/4004M is 97.0 ± 1.7% at 36 months (reference the February 1993 Product Performance Report in Appendix C). Crush fracture is the primary source of lead failures to date, with rates comparable to that of earlier bipolar lead designs.

Over the past several months Medtronic and FDA have had numerous discussions about the occurrences of failure associated with MIO in the Model 4004/M lead. As of February 28, 1993, Returned Product Analyses has identified 22 MIO failures out of approximately 74,000 leads implanted (.030%). MIO failures in previous lead designs tend to predominate in 3 areas: proximally in the pacemaker pocket, medially in the clavicular region, and distally near the ring electrode. With Models 4004/M, platinum sputter coating appears to reduce the occurrence of MIO proximally and medially. The majority of the MIO failures (20 of 22) occurred distally. Distal failure occurs between the ring electrode and the AV valve and appear to be related to flexing of the lead associated with ventricular contractions.

Initial Solution A testing was conducted under static conditions and gave no indication of this failure mechanism. Currently testing is underway to develop a dynamic Solution A test to study factors affecting this

failure mechanism and potential corrective actions. To date, we have been able to induce failures and are conducting experiments to understand contributing factors.

In order to illustrate the similarities and differences between the brady and tachy leads, a side-by-side comparison of the Model 6966 to the 4,000 series brady leads is presented in a table following this response. Note that only bipolar, polyurethane, brady leads from the 4,000 series are presented (includes Models 4016A, 4058/M, 4024, 4004/M and 4012/4082). This is due to their similarity of design characteristics to the 6966, and also because these brady leads are being, or were, widely used in the field, and therefore present with comprehensive data from the Chronic Lead Study and Medtronic's returned product analysis. Tests performed to qualify the brady leads were the same as those used for the tachy leads (except for high voltage system and crush testing). All tests are consistent with Medtronic standards and requirements for implantable cardiac leads (reference response to #34). Drawings of these brady leads are also presented following the comparative tables.

Some common features to all the leads in the table are the [redacted] conductor coil, coaxial coil design, polyurethane insulation [redacted] and/or [redacted] and platinum alloy electrode material. Like the 6966 lead, the Models 4016A, 4058/M and 4024 also have platinum coating on the conductor coil and [redacted] as the inner insulation. Individual lead differences include the electrode fixation mechanisms, i.e., screw-in helix versus tines and the [redacted] versus [redacted] insulation usage. Using [redacted] insulation provides more stiffness, and greater resistance to insulation failure, whereas [redacted] provides for greater ease of handling.

As presented in the lead comparison table, the brady lead most similar to the 6966 lead is the 4016A. Both have [redacted] polyurethane as the inner(most) insulation, [redacted] for the middle/outer insulations, distal screw-in fixation mechanisms, similar French (introduction) sizes and virtually identical insulation dimensions. Only the coil dimensions vary slightly. Note that the 4058/M lead is also very similar to the 4016A; the only substantive change is the introduction size, 9 French. Model 4016A and 4058/M leads have shown excellent clinical performance; for the 4016A actuarial survival is 98.2% at three years (3,800 implants) and for the 4058/M actuarial survival is 99.7% at three years (37,000 implants), reference the CLS and returned product analysis as presented in the Medtronic Product Performance Report, Appendix C.

As previously presented, the 6966 lead has a larger body diameter than the brady leads. This is to be expected given the tripolar coaxial design of the lead. Given the larger French size of the 6966, it is more susceptible to crush between the clavicle and rib than the smaller French

leads. Lead fracture due to crush in this area is, however, a recognized failure mechanism for all transvenous leads implanted via subclavian insertion, (brady or tachy leads). This is vigorously addressed in product labeling (lead technical manuals) and includes appropriate cautions about the use of the procedure.

Also, the larger diameter of the 6966 lead body and presence of a defibrillation coil electrode proximal to the distal pace/sense ring of the 6966 lead imparts more stiffness to it than the brady leads. Hence, there is less lead body movement below the valve when the 6966 is implanted in the right ventricle as compared to a brady lead. This was clearly evident in the videotape comparing the in-vivo flexing of both a brady and tachy lead (presented in FDA/Medtronic meeting of February 18, 1993). Decreased flexing of the 6966 lead below the valve is our basis for expecting flex-related MIO will not be a significant failure mechanism of the 6966 lead.

Analysis of Transvene Model 6966 Lead and Clinical Presentation

The Model 6966 tripolar tachy lead is comparatively less flexible than brady leads. Therefore, distal MIO as evident in a very small percent (.030%) of brady 4004/4004M leads is not necessarily indicative of a similar occurrence in the 6966 lead. A videotape illustrating the clinical flex performance differences between brady and tachy leads was presented during the FDA/Medtronic meeting on February 18.

Analysis of the Model 6966 lead, as it relates to the potential for MIO, indicates that it would be more likely to occur on the middle versus the outer or innermost insulations. Lead failure due to MIO typically is found on the inner insulation on returned bipolar brady leads. Therefore, this failure mechanism is not expected to significantly affect the (b)(4) outer insulation of the 6966 lead. Should MIO occur on the outer insulation of the 6966 lead, the net effect would be an increased defibrillation electrode surface area. This would not be expected to significantly affect system performance. Additionally, the more resistant properties of (b)(4) (to MIO), of the 6966 innermost insulation, are expected to further reduce the potential for MIO (99.7% survival Model 4058/M at three years, see Product Performance Report, Appendix C).

For the Model 6966 lead, should the middle, (b)(4) insulation fail, it would likely present initially as an intermittent short (as is more typical with brady leads) and can progress over time if not identified and treated, to a hard (direct) short. These could manifest initially as oversensing, and ultimately as integrated bipolar sensing, respectively (intermittent versus hard short). In the case of a hard short of the middle insulation, specifically, shorting the pacing tip to the common

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defibrillation electrode, an integrated bipolar sensing system is created. In this type of system, sensing occurs between the unipolar pacing tip and the common defibrillation electrode (versus standard bipolar sensing between the pace/sense tip and the ring electrodes). This type of sensing system is identical to the (b)(4) (b)(4) currently in clinical trials, and also to Medtronic's historic Transvene RV lead, the Model SP2100 lead. These type of integrated systems have been shown to be clinically acceptable. Note that fifteen Model SP2100 leads were implanted at the start of the Transvene clinical study. There have been no observations or reported problems related to the SP2100 lead performance. (Data from the SP2100 lead have been incorporated in the clinical experience analysis reported in this PMA application.)

Intermittent sensing could result in oversensing, if the detection criteria are also met, and this could result in delivery of inappropriate, i.e., not needed, therapies. This can be considered a "safe failure" given the system would "err" by oversensing (versus undersensing) and the patient could receive an unnecessary therapy. Also, patients are instructed to report therapies to their physicians; this facilitates identification of any inappropriate therapy.

Recently, a Model 6884[1] lead was explanted after 27 months when the patient received a heart transplant. The lead was fully functional at explant, however, returned product analysis has indicated the presence of some MIO in the clavicular region. Transvene leads, like brady leads, are implanted by subclavian insertion and are susceptible to being crushed between the clavicle and first rib. As indicated above, with brady leads this can result in conductor fractures, insulation failures or both. Analysis of the specific Model 6884 lead is ongoing and a more detailed report will be provided in approximately 30 days.

It should be noted that MIO is only one potential failure mechanism of implantable leads. As discussed, others include fracture due to crush in the area of subclavian insertion, environmental stress cracking due to stresses the in-vivo environment may impart to the lead and lead dislodgement.

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[1] The Model 6884 lead is the earlier version of the Model 6966 lead and differs only in the connector pin configuration; the 6884 has a (b)(4) high voltage connector pin and the 6966 has a (b)(4) high voltage connector pin. Otherwise the leads are the same.

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Transvene Clinical Assessment Experience

Given over 2000 worldwide Transvene patients implanted to date, ranging from zero to forty months implant duration, there have been no reports of undersensing, insulation failures, or oversensing that could not be managed via reprogramming. Furthermore, the benefits of Transvene implantation are dramatically apparent from the perspective of perioperative mortality, 0.7 percent for Transvene versus 5.3 percent for epicardial implants. Transvene survival from SCD is 99.5 percent and overall survival is 93.3 percent at one year. Additionally, Transvene implants, on average, require 8 days in hospital versus 11 days for an epicardial system; a significant cost savings. In summary, the benefits of the Transvene system performance clearly surpass the potential for MIO, or other potential failure mechanisms, in the 6966 lead.

Conclusions

Although Medtronic cannot assure that MIO or other lead failure mechanisms will not occur in the Model 6966 lead, the actual benefits of the Transvene system, as previously discussed, would appear to exceed the potential risk due to MIO. Analysis shows that the potential for MIO to occur in the 6966 lead would result in a "safe failure." Note that preclinical and animal testing cannot completely simulate the long-term implant environment, thereby eliminating all potential for lead failures in-vivo. This was recognized by Congress in implementing the Postmarket surveillance provision in the Safe Medical Device Act of 1990. It is clear that postmarket surveillance mechanisms, e.g., returned product analysis and chronic lead monitoring, are more appropriate mechanisms for evaluating and managing potential failure mechanisms of implantable cardiac leads.

FAILURE MECHANISMS

(CLINICAL/ELECTRICAL FAILURES FROM RETURN PRODUCT ANALYSIS)

MECHANISM	MODEL 4004/4004M	MODEL 4058/4058M
(b)(4)	(b)(4)	

TACHY/BRADY LEAD COMPARISON

Parameter	Model 6966	Model 4016A	Model 4058/M1
(b)(4)			

(b)(4)

TACHY/BRADY LEAD COMPARISON (CONTINUED)

Parameter	Model 4024	Model 4004/M[1]	Model 4012/4082[1]
(b)(4)			

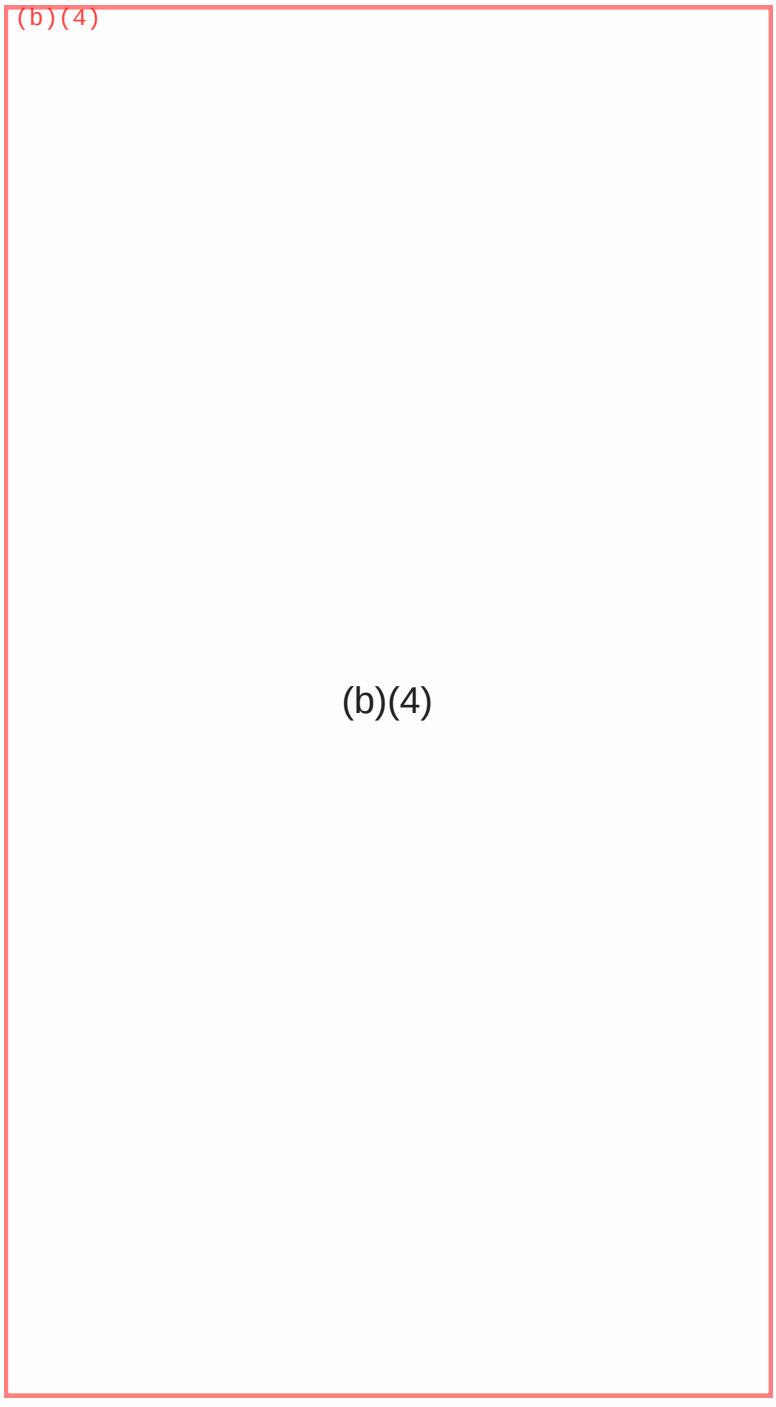
(b)(4)

(b)(4)

(b)(4)

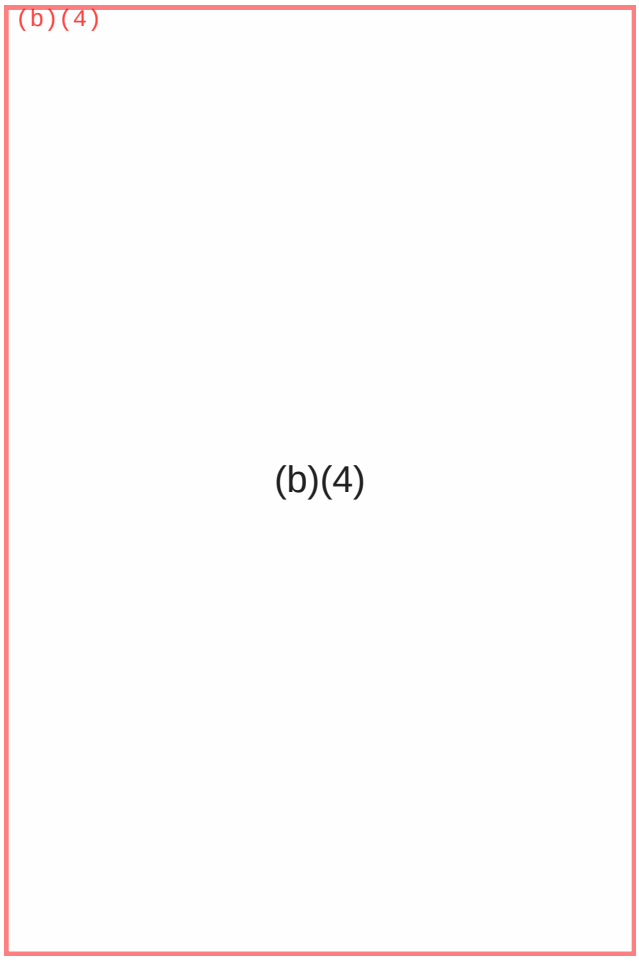
MODEL 4016A

(b)(4)



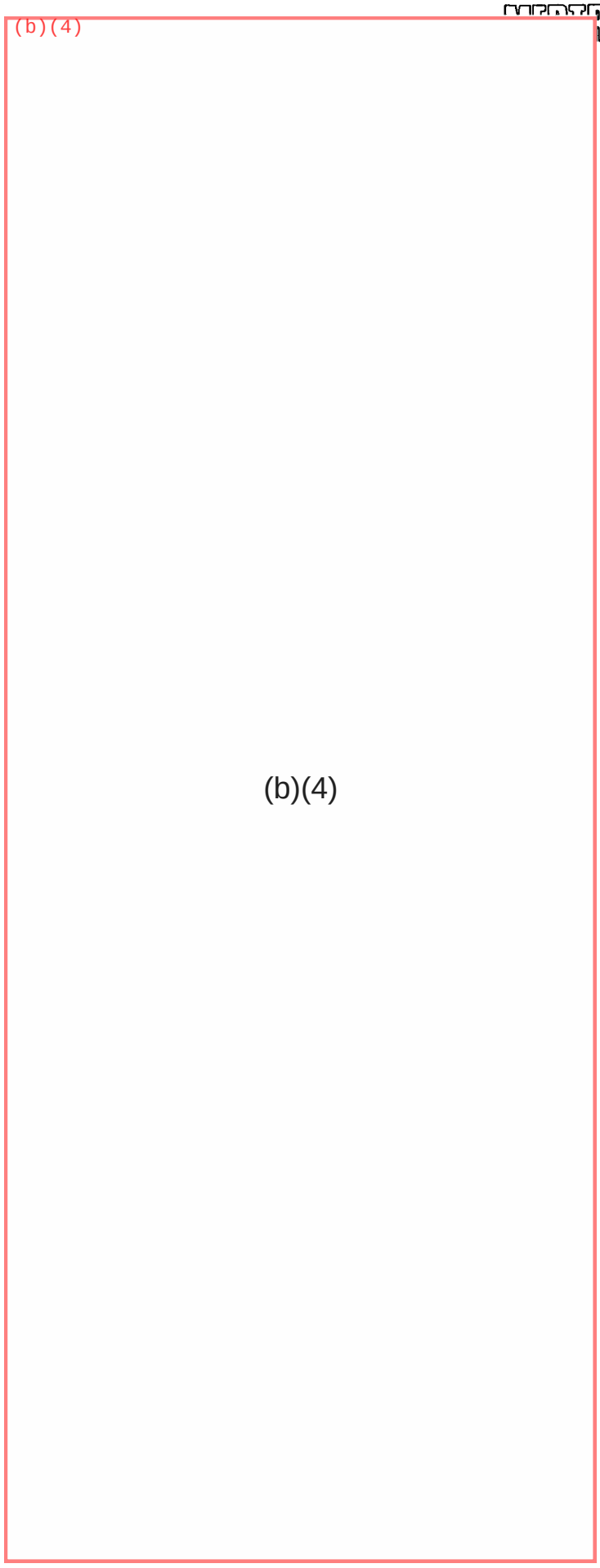
MODEL 4016A

(b)(4)



MODEL 4016A

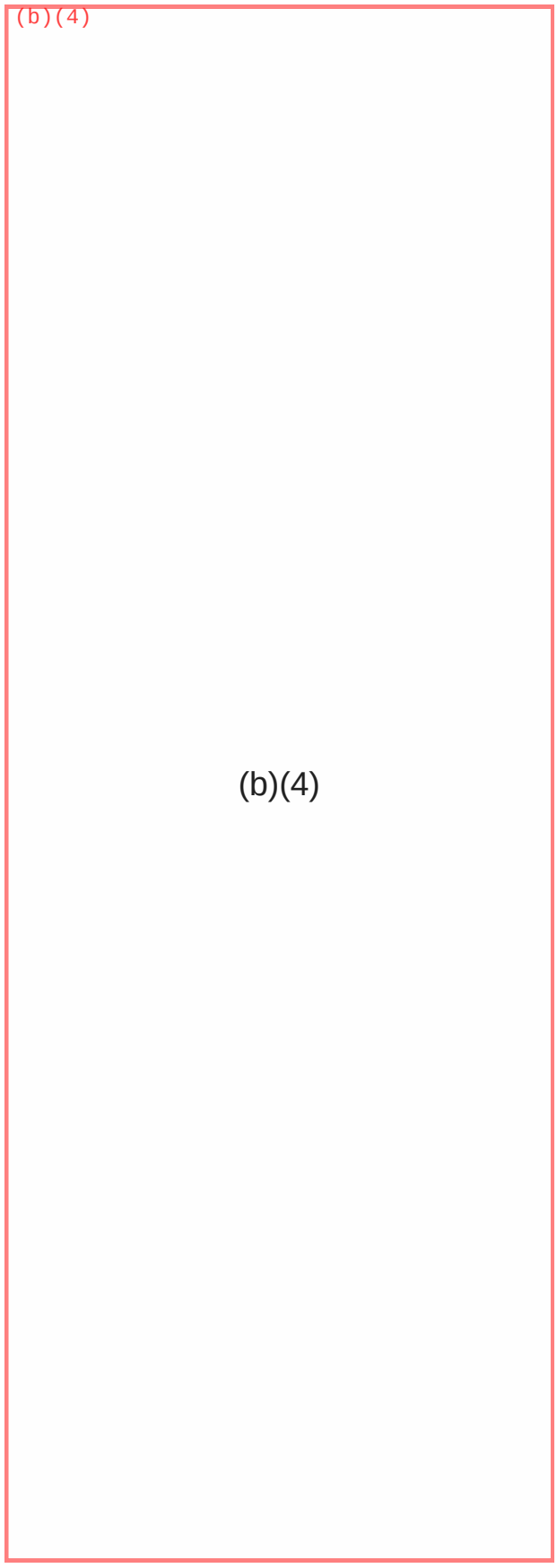
(b)(4)



MODEL 4016A

250

(b)(4)



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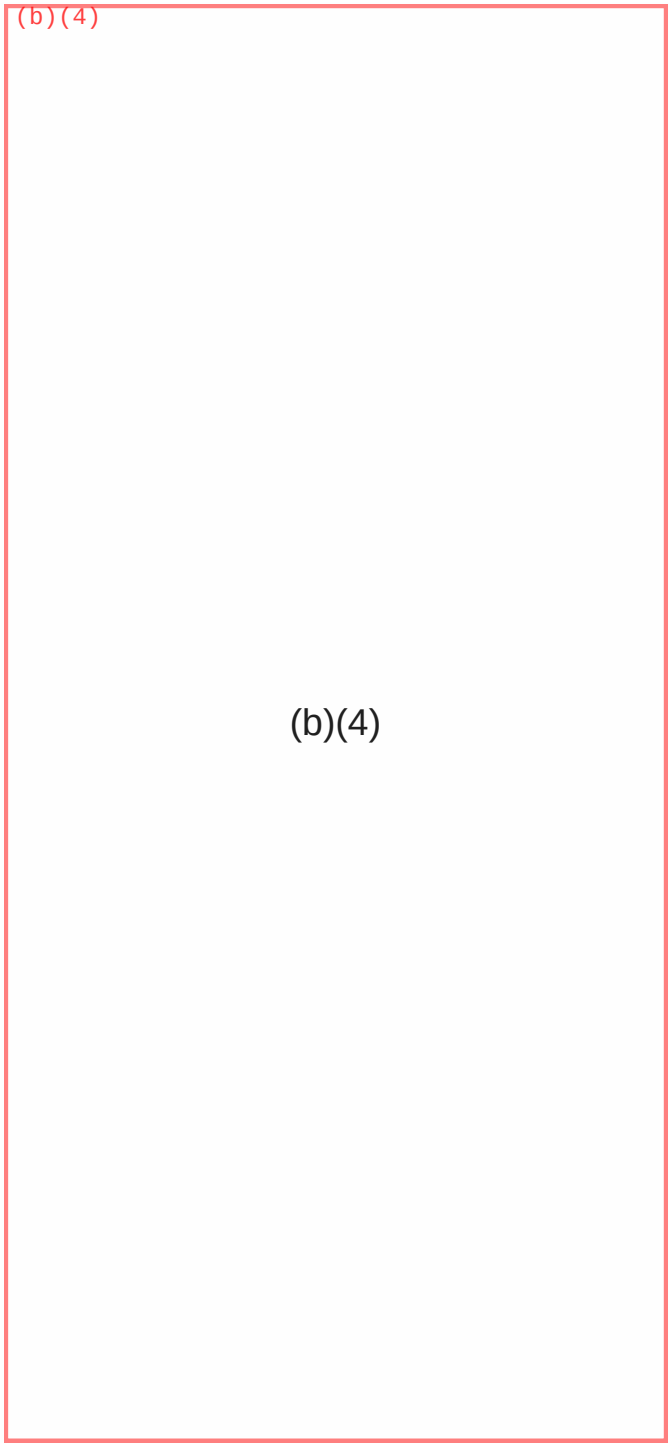
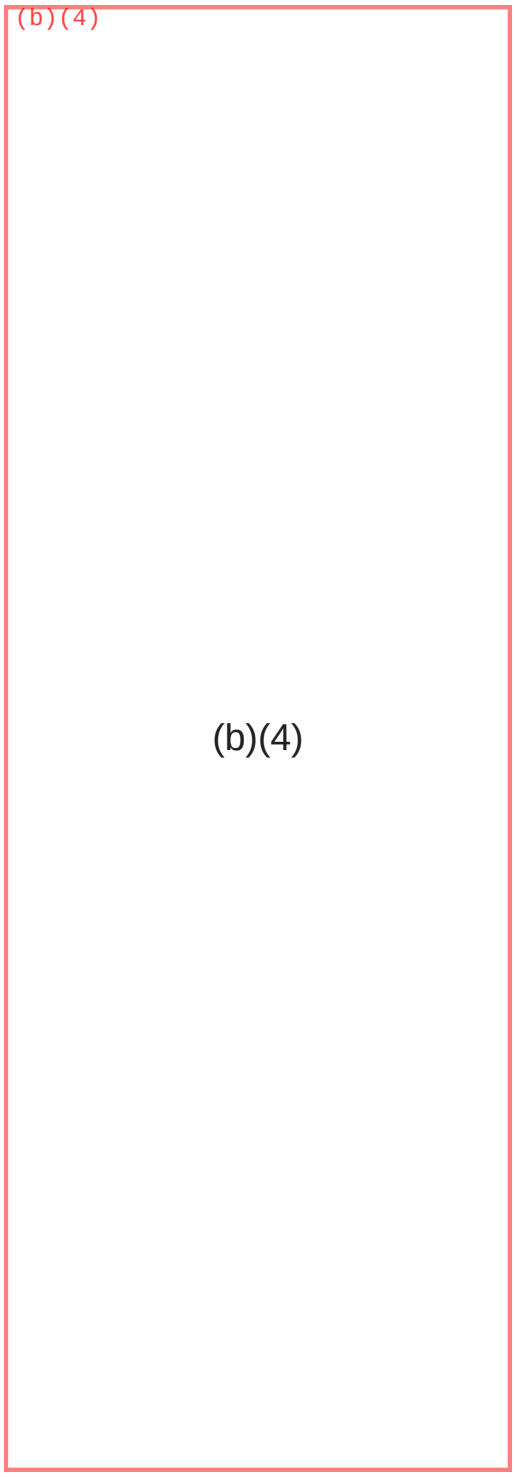


MODEL 4058/M

(b)(4)



B

(b)(4)

(b)(4)

MODEL 4058/M

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(b)(4)

(b)(4)

MODEL 4024

ASSEMBLY

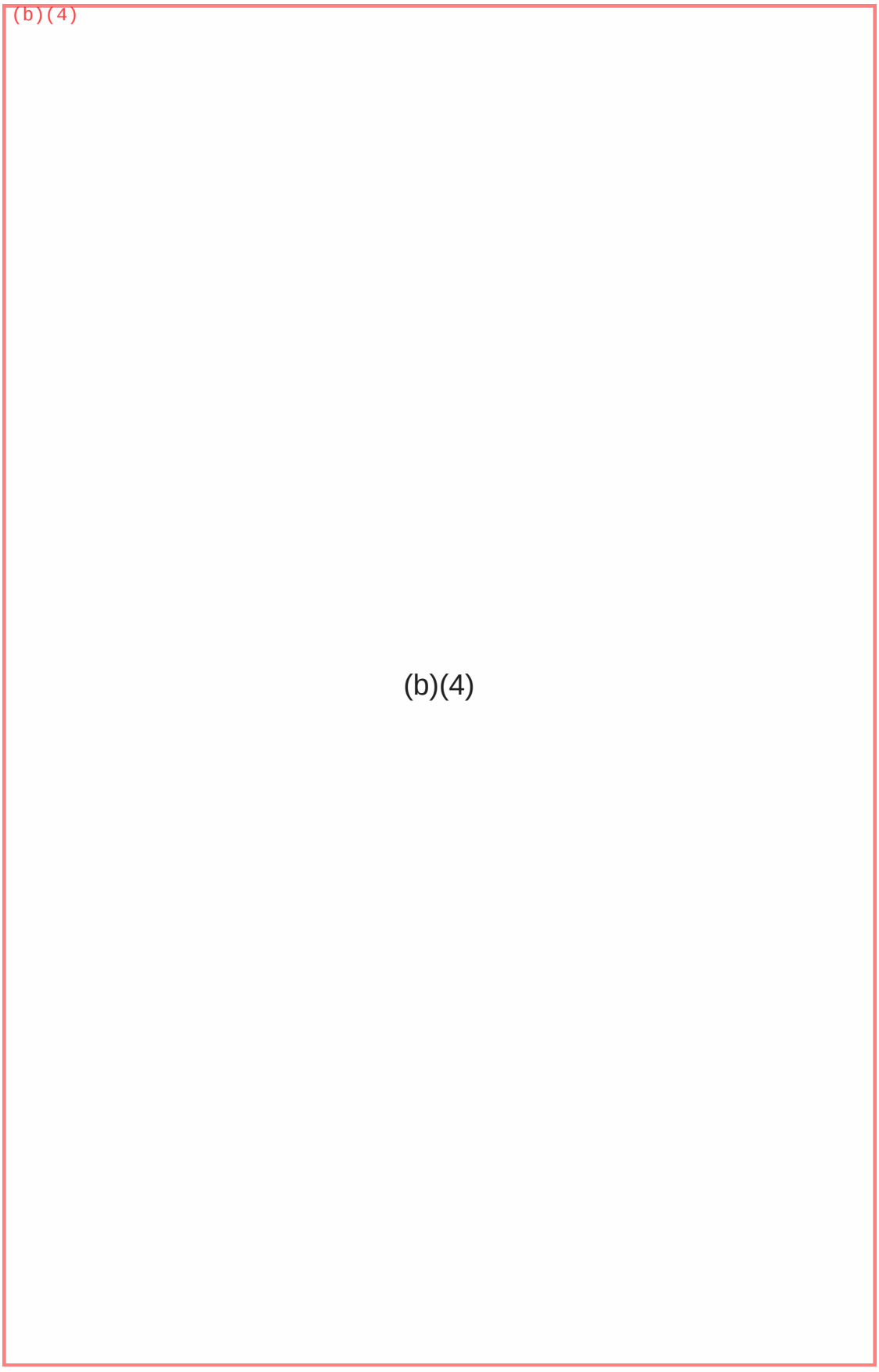
(b)(4)

(b)(4)

MODEL 4024

TIP AND CONNECTOR ASSEMBLIES

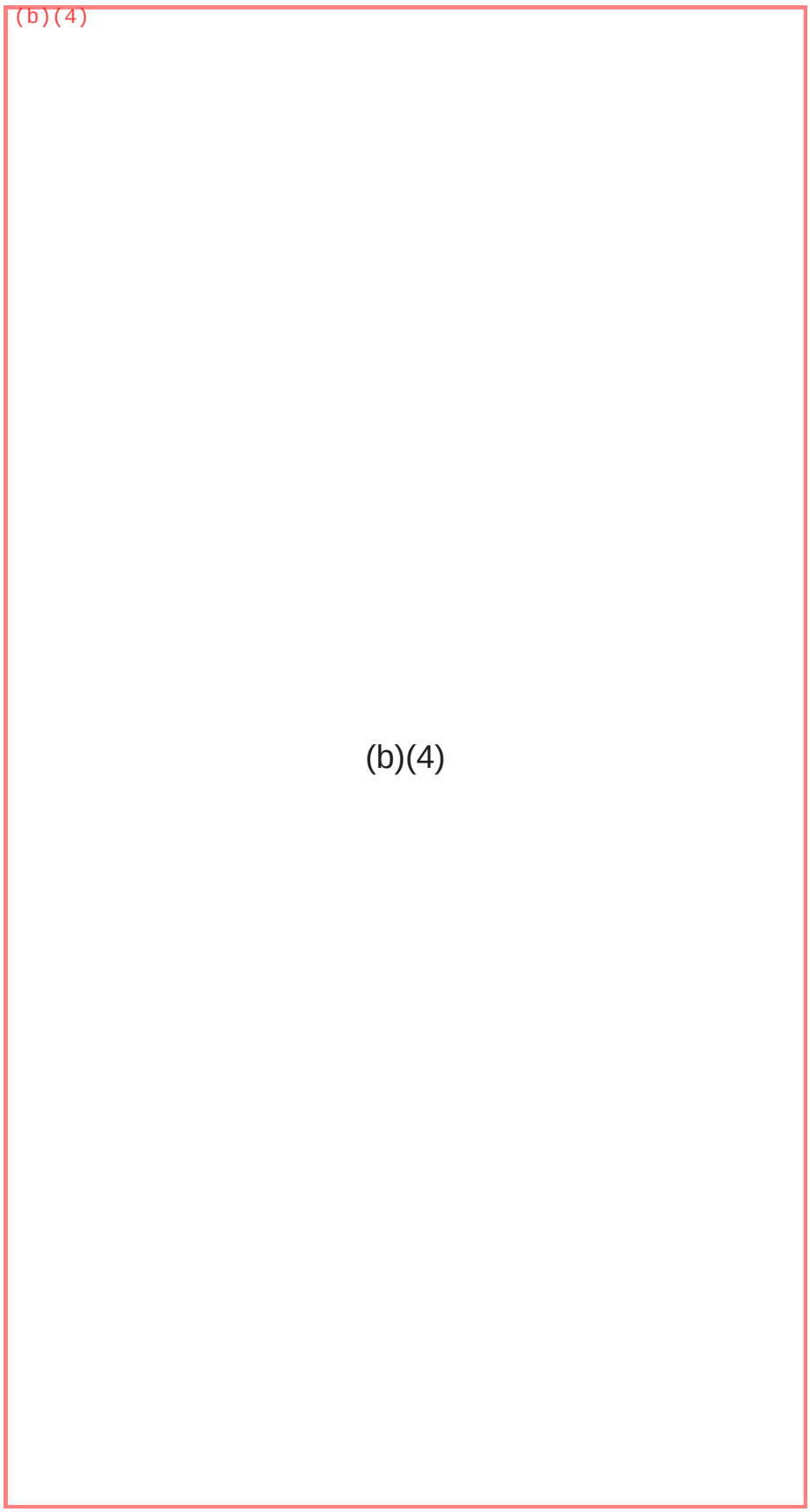
(b)(4)



MODEL 4004M

CONNECTOR ASSEMBLY

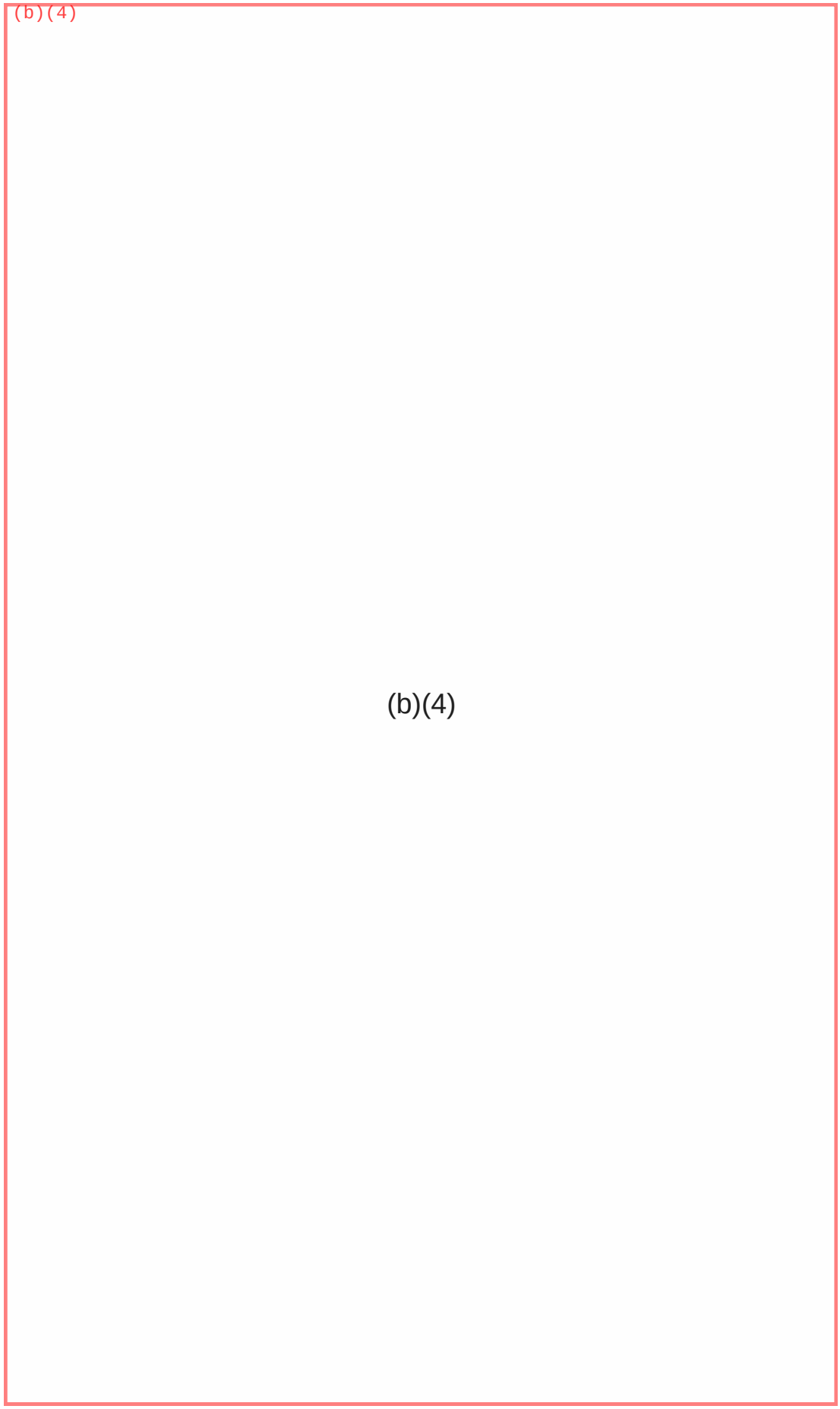
(b)(4)



MODEL 4004M

DISTAL ASSEMBLY

(b)(4)



MODEL 4082

CONNECTOR ASSEMBLY

37. **A copy of the Summary of Safety and Effectiveness which includes the updated data must be provided.**

RESPONSE:

See Attachment 3.

3

Summary of Safety and Effectiveness (March 26, 1993)

A. Indications For Use

The Medtronic PCD Model 7217B Multiprogrammable Tachyarrhythmia Control System with Nonthoracotomy Cardioversion and Defibrillation Electrodes (hereafter referred to as the PCD Transvene System) is intended to treat patients at risk of sudden cardiac death due to ventricular tachyarrhythmias. Indications for use include:

- Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or
- Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.
- Patients undergoing replacement of a previously implanted implantable cardioverter defibrillator.

The patients who meet the above patient selection criteria should have also undergone a complete cardiological evaluation that includes electrophysiological testing. Electrophysiologic evaluation and testing of the safety and efficacy of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the PCD Transvene System.

The PCD Transvene System components, except for the defibrillation lead system, are identical to the PCD Epicardial System which was unanimously recommended for approval by the FDA Advisory Panel on February 3, 1992 and FDA approved on February 11, 1993.

Market approval is not being sought for use of the PCD Device with other manufacturers transvenous defibrillation lead systems. In addition, market approval is not being sought for the use of the PCD Transvene lead system with other manufacturers implantable cardioverter defibrillators.

B. Description of the Transvene Lead/PCD System

The Medtronic Tachyarrhythmia Control System consists of two fundamental configurations: (1) the implantable configuration and (2) the external configuration. Both configurations use the Transvene lead system. See Figure III B-1

The implantable configuration is composed of a Pacer-Cardioverter-Defibrillator (PCD) device, implantable leads, and a programmer. The PCD device is an implantable, multiprogrammable, automatic tachyarrhythmia control device.

The external configuration is composed of an External Tachyarrhythmia Control Device (ETCD), a patient cable, implantable leads, and a programmer. The ETCD is an externally-operated, multiprogrammable, tachyarrhythmia control device.

Intended Uses - Transvene Leads

Model 6963 Lead

The Medtronic Transvene Model 6963 Unipolar, Coronary Sinus or Superior Vena Cava, Transvenous Lead features an electrode for the delivery of cardioversion and defibrillation therapies. It is intended for long-term use in the coronary sinus or superior vena cava and is designed to be used with an implantable tachyarrhythmia control device along with at least one other lead, such as the Model 6966 Tripolar, Right Ventricular, Transvenous Lead.

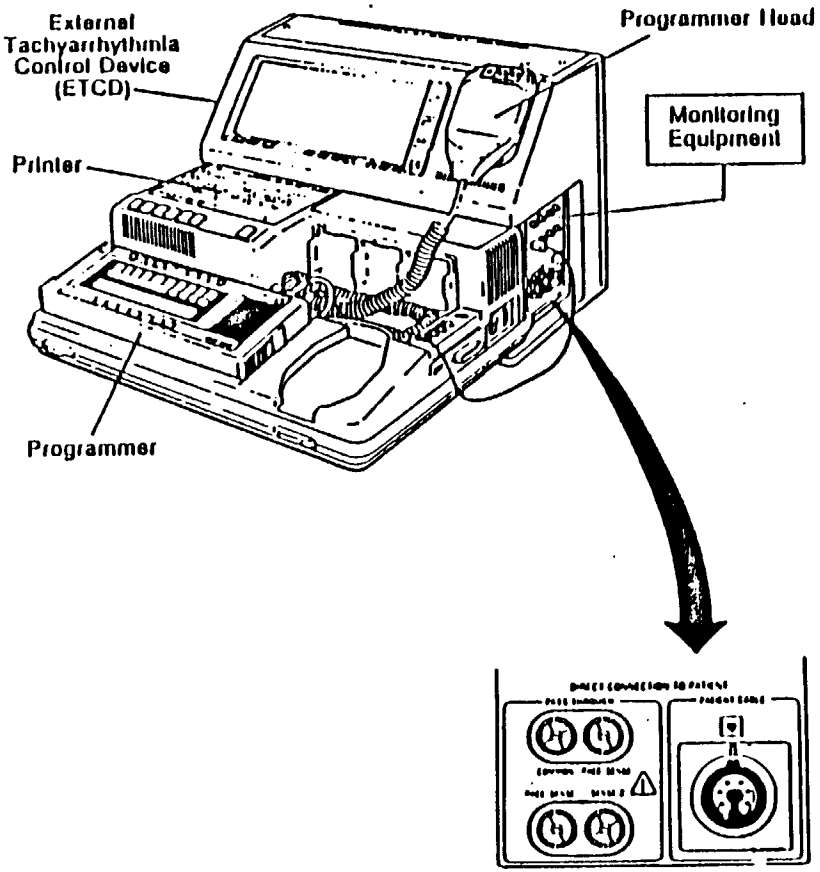
The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

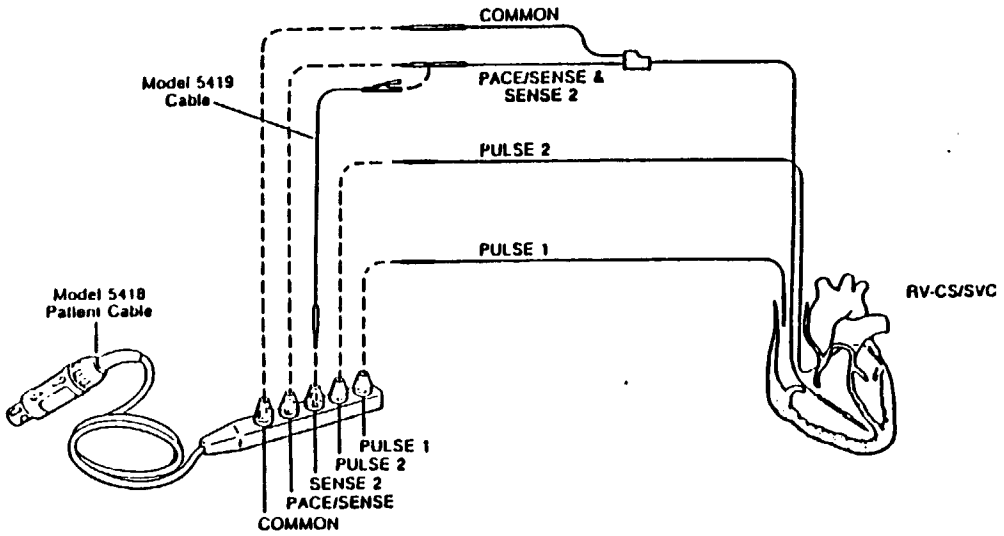
Model 6966 Lead

The Medtronic Transvene Model 6966 Tripolar, Endocardial, Screw-In Lead is designed for pacing, sensing, and delivering cardioversion and defibrillation pulses in the ventricle. The lead has application where implantable tachyarrhythmia control systems are indicated.

The Model 6966 lead has a helical electrode made of platinum alloy that can be actively fixed in the endocardium. The helix can be extended or retracted by rotating the lead connector pin with a special fixation tool.

Active fixation leads are particularly beneficial for patients who have smooth or hypertrophic hearts where lead dislodgement may be potential a problem.





Connections to Model 5418 Patient Cable for
Typical Simultaneous or Sequential Pathway (RV-CS/SVC).

FIGURE III B-1

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The three electrodes of this lead are the coil, ring, and helix:

The **defibrillating coil electrode** is most proximal to the pulse generator and connects electrically to the connector pin of the unipolar leg of the bifurcation. This unipolar leg will not accept a stylet.

The **ring electrode** is proximal to the helix and connects electrically to the connector ring of the bipolar leg of the bifurcation.

The **helix tip electrode** is most distal to the pulse generator and provides active fixation in the endocardium. It can be extended or retracted by rotating the lead connector pin with a special fixation tool. The helix electrode connects electrically to the connector PIN of the bipolar leg of the bifurcation. This bipolar leg is the only one that will accept a stylet.

The helix tip electrode and the ring electrode may be used for bipolar pacing and sensing; the coil electrode is intended to be used for delivery of cardioversion and defibrillation pulses.

The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

Model 6999 Lead

The Medtronic Model 6999 Unipolar, Subcutaneous, Oval, Patch Lead features an electrode for the delivery of cardioversion and defibrillation therapies. It is intended for long-term use and is designed to be used with an implantable tachyarrhythmia control device along with at least one complementary defibrillating electrode and a pacing/sensing lead; a third defibrillating electrode may also be used.

The lead has application for patients in whom implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

Intended Uses - PCD Device

The Model 7217B PCD device is intended for use in patients who are at high risk of sudden death due to ventricular tachyarrhythmia.

Current medical research indicates that such patients should:

- have survived at least one episode of a cardiac arrest, presumably due to a ventricular tachyarrhythmia as evidenced by resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; or

- in the absence of a prior cardiac arrest, have recurrent, sustained ventricular tachycardia that occur spontaneously or can be induced, despite the most efficacious antiarrhythmic drug therapy that can be tolerated chronically.

Extensive electrophysiologic evaluation and testing of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the Model 7217B PCD device. Before permanently programming the PCD device to the automatic detection and delivery of the VT and/or VF therapies, the patient should have demonstrated a satisfactory response to the proposed therapy.

Intended Uses - ETCD

The Model 5355 External Tachyarrhythmia Control Device is intended for use in conjunction with an antitachycardia/defibrillation lead system during diagnostic studies for implanting the Model 7217B PCD device.

Indications for use of the ETCD include:

- Patients experiencing recurrent episodes of ventricular tachyarrhythmia,

- Patients who survived a cardiac arrest due to a ventricular tachyarrhythmia and are at risk for repeated episodes,

- Patients who are undergoing an assessment of the efficacy of antitachycardia pacing, cardioversion, or defibrillation therapies in anticipation of an implantable cardioverter-defibrillator.

Components of the System

A list of components used in the system is given below. It is separated into a listing of those components for which market approval is sought and those components that are now commercially available. Market approval is not being sought for use of the PCD Device with other manufacturers transvenous defibrillation lead systems or for the use of the PCD Transvene lead system with other manufacturers implantable cardioverter defibrillators.

Seeking Approval:

Transvene Leads
- Model 6963
- Model 6966
- Model 6999

Pacer-Cardioverter-Defibrillator (PCD) Device
- Model 7217B

External Tachyarrhythmia Control Device (ETCD)
- Model 5355 ETCD
- Model 5418 Patient Cable
- Model 5419 Patient Cable
- Model 5414 Test Load
- Model 5417 EGM Cable

Programmer Software Cartridge
- Model 9788 - Memory Module for 7217B PCD Device and 5355 ETCD Devices

Lead Accessories
- Model 6701 Lead End Cap

Commercially Available:

Programmers Model 9710 and accessories

Printers Model 9751/9712

Components Used in the Implantable Configuration

The implantable configuration is composed of a PCD Device, lead system, and a 9710 Programmer with applicable software cartridge. The implantable device is a Model 7217B PCD Device. The PCD device requires an appropriate lead system consisting of up to three cardioversion/defibrillation electrodes. See Figure III B-2. The Transvene leads used with the Model 7217B PCD Device are the Models 6963, 6966, and 6999.

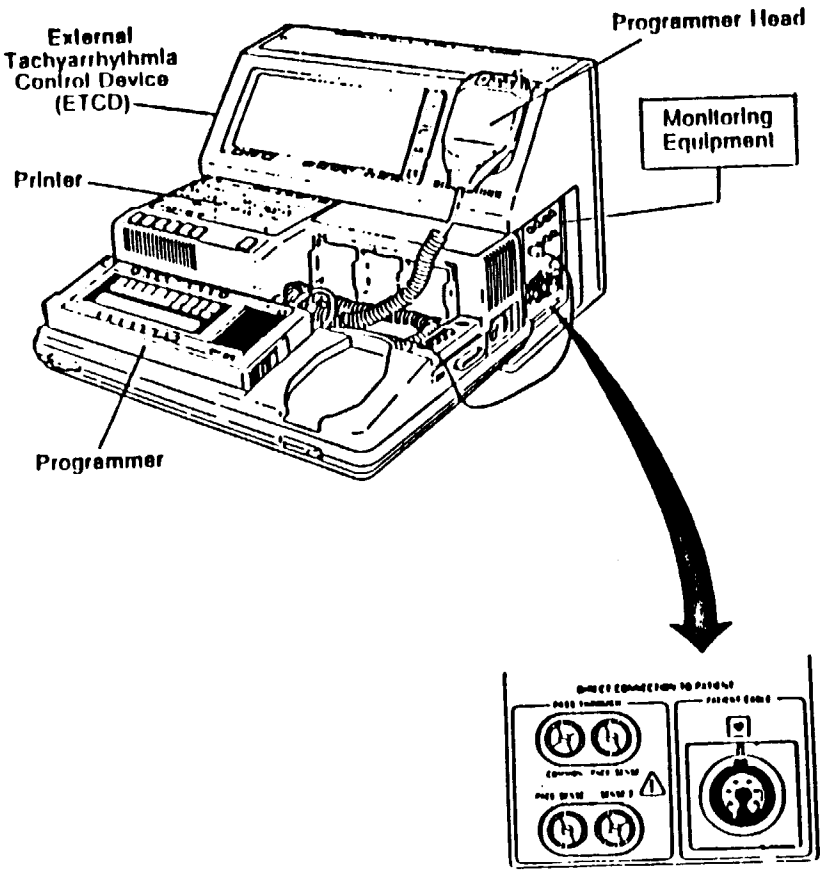
The Model 9710 Programmer is commercially available. Two printers are also commercially available. When higher printing speeds are desired, it is recommended that the programmer be used with the faster printer, the Model 9751. If slower printing speeds are acceptable, as may be the case in some follow-up situations, the Model 9710 Programmer can be used with the battery-powered Model 9712 Printer.

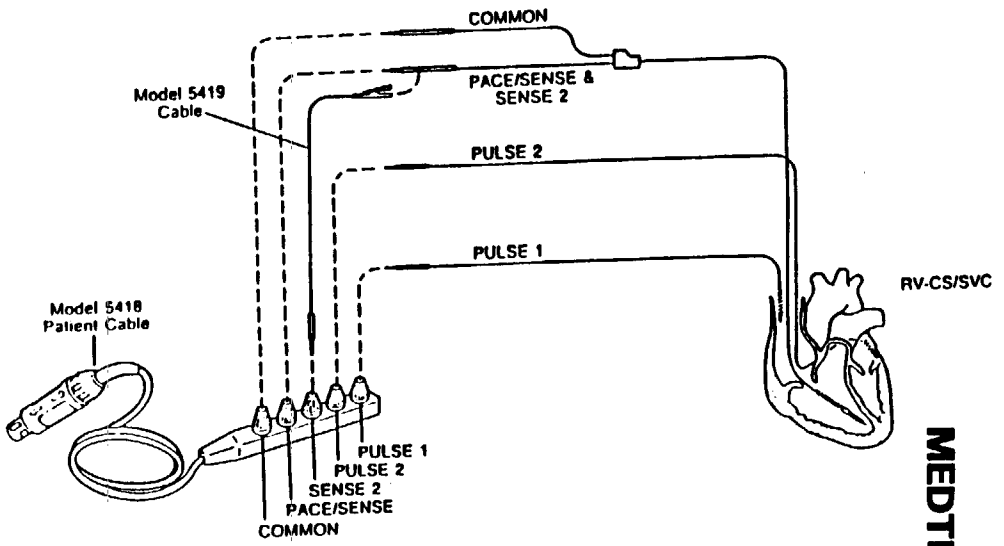
Components used in the External Configuration

The external tachyarrhythmia control system is composed of the Model 5355 ETCD, a Model 5418 Patient Cable, a Model 5419 cable, lead system, and a Model 9710 Programmer with applicable software cartridge, see Figures IV-A-3, 4. The ETCD uses replaceable batteries as its power source. The Model 5418 Patient Cable and Model 5419 Cable are designed to connect the Transvene leads to the ETCD. Like the implantable system, the ETCD uses the same Transvene leads (Models 6963, 6966, and 6999).

Figure II-B-2

Non-Thoracotomy Lead System for PCD





Connections to Model 5418 Patient Cable for
Typical Simultaneous or Sequential Pathway (RV-CS/SVC).

Figure IV-A-3

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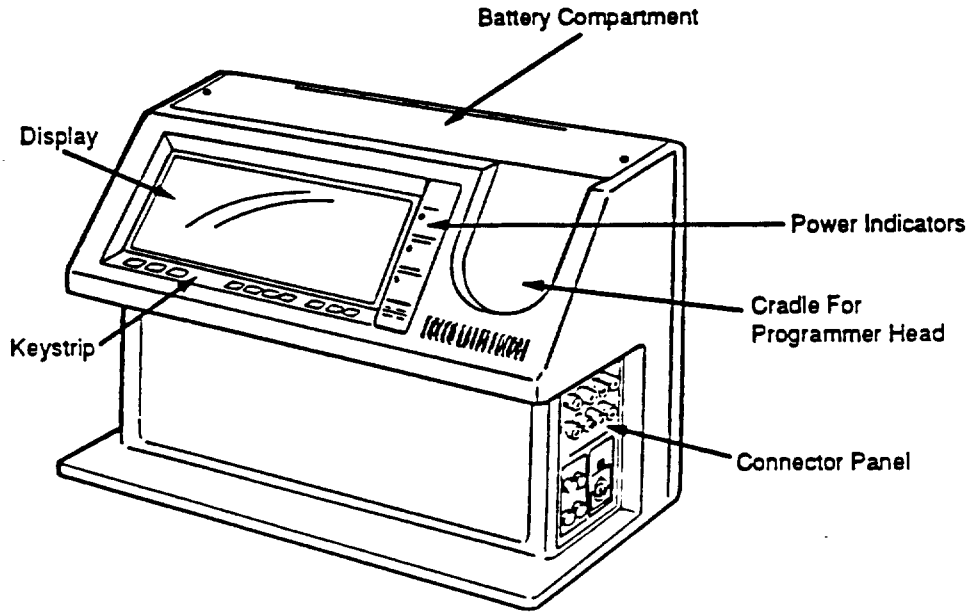

Figure IV-A-4. Model 5355 External Tachyarrhythmia Control Device

Purpose of the System

PCD System Configuration

The PCD Device is an implantable device designed to detect episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF), and upon detection, automatically deliver the appropriate therapy or a progression of therapies programmed by the physician for each patient. The available therapy types that can be programmed are overdrive pacing, cardioversion, and defibrillation. The PCD Device also has bradycardia pacing capability. The Transvene leads allow the PCD device to deliver these therapies to the heart.

ETCD System Configuration

The ETCD is an external tachyarrhythmia control device designed to deliver overdrive pacing, cardioversion, defibrillation, and bradycardia therapies in the same fashion as the PCD device. The ETCD can be programmed to automatically deliver overdrive pacing therapy upon detection of VT. When used as a component of a system that includes the appropriate Medtronic programmer and applicable software cartridge, the ETCD can deliver manually-initiated VT pacing, cardioversion, and defibrillation therapies. The ETCD allows the assessment of the Transvene lead system characteristics and aids in the assessment of lead system pacing and sensing characteristics.

Overview of System Features

General

The PCD device is designed to automatically detect episodes of VT or VF and, upon detection, deliver the appropriate programmed pacing, cardioversion, or defibrillation therapies. The device has two independently programmable detection and therapy procedures, one for VT and a second for VF.

When used as a component of a system that includes the appropriate Medtronic programmer and dedicated software, the ETCD is designed to deliver manually initiated cardioversion and defibrillation therapies. The ETCD is also designed to detect episodes of VT and VF. It can automatically deliver VT overdrive therapies (burst and ramp) upon detection of a VT.

VT Detection and Therapy

Both the PCD device and ETCD use a VT detection algorithm which can use up to three separately programmable criteria as it monitors the cardiac cycle length to identify the presence of a tachycardia. Upon detection, the devices deliver their first programmed VT therapy. If the VT episode persists and is again detected, up to three additional independently programmable VT therapies may be delivered to restore the patient's normal cardiac rhythm. This progression of four VT therapies can be tailored to each patient's need. For the PCD device the therapies may be selected from two methods of overdrive pacing (burst and ramp) and synchronized cardioversion.

For the ETCD the same overdrive pacing therapies can be automatically delivered, with cardioversion therapy being available as a manual therapy.

VF Detection and Therapy

The VF Detection algorithm monitors the cardiac cycle length to identify a VF episode. Upon detection, the PCD device provides a programmable high energy defibrillation pulse for VF therapy. Up to a maximum of four VF therapies may be delivered for ongoing detected VF episodes. Each defibrillation therapy consists of one (single pulse) or two (simultaneous or sequential) high voltage pulses designed to restore the normal cardiac rhythm.

For the ETCD, each cardioversion or defibrillation therapy, which must be initiated manually via the programmer, also consists of one high-voltage pulse or two (simultaneous or sequential) high-voltage pulses in the same fashion as the PCD devices.

Bradycardia Therapy

For both the ETCD and PCD devices, bradycardia pacing is delivered in the VVI mode. Asynchronous, (VOO), pacing is not available, and is avoided even with magnet application since this type of pacing has increased potential to initiate ventricular arrhythmias in patients receiving this system.

B

Lead Systems

The PCD Device and the ETCD perform pacing, sensing, cardioversion, and defibrillation through multiple electrodes in the lead system. Listed below are the electrodes and their function:

- The PACE/SENSE electrodes are incorporated in the right ventricular defibrillation lead. These electrodes function as the sensing circuit and deliver pacing pulses. The PACE/SENSE electrodes are used for sensing in conjunction with the SENSE2 electrode.
- The COMMON electrode is an electrode coil that serves as the cathode for cardioversion, defibrillation, and pacing.
- The PULSE2 electrode is an electrode coil that serves as the anode for cardioversion and defibrillation.
- The PULSE1 electrode is an optional electrode coil that serves as an additional anode for sequential and simultaneous cardioversion and defibrillation.

Cardioversion and defibrillation current pathways are between the PULSE2 and COMMON electrode coils and, if the additional lead is implanted, between the PULSE1 and COMMON electrode coils.

Other Capabilities

The physician may use the ETCD or the PCD devices to conduct noninvasive electrophysiologic studies (EPS) via the programmer with the appropriate software cartridge. The physician can also manually deliver various therapies via the programmer to manage an induced or spontaneous tachyarrhythmia.

The PCD device will provide the physician with information, via the Programmer, about its present programmed status and data on its operation accumulated between office visits. This information may be printed and retained in the patient's file.

The PCD Device and ETCD can also transmit an electrogram to the programmer. The electrogram is the electrical signal sensed on the leads.

A programmer-generated set of symbols, termed Marker Channel™, allows real-time visualization of sensing, pacing, detection, and therapy events occurring within the device.

In addition, the ETCD provides a display of measurements and other information related to delivered cardioversion and defibrillation pulses.

With this information and other features, the ETCD can be used to assess the suitability of the lead system and its placement for individual patients.

PCD Battery Longevity Expectations

The longevity of the Model 7217B PCD Device depends upon several factors, including programmed bradycardia pacing parameters, the percentage of paced to sensed events, the pacing load, and on the frequency of high voltage capacitor charging. The longevity projections found in Table IV-A-1 apply under the following conditions:

- 65 ppm pacing rate,
- 5.4 V pacing pulse amplitude,
- 0.49 ms pacing pulse width, and
- 500 ohm pacing lead.

Projected Longevity[1]
Table IV-A-1

Pacing/Sensing	34 Joule Charging Frequency	Average Longevity Model 7217B
100% Sensing	Quarterly	5.0 years
15% Pacing	Monthly	4.2 years
100% Pacing	Monthly	3.4 years

The longevity of the device decreases with the following:

- An increase in pacing rate,
- An increase in pacing amplitude,
- A decrease in pacing impedance,
- An increase in pacing pulse width,
- An increase in the percentage of bradycardia paced to sensed events, or
- An increase in the charging frequency.

Each 34 Joule charging cycle will typically decrease the longevity of the device by approximately six days.

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[1] These preliminary longevity projections are based upon accelerated battery data and device modeling. They include an estimate of five months between time of manufacture of a PCD device and its implant. If a device was stored for the full twelve-month shelf life, the average longevity would be reduced an estimated 4.3 to 5.9 months, depending on device use. With the stated condition, 100% pacing and monthly 34 Joule charging cycles, the minimum longevity of the device will be 2.5 years (7217B). Average refers to the projected mean longevity of the modeled run of PCD devices at the stated conditions. Minimum longevity means that virtually all (i.e., 99.9%) of all modeled production run of PCD devices will attain the value given.

C. Alternative Practices and Procedures

The use of implantable defibrillators in patients with drug refractory ventricular tachycardia/ fibrillation (VT/VF) and in survivors of sudden cardiac death has reduced the arrhythmic mortality in these patients. Other treatments available to treat ventricular tachyarrhythmias include antiarrhythmic drug therapy, ventricular tachycardia surgery, transthoracic defibrillation and other market released implantable defibrillators with epicardial defibrillation lead systems.

D. Marketing History

All of the Medtronic Transvene Tachyarrhythmia Control System device components which have been implanted in the U.S. to date have been part of the IDE clinical study and have followed the FDA approved investigational protocol. In November 1991, the Medtronic PCD Transvene System, and respective components described in this submission, were market released in Europe. In March 1991, the Medtronic PCD Epicardial System, and respective components, were market released in Europe. And in February 1993, the FDA approved the Medtronic PCD Epicardial System.

E. Adverse Effects

Potential adverse effects which may be associated with the use of the PCD Device include but are not limited to: failure to detect ventricular tachycardia or ventricular fibrillation; failure to terminate ventricular tachycardia or ventricular fibrillation; delivery of pacing or shock therapy when no ventricular tachyarrhythmia is present, which would precipitate an episode of ventricular tachycardia or ventricular fibrillation; acceleration of a ventricular arrhythmia; failure to capture after a shock delivery; discomfort or pain during or following the delivery of electrical shock; or infection.

The following additional, potential adverse effects associated with all pacemaker systems include loss of normal pacemaker function due to battery failure or other component failure, inability to program a pacemaker pulse generator because of programmer failure, infection, erosion, undesired muscle or nerve stimulation, and inadequate sensing or pacing. Any demand pulse generator can be affected by magnetic, electrical and electromagnetic signals of sufficient strength or with characteristics which mimic cardiac function. Possible effects of electrical interference on pulse generator operation include reversion to asynchronous pacing, inhibition of output pulses and rapid synchronous pacing. Certain environmental sources can couple sufficient energy into a cardiac pacing system to damage the pulse generator or cardiac tissue adjacent to the electrodes.

Failure of the pulse generator system to function properly may result in the patient experiencing the symptoms for which the pulse generator was originally indicated.

The potential complications related to the use of the PCD Transvene Lead System include, but are not limited to, the following patient-related conditions: fibrillation, air embolism, cardiac perforation, heart wall rupture, cardiac tamponade, pericardial rub, infection, myocarditis, constrictive pericarditis, pneumothorax and hemothorax. Other potential complications related to the lead system include, but are not limited to, the following: lead dislodgement, lead conductor fracture, and insulation failure.

The above referenced information is provided in the labelling of the PCD Transvene System.

F. Summary of Studies

To validate the performance of the Medtronic Tachyarrhythmia Control System nonclinical laboratory (bench) testing, animal studies and human clinical trials were performed. All of the nonclinical bench and animal testing demonstrated that the devices are safe and performed according to design intent.

The nonclinical laboratory (bench) testing provides information relative to the Model 6966, Model 6963 and Model 6999 Transvene Leads, Model 7217B PCD, Model 5355 ETCD, and Model 9788 Memory Module.

The animal studies were performed to evaluate acute and chronic performance PCD Transvene System and to validate that the PCD and ETCD System are safe for human use.

Finally, human clinical trials were performed to evaluate the safety and effectiveness of the PCD Transvene System in treating patients with life-threatening ventricular arrhythmias.

All of the studies have demonstrated that the PCD Transvene System functions safely and is appropriate for human use.

The following summaries are provided in this section.

1. Model 6966, Model 6963 and Model 6999 Nonclinical Testing

2. Non-clinical Testing of the Related Components of the Transvene Lead system: Models 7217B PCD, Model 5355 ETCD and Model 9788 MemoryMod Model 7217B PCD Nonclinical Testing

3. Animal Testing

4. Clinical Study of the PCD Transvene System

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1. Model 6966, Model 6963 and Model 6999 Defibrillation Leads: Summary of Nonclinical Testing

To validate the performance of the Medtronic Tachyarrhythmia Control System nonclinical laboratory (bench) testing, animal studies and human clinical trials were performed. All of the nonclinical bench and animal testing demonstrated that the devices are safe and performed according to design intent.

The nonclinical laboratory (bench) testing provides information relative to the Model 6963 CS/SVC lead, Model 6966 RV lead, Model 6999 SQ patch lead, and related system components.

a. Electrical Testing

Electrical D.C. resistance testing was performed to ensure proper functioning of the Model 6963, 6966 and 6999 leads.

Seventeen Model 6963, thirty-five Model 6966 and eighteen Model 6999 leads were submitted for testing. Electrical resistance was measured utilizing a milliammeter under ambient room conditions. All samples measured were within the individual design specifications.

b. Environmental Analysis Testing

The purpose of the testing was to subject the lead to temperature extremes to determine the lead's resistance to the thermal stresses when transported from extremes of climate.

Thermal Shock

Fifteen Model 6963 and thirty-five Model 6966 leads were subjected to five cycles from -45°C to 70°C with a soak time of thirty minutes at each temperature extreme with a transfer time of one minute. Thirty-five Model 6999 leads were subjected to five cycles from -40°C to 66°C with a soak time of thirty minutes at each temperature extreme with a transfer time of one minute.

After the thermal shock testing was completed visual inspection and electrical resistance measurements were performed. There were no visual defects and the electrical D.C. resistance of all the samples met the design specification.

c. Mechanical Testing

The purpose of the mechanical testing was to determine the mechanical integrity of the leads to ensure that the devices are safe, reliable, and suitable for their intended use and conform to design specifications. The leads and/or assemblies were subjected to the following:

- flex testing
- composite pull strength testing
- crimp/weld pull strength testing
- insertion/withdrawal force testing
- A.C. impedance/leakage testing

Flex Testing

The flex testing consisted of mounting the insulated conductor coils and uninsulated electrode coils of the Models 6963, 6966 and 6999 in a lead flex test fixture. The insulated conductor coils and uninsulated electrode coils were flexed under ambient room conditions at a specified radius. Eleven samples were used in each test. Samples exceeded specifications and therefore are considered to be satisfactory for their intended use.

Lead Joint Tensile Strengths

Pull testing of the various lead joints is conducted to ensure that the integrity of the joint meets the design specification and is, therefore, adequate for its intended application. The testing conducted consists of a composite pull test which evaluates the overall pull strength of the lead and crimp pull testing that evaluates the crimped connections of the leads to assure specification conformance.

Composite Pull Strength

Leads were boiled in Ringer's solution or soaked in normal saline and pull tested, while wet (the lead is usually cut in half to facilitate fixturing limitations) utilizing a tensile testing machine. The samples were pulled until failure at a rate of five inches per minute. The initial failures were then analyzed statistically for the confidence level in meeting the specification for the composite lead which is 1.0 lb. minimum.

Model 6963 data demonstrates that with a 95% confidence at least 97% (distal) and 99.9% (proximal) of the leads will meet or exceed the specification.

Model 6966 data demonstrate that with a 99% confidence at least 99.9% of the leads will meet or exceed the specification.

Model 6999 data demonstrate that with a 99% confidence at least 99.9% of the leads will meet or exceed the specification.

Therefore, Models 6963, 6966 and 6999 leads, with respect to composite pull strength, are adequate for their intended use.

Crimp/Weld Pull Strengths

Crimp and weld pull strength tests were conducted to evaluate the strength of the connections to ensure that they meet the design specification and are, therefore, adequate for their intended application. The connections tested are:

- Distal crimp sleeve to conductor coil crimp (6963)
- Double crimp core to conductor coil crimp (6963)
- Electrode coil to double crimp core weld (6963)
- Electrode coil to distal crimp sleeve weld (6963)
- Tip crimp sleeve to conductor coil crimp (6963)
- Connector pin to conductor coil crimp (6963 and 6999)
- Helix electrode to inner conductor coil crimp (6966)
- Electrode ring to middle conductor coil crimp (6966)
- Transition sleeve to electrode coil weld (6966)
- Transition sleeve to outer conductor coil crimp (6966)
- Fixed connector pin to outer conductor coil crimp (6966)
- Connector ring to middle conductor coil crimp (6966)
- Rotating connector pin to inner conductor coil crimp (6966)
- Manifold crimp sleeve to conductor coil crimp (6999)
- Manifold crimp sleeve to electrode coil (b)(4) crimp (6999)
- Manifold crimp sleeve to electrode coil (b)(4) crimp (6999)

Subassemblies were submitted for testing and pull tested by using a tensile testing machine. The samples were pulled until failure at a rate of four inches per minute.

Pull strength testing consisted of a minimum of 15 subassemblies of each crimp connection and a minimum of

7 subassemblies of each weld connection All samples tested exceeded the individual specification. The test results indicated that with a 95% confidence, at least 95% of the leads will have crimp and weld strengths that exceed the specification.

Therefore, the Model 6963, 6966 and 6999 leads, with respect to crimp and weld connection pull strengths, are adequate for their intended use.

Insertion/Withdrawal Forces

Insertion/withdrawal forces are measured to ensure compatibility with the implantable device without causing damage to the lead. Twenty five each of the lead Models 6963, 6966 and 6999 were tested with the Model 7217B PCD Device connector modules. There were no physical changes and all measurements met the design specification.

A.C Impedance/Leakage Testing

Fluid leakage tests are conducted on the lead assemblies/implantable device connector to determine leakage. Ten of each lead model Models 6963, 6966 and 6999 were tested with the Model 7217B connector modules. A.C. impedance was measured from the PCD device case to the lead connections while immersed in fluid. All samples met the design specification.

d. Biocompatibility Testing

The materials used in the Models 6963, 6966 and 6999 that are directly exposed to body tissue are:

- Polyurethane
- Silicone rubber (methylvinylpolysiloxane)
- Silicone rubber/titanium dioxide
- Platinum/Iridium

These materials have been shown to be biocompatible through many years of use in Medtronic permanent implantable endocardial/myocardial permanent pacing leads. In addition to extensive implant experience with these materials, standard biocompatibility tests have been performed to verify the biocompatibility of the above-listed materials. Testing has demonstrated that all materials are nonhemolytic, nonpyrogenic, nontoxic, nonmutagenic and

biocompatible. Therefore, the materials passed the tests and are considered suitable for human implant. The materials used in the Models 6963, 6966 and 6999 are identical to those used in other commercially available Medtronic pacing leads.

e. Lead System (Life) Testing

In addition to the aforementioned tests, the Transvene leads were subjected to system, or life, testing. Further testing also evaluated the leads with respect to crush resistance. Testing included subjecting the leads to soaking, flexing and high-voltage pulsing. A separate test evaluated crush performance. The purpose of these tests was to subject the leads to severe conditions and assess the overall integrity of the system.

D.C. resistance values and intermittance data measured before and after being subjected to soaking, multiple flexing and high voltage pulsing, as well as crushing, demonstrated the non-thoracotomy leads satisfied requirements and are therefore acceptable for their intended use.

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2. Non-clinical Testing of the Related Components of the Transvene Lead system: Models 7217B PCD, Model 5355 ETCD and Model 9788 MemoryMod

Non-clinical testing of these components was provided Volume 4 of the original PMA application (P900061) dated September 27, 1990, Volume 3 of the amendment dated March 8, 1991, and Volume 2 of the amendment dated August 30, 1991. A summary of the test results for each of the components is provided.

Model 7217B PCD: Summary of Nonclinical Testing

Testing of the Model 7217B pulse generators and the peripheral devices that comprise the system, i.e., the Pacing System Analyzers, the Model 9710 Programmer utilizing the Model 9788 MemoryMod and the Model 9751 Printer have been tested and found to be acceptable. All aspects of system interaction and operation are in accordance with the Model 7217B PCD Device and Model 9788 technical manuals and system specifications. Therefore, the Medtronic Tachyarrhythmia Control System, in its entirety, is acceptable for its intended use.

Model 9788 Memory Module: Summary of Nonclinical Testing

The Medtronic Model 9788 MemoryMod Cartridge was designed for insertion into the commercially available Model 9710 Programmer. When inserted, it becomes an integral part of the non-invasive programming system for the implantable PCD devices to establish pacing, ventricular tachycardia (VT) detection and therapy, ventricular fibrillation (VF) detection and therapy, and electrophysiological study (EPS) capabilities of an implanted pacemaker/ cardioverter/defibrillator (PCD). Both the Model 7217B PCD device and the Model 5355 ETCD are programmed with the Model 9788 MemoryMod cartridge when used with the Model 9710 Programmer.

Testing of the Model 9788 MemoryMod cartridge has demonstrated conformance to specification requirements. Therefore, the Model 9788 MemoryMod is acceptable for its intended use with the Model 7217B PCD Devices and the Model 5355 ETCD Device.

Model 5355 ETCD: Summary of Nonclinical Testing

Testing of the Model 5355 ETCD and respective accessories has shown conformance to specification requirements. Therefore, the Model 5355 ETCD Device/accessories are acceptable for their intended use.

3. Animal Testing

The information presented in this section is an accumulation of several studies, some of which FDA has previously reviewed in IDE submissions (G870102). These studies demonstrate the safety of the Transvene lead Models 6963, 6966 and 6999.

A variety of non-thoracotomy leads were evaluated in a series of four canine studies. Descriptions of the leads, as well as the study number(s) (1, 2, 3 or 4) in which they were evaluated, are presented below.

Description: Non-thoracotomy Leads

CORONARY SINUS/SUPERIOR VENA CAVA LEADS

Model 6963, evaluated in Study No. 4, is a silicone, unipolar, coronary sinus or superior vena cava lead with a 6.5 mm connector and platinum alloy electrode for delivery of cardioversion and defibrillation therapies.

Model 6881, evaluated in Study Nos. 2, 3 and 4 is functionally equivalent to the Model 6963 except the 6881 has a 3.2 mm connector.

Model 10285, evaluated in Study No. 1, is the temporary version of the Model 6963/6881.

RIGHT VENTRICULAR LEADS

Model 6966, evaluated in Study No. 4, is a polyurethane, tripolar, extendable/retractable, screw-in lead with a 6.5 mm connector and platinum alloy electrode for delivery of cardioversion and defibrillation therapies. Additionally, the 6966 has a 3.2 mm connector for pacing and sensing.

Model 6884, evaluated in Study Nos. 2 and 3, is functionally equivalent to the Model 6966 except the 6884 has a 3.2 mm connector in place of the 6.5 mm connector for the cardioversion-defibrillation electrode.

Model 10284, evaluated in Study No. 1, is the temporary version of the Model 6966/6884.

SUBCUTANEOUS PATCH LEADS

Model 6999, evaluated in Study No. 4, is a silicone, unipolar, oval, subcutaneous patch with a 6.5 mm connector and platinum alloy electrode coils that are partially embedded in the silicone patch for delivery of cardioversion and defibrillation therapies. Additionally, the patch is embedded with (b)(4) (b)(4)

Model 6895, evaluated in Study Nos. 2 and 3, is functionally equivalent to the Model 6999 except the 6895 has a 3.2 mm connector and is covered with (b)(4) (b)(4)

Model 10317, evaluated in Study No. 3, is functionally equivalent to the 6895 except it is embedded on the outer edge with (b)(4) (b)(4)

Although model numbers differ, all leads in each of the three groups are functionally equivalent. The various model numbers reflect an evolution of temporary to transvenous lead development, as well as minor changes, such as the connector pin modification from 3.2 mm to 6.5 mm.

Additional devices were used to evaluate the non-thoracotomy lead studies in canines. These are described below.

External Devices for Implant Support

Model 5355 External Tachyarrhythmia Control Device (ETCD)

The Model 5355 ETCD provides the same detection capabilities as the implantable Model 7217B PCD Device. Therapies are identical except that the maximum output energy is 40 joules (J) and automatic defibrillation and cardioversion are not available in the Model 5355. The Model 5355 ETCD provides measurement and display of output waveform parameters and ETCD status, an isolated electrogram signal, and passthrough connections of pacing and sensing electrodes to external instrumentation.

Model 2394 External Cardioverter/Defibrillator (ECVD)

The Model 2394 ECVD instrument can deliver: (1) a single stimulation pulse on one output channel, or (2) a pair of pulses, delivered individually on the two different output channels. Monophasic and biphasic pulses are provided, output capacitance can be varied between 10 and 150 microFarads (mf) depending on which external capacitor modules are used, and pulse width

can be specified as a fixed duration (0.1-19.9 ms) or "tilt" (10-90%). Pulse output voltages can range between 50 and 1090 volts and may be delivered asynchronously (upon manual command) or synchronized with an intrinsic sensed event.

Model 2376 External Cardioverter/Defibrillator (ECVD)

The output stimulation parameters of the Model 2376 are very similar to those of the Model 2394 except for the following modifications:

- All pulses are monophasic, truncated, exponential waveforms.
- Output capacitance is fixed at 50 microFarads and pulse width is determined by a fixed pulse duration only.
- Pulse output voltages can range between 50 and 1090 volts and may be delivered asynchronously (upon manual command) or synchronized with an intrinsic sensed event.

Study Methods

All canine studies were conducted according to the 1966 and 1970 Animal Welfare Acts, 1985 NIH Laboratory Animal Use and Care Guidelines and GLP regulations. Adult mongrel canines were used for all studies. The dogs weighed 20 kg or more.

Specific details of each study are presented in the following "Animal Studies/Results" section.

Each study is briefly described below. Both acute and chronic studies were performed to assess the toxicity of the non-thoracotomy lead system as well as its stability over time.

Study #1: Acute Toxicity Testing of Non-thoracotomy Leads

The objective of this study was to quantify the amount and nature of shock-induced damage to the myocardial tissue resulting from multiple, high energy defibrillation shocks delivered through transvenous defibrillation leads and a subcutaneous patch. This information has previously been submitted to the agency in the Non-Thoracotomy IDE, reference Document Control Number G870102/S23; FDA Approved October 4, 1990. Lead models evaluated in this study are functionally equivalent to the Models 6963, 6966 and 6999. Results of these studies revealed only minimal shock-induced necrosis (<0.1-0.5 percent by weight), which did not result in functional impairment of the cardiac tissue. Therefore, the use of the Model 6963, 6966 and 6999 leads did not result in significant myocardial damage in canines and could be safely implanted in humans.

Study #2: Model 6881, 6884 and 6895 Chronic Lead Evaluation

The objective of this study was to evaluate the suitability of the lead system for human clinical use. Lead models evaluated in this study are functionally equivalent to the Models 6963, 6966 and 6999. Study results demonstrate that the performance of the non-thoracotomy lead system when used with the PCD and ETCD devices is in conformance with system design and expected operation.

One canine in this study has presented with two mastocytomas; a common type of skin tumor in middle-aged canines. This observation is not related to the PCD system, nor is it relevant to the clinical application of the PCD system. The tumors were excised and the animal remains in good health.

Study #3: Model 6881, 6884 and 6895 Chronic Lead Defibrillation Study

This study is an evaluation of the chronic stability of the non-thoracotomy lead system via the monitoring of defibrillation and pacing thresholds. In addition, histopathological examinations have been performed to assess the amount and nature of shock-induced damage to the myocardial tissue resulting from defibrillation shocks. Lead models evaluated in this study are functionally equivalent to the Models 6963, 6966 and 6999. Results demonstrate stable pacing, sensing and defibrillation thresholds over time. Additionally, histopathology analysis shows no cardiac tissue damage due to delivery of defibrillation shocks.

Study #4: Model 6963, 6966 and 6999 Chronic Lead Defibrillation Study

This study is an ongoing evaluation of the non-thoracotomy lead system to assess chronic defibrillation threshold stability, pacing thresholds, intracardiac sensing capabilities and tissue damage. Results indicate the lead system performs as intended; DFTs and pacing thresholds have remained stable throughout the study (60 weeks) and intracardiac sensing is appropriate. Additionally, pathology data, to date, indicates minimal localized trauma to the cardiac tissue (<0.05 percent by weight).

Conclusion

All of these canine studies have demonstrated that the non-thoracotomy lead system, which includes the Model 6963 CS/SVC lead, 6966 RV lead and 6999 SQ patch lead, functions safely and is therefore appropriate for human use.

4. Summary of Clinical Experience

A. Introduction

The efficacy and safety of implantable cardioverter defibrillator (ICD) therapy for recurrent ventricular tachycardia (VT) and ventricular fibrillation (VF) has been well established. The current market released device (Medtronic Model 7217B with Epicardial Cardioversion/Defibrillation Leads) incorporates multiprogrammability, multiple detection and therapeutic options for the treatment of ventricular tachycardia and fibrillation. The current system, while providing lifesaving treatment of ventricular arrhythmias, requires a significant surgical procedure (thoracotomy, median sternotomy, etc.) for the placement of the epicardial lead system. The need to reduce the surgical mortality and morbidity associated with epicardial cardioversion/defibrillation lead systems has lead to the development of the PCD® Transvene™ System.

This report represents a full report of Medtronic's clinical experience with the Medtronic PCD® Model 7217B Multiprogrammable Tachyarrhythmia Control System with Transvene™ Cardioversion and Defibrillation Electrodes (Reference IDE G870102). The data included in this analysis is all data that was received by Medtronic and entered onto the clinical database as of **February 1, 1993.**

The PCD® Model 7217B Multiprogrammable Tachyarrhythmia Control System described in this submission is identical to the system which was recommended for approval by the FDA advisory panel on February 3, 1992, with the addition of Transvene™ leads.

The data analysis is organized in functional rather than chronological categories in order to present a complete picture of each of the PCD® Device's various functions. The sections included in this summary are:

- Indicated Patient Population/Therapeutic Options
- PCD Therapy Applications
- Indicated Patient Population
- Study Objectives and Protocol Summary
- Overview of Clinical Experience
  - Implant Data
  - Spontaneous VT/VF Episode Experience

Overall Success Rate
- Complications and Observations
- Inactive Patients
- Patient Deaths
- Clinical Experience by Primary Indication
- Patients not Meeting Implant Criteria
- Comparison to AICD Clinical Experience
- Comparison to PCD® Epicardial Clinical Experience
- PCD® Transvene™ System Performance

This summary provides an overview of the clinical experience which verifies that the PCD® Transvene™ System is safe and effective in the indicated patient population.

B. Indicated Patient Population

B.1 Patient Population

The PCD® Transvene™ System is intended to treat patients at risk of sudden cardiac death due to ventricular tachyarrhythmias which have been shown to be reliably terminated, and in the case of VF, terminated at an energy level below the maximum output of the PCD® Device.

Results provided in this application will support Medtronic's request for market release of the PCD® System for use in the following patient population:

- Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or

- Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

Malignant ventricular tachyarrhythmias remain a major unsolved problem in the management and prevention of coronary artery disease. It is estimated that 450,000 people experience sudden cardiac death annually, and 80%-90% of these events are caused by ventricular fibrillation. (Gillum RF. Sudden coronary death in the United States. Circulation 1989; 79:756-765.)

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Survivors of out-of-hospital cardiac arrest not associated with acute myocardial infarction are at risk for recurrent cardiac arrest as reported by Wilber, et al.(Wilber, et al. Out-of-Hospital Cardiac Arrest - Use of Electrophysiologic Testing in the Prediction of Long-Term Outcome. NEJM 1988; Vol.318:19-24.). In this study group of 166 survivors of out-of-hospital cardiac arrest, ventricular arrhythmias were inducible in 131 patients (79%) and were suppressed by antiarrhythmic drug therapy or surgery (or both) in 91 patients (72%). During a median follow-up of 21 months, cardiac arrest recurred in 29 patients: 11 in whom inducible arrhythmias had been suppressed, 12 in whom inducible arrhythmias persisted and 6 in whom arrhythmias could not be induced at initial electrophysiologic study.

C. PCD® Transvene System Therapy Applications

The PCD® System is intended to treat patients at risk of sudden cardiac death due to ventricular tachyarrhythmias and/or recurrent ventricular tachycardia.

For this patient population, the primary benefits from the use of the PCD® System center on the detection and termination of life-threatening ventricular arrhythmias. The use of the PCD® Transvene™ system allows for the application of identical therapies as an epicardial system without requiring an open chest procedure for implantation of the lead system. This less invasive surgical approach allows the system to be applied in patients who may not be able to undergo an open chest procedure. The use of pacing therapies for the treatment of ventricular tachycardia reduces patient trauma associated with higher energy cardioversion pulses and extends the longevity of the PCD® pulse generator.

The PCD® System allows the titration of therapies for patients with ventricular tachycardia while providing critical defibrillation backup. Multiple detection algorithms are designed to allow the device to distinguish ventricular tachycardia from sinus tachycardia and atrial fibrillation. In addition, independent detection algorithms for VT and VF allow the delivery of different types of therapy for each of these two arrhythmias. The incorporation of antitachycardia pacing algorithms allows the use of pacing for the termination of well tolerated ventricular tachycardia. These algorithms, which are rate adaptive, can adapt

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to changes in the ventricular tachycardia and successfully terminate the episode. Defibrillation therapy is important in the event that an episode of VT accelerates to VF whether spontaneously or as a result of a delivered therapy. The incorporation of multiple cardioversion and defibrillation pathways (SINGLE, SEQUENTIAL and SIMULTANEOUS) allows the physician to provide an adequate cardioversion/defibrillation efficacy safety margin for all patients. The capacity to provide programmable extrastimuli pacing allows noninvasive electrophysiologic studies to be performed. The potential benefits from permanent cardiac pacing provide support for chronic and transient episodes of bradycardia.

Finally, the benefits of programmability of tachyarrhythmia detection and therapy parameters, VVI parameters, and stored telemetry data on the delivery of therapy may avert the need for reoperation in the event of changing patient conditions or complications.

D. Study Objectives and Protocol Summary

The clinical study was designed to evaluate the operation, safety and effectiveness of the PCD® System components in detecting and treating episodes of ventricular tachycardia and ventricular fibrillation.

The analysis focuses on data supporting the safety and effectiveness of the PCD® system, including the implantable pulse generator and associated transvenous lead system and its therapy in this patient population. The analysis includes the clinical experience with the PCD® system, pace/sense, detection and therapy functions in both the acute and chronic implant settings. In addition, data is provided on clinical observations, clinical complications and deaths in this patient population. The analysis will also provide data demonstrating the safety and effectiveness of the Model 5355 ETCD.

This summary presents safety and efficacy evaluation performed on 757 patients, 657 of which have implant durations equal to or greater than six months.

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Clinical data was collected at the following study points to support the safety and efficacy of the PCD® System:

Pre-implant Patient Assessment
Lead System Testing at Implant
Implantable Pulse Generator Testing at Implant
Pre-hospital Discharge Testing
Follow-up Evaluation 1 and 3 months post implant then at 3 month intervals

Patients were evaluated prior to hospital discharge and/or one (1) month post implant, three months post-implant and then at intervals of every three months. In some cases additional testing was performed at physician discretion to evaluate spontaneous events and/or potential clinical complications.

Medtronic collected all clinical data on the PCD® System and its components under the clinical protocol outlined in the Investigational Plan. A common protocol was used on all study patients on a worldwide basis.

International centers were subject to the appropriate requirements (e.g., the Declaration of Helsinki) in order that the data met the statutory requirements of the FDA. All clinical data, U.S. and International, obtained with the PCD® System with Transvene™ Leads is included in this report.

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E. Overview of Clinical Experience

This report covers a total of 762 implants in 757 patients of the PCD® Device with the Transvene™ Defibrillation Lead System. A total of 78 investigative centers participated in the clinical trial with 35 centers in the U.S. and 43 Internationally. The first implant occurred internationally on October 20, 1989, and the first implant in the U.S. occurred on October 16, 1990. Table E-1 shows the distribution of Model 7216A and Model 7217B patients between U.S. and International investigators.

PCD® Transvene™ System
Implant Distribution

	Total	U.S.	Int'l
7216A	18 (2.4%)	3 (0.7%)	15 (4.8%)
7217B	744 (97.6%)	444 (99.3%)	300 (95.2%)

Table E-1: PCD® Transvene™ System - Implant Distributions - 2/1/93

The mean documented implant duration for this patient population is 11.7 months and ranged from implant to 37.4 months. The cumulative implant duration is 8894.8 months. There are 657 patients with implant durations equal to or greater than six months. Table E-2 provides the distribution of follow-up quantity of patients by data form type.

PCD® Transvene™ System
Follow-Up Quantity
by Data Form Type

(b)(4)

(b)(4)

Table E-2: PCD® Transvene™ System - Follow-Up Quantity - 2/1/93

The patient population enrolled in the clinical trial was predominately male (80.6%) with a mean age of 59.4 years. In half of the patients (49.8%), the primary indication for implant was recurrent, sustained ventricular tachycardia without an episode of sudden cardiac death. Sudden Cardiac Death was the primary indication for 37.1% of the patients and SCD in combination with recurrent, sustained VT was the primary

indication in 13.1%. Coronary artery disease was the primary heart disease in 74.1% of the patient population with a mean reported ejection fraction of 35.6% Table E-3 provides a data summary on these patients. Also included is the data summary of the patients with 6 months and 12 months of follow-up.

PCD® Transvene™ System Data Summary			
	All Patients (3 Electrode Systems)	Patients with **6** months of Follow-up	Patients with **12** months of Follow-up
Number of Patients	757	657	393
Device Months Follow-up	8894.8	8602.6	6454.6
Mean Follow-up Time	11.7 mo	13.0 mo	16.3 mo
Maximum Follow-up Time	37.4 mo	37.4 mo	37.4 mo
Number, % Male **Number, % Female**	610 80.6% 147 19.4%	527 80.2% 130 19.8%	310 78.9% 83 21.1%
Mean Age	59.4 yrs	59.1 yrs	58.8 yrs
Primary Indication: **SCD** **VT** **SCD/VT**	 281 37.1% 377 49.8% 99 13.1%	 249 37.9% 326 49.6% 82 12.5%	 150 38.2% 191 48.6% 52 13.2%
Coronary Artery Disease	561 74.1%	483 73.5%	272 69.2%
Mean Ejection Fraction	688 35.6%	595 36.6%	357 38.0%
Defibrillation Pathway: **Sequential** **Simultaneous** **Single**	 574 75.3% 178 23.4% 10 1.3%	 496 74.9% 156 23.6% 10 1.5%	 296 74.9% 93 23.6% 6 1.5%
Mean LED	16.0J (N=702)	16.0J (N=609)	15.6J (N=365)
Mean DFT	14.8J (N=316)	14.8J (N=277)	14.3J (N=184)
Spontaneous VT: **Number of Patients** **Number of Episodes** **% Success**	 316 10027 98.4%	 288 8820 98.3%	 186 6338 99.0%
Spontaneous VF: **Number of Patients** **Number of Episodes** **% Success**	 317 1982 98.4%	 292 1742 98.3%	 176 1105 98.6%
One Year SCD Survival	99.5%	99.7%	100.0%

Table IF-2: PCD® System Data Summary - All Transvene™ Patients versus Transvene™ Patients with 6 mo Follow-up - 2/1/93

E.1 Implant Data

Implants of the PCD® Device may use two or three Transvene™ leads. The physician has the flexibility to use whichever lead system best meets the patient's needs.

Table E-4 illustrates the lowest energy of defibrillation (LED) and defibrillation threshold (DFT) for the implanted lead systems. The implant criteria for the PCD® Device was 3 of 4 episodes of VF successfully terminated at 18 Joules or less with a given lead configuration. Some patients did not have a LED at implant. The LED is only identified if the investigator reported the induced rhythm as VF. Conversion of VT or V Flutter (as defined by the physician) to sinus rhythm was not included in the determination of the LED. In addition, it is not a protocol requirement to obtain a DFT at implant. However, recommendations have been provided to those institutions that prefer to obtain DFT's during the implant procedure.

PCD® Transvene™ System Mean LED and DFT Values				
Lead System	**Implant Frequency**	**Mean LED**	**Implant Frequency**	**Mean DFT**
All Systems	702	16.0J	316	14.8J
RV-SVC-SQ	455	16.7J	187	15.8J
RV-CS-SQ	210	14.6J	110	12.8J
RV-CS-SVC	37	15.2J	19	16.0J

Table E-4: PCD® Transvene™ System - LED and DFT Values - 2/1/93

The mean implant Lowest Energy of Defibrillation (LED) for all lead systems was 16.0J and mean implant Defibrillation threshold (DFT) for all lead systems was 14.8J. As the mean DFT's and LED's indicate, VF was reliably terminated at an energy value below the maximum output (34 Joules) of the PCD® Device.

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E.2 Spontaneous VT and VF Episode Experience

A total of 458 patients (60.5%) have experienced a spontaneous ventricular tachyarrhythmia episode that has been detected and treated by the PCD® Device. A total of 141 patients experrienced VT only, 142 patients (18.8%) experienced VF only and 175 patients (23.1%) experienced both an episode of VT and VF.

There have been a total of 12,009 episodes of spontaneous VT or VF as detected by the PCD®. The overall PCD® Device success rate in terminating spontaneous VT/VF episodes as detected by the PCD® is presented in Table E-5.

PCD® Transvene™ System
Success Rate in Terminating Spontaneous VT/VF Episodes

	Number of Episodes Successful	Total Number of Episodes	Efficacy Rate
VT	9864	10,027	98.4%
VF	1951	1982	98.4%
Total	11,815	12,009	98.4%

Table E-5: PCD® Transvene™ System - Success Rate for Spontaneous VT/VF Episodes - 2/1/93

E.2.1 Spontaneous VT

For the purposes of this clinical trial, spontaneous VT was defined as those episodes that satisfied the programmed VT detection criteria. Specifically, all programmed VT detection criteria must be fulfilled to detect a VT episode. Successful termination of the episode was defined as satisfying the VT episode termination criteria.

To date, 10,027 spontaneous episodes of VT have been detected by the PCD® Device in 316 patients. The mean number of episodes per patient with VT was 31.7 and ranged from 1 - 531 episodes.

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Most spontaneous VT episodes (90.7%) were successfully treated with VT Therapy #1 and 98.4% were successfully treated with one of the four programmable VT therapies.

Of the 9864 successfully terminated spontaneous VT episodes, 91.4% were treated with one of the programmed antitachycardia pacing therapies incorporated in the PCD® Transvene™ System. The clinical benefit of tiered therapy is the reduction of delivery of high energy shocks for the treatment of stable recurrent ventricular tachycardia. This greatly enhances the patient acceptance of ICD therapy since antitachycardia pacing is usually not perceived by the patient.

Sixty patients experienced 163 (1.6%) episodes in which the PCD® Device was ineffective in terminating a spontaneous episode of VT despite delivery of all four programmed VT therapies. Thirty-nine patients experienced 95 ineffective episodes that were due to sinus tachycardia or atrial fibrillation/flutter (SVT) with a rapid ventricular response that had been detected as VT. These episodes were resolved with either modification of programmed parameters or of antiarrhythmic drug therapy. It should be noted that the PCD® Device responded appropriately based on the programmed detection parameters.

The remaining 68 episodes occurred in 21 patients in which the programmed VT therapies were ineffective in terminating a spontaneous VT episode. **No patient deaths occurred as a result of ineffective VT therapy.** Reprogramming and pharmacologic intervention resolved these events.

E.2.2 Spontaneous VT Episode Experience By Primary Indication

The primary indications for implant of the PCD Transvene System were sudden cardiac death (**SCD**), recurrent sustained ventricular tachycardia (**VT**) and sudden cardiac death associated with recurrent sustained ventricular tachycardia (**SCD/VT**). Spontaneous VT episode efficacy by primary indication is provided in Table E-6. The overall efficacy for spontaneous VT episodes is greater than 98% for each of the patient groups. There is no difference in therapy efficacy among the patient's indications. Table E-6 contains the spontaneous VT episode therapeutic efficacy.

PCD® Transvene™ System
Spontaneous VT Episode Therapeutic Efficacy
By Primary Indication

Indication	# Episodes Successful	# Total Episodes	% Success
SCD	1148	1157	99.2%
VT	7450	7591	98.1%
SCD/VT	1266	1279	99.0%
Total	9864	10027	98.4%

Table E-6: PCD® Transvene™ System - Spontaneous VT Episode Efficacy by Primary Indication -2/1/93

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E.2.3 Spontaneous VT Episode Experience By Therapy Type

The PCD® Device incorporates three programmable VT therapy types, RAMP, BURST and CARDIOVERSION, for the treatment of recurrent ventricular tachycardia. Spontaneous VT episode efficacy by programmed therapy type is provided in Table E-7.

PCD® Transvene™ System
Spontaneous VT Episode Efficacy
By Programmed Therapy Type

VT Therapy Type	# Success	# Attempts	% Efficacy
Ramp	4903	5374	91.2%
Burst	4266	4738	90.0%
Cardioversion	695	818	85.0%

Table E-7: Spontaneous VT Episode Efficacy by Therapy Type - 2/1/93

E.2.4 Spontaneous VF

For purposes of this clinical trial, VF is defined as those episodes that satisfy the programmed VF detection criteria. Specifically, all programmed VF detection criteria must be fulfilled to detect a VF episode. Successful termination of the episode is defined as satisfying the VF detection criterion for episode termination.

To date, 2491 spontaneous episodes of VF have been detected by the PCD® Device in 317 patients. The mean number of episodes per patient was 7.9 and ranged from 1 - 262 episodes. A review of the chart per investigator for this patient that experienced the 77 episodes of VF revealed that 75 were most likely due to atrial fibrillation. VF detection parameters were modified in this patient.

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Most (91.3%) spontaneous VF episodes were successfully treated with VF Therapy #1 and 99.1% were successfully treated with one of the four programmable VF therapies.

Sixteen patients experienced 31 episodes (1.3%) in which the PCD® Device was ineffective in terminating a spontaneous episode of VF despite delivery of all four programmed VF therapies. Nine patients had 22 reported ineffective VF spontaneous episodes that were due to sinus tachycardia or atrial fibrillation with rapid ventricular response rather than VF. Reprogramming and pharmacologic intervention resolved these problems.

Four patients experienced 5 ineffective episodes that were detected as VF by the PCD® System. One of these patients (b)(6) required external defibrillation to convert the VF episode. This patient's antiarrhythmic drug regimen was modified to improve defibrillation efficacy. Another patient (b)(6) had an episode recorded as ineffective on the event counters but presented in sinus rhythm. Subsequent evaluation demonstrated appropriate PCD® function. Another of these patients (b)(6) had two spontaneous episodes of VT that were detected as VF by the PCD® while in the hospital for progressive CHF. These episodes required external cardioversion. The patient requested the PCD® be turned OFF. Patients was alive at the last known follow-up. The last of these four patients (b)(6) experienced cardiac arrest at home and was found by the paramedics to be in sinus rhythm. While on a monitor the patient developed VF. The PCD® delivered the programmed therapy which terminated the episode but the patients developed EMD, arrived at the ER comatose and died.

Four patients (one patient (b)(6) experienced 2 episodes due to AF but is described below again) experienced 4 episodes in which the PCD® detected the episodes as VF but were actually episodes due to extraordinary circumstances. One patient (b)(6) experienced an episode where all four therapies

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failed secondary to RV lead fracture. The patient had Twiddlers Syndrome. Reoperation was required. It appears that the inappropriate therapy was not due to VT/VF but due to noise. Another patient (b)(6) had a surgical procedure (CABG) where the CS lead dislodged post surgery. The episode that was detected was due to the lead dislodgment. The third patient (b)(6) had incessent episodes of fast VT (cycle length 280 ms) that were eventually resolved by drugs. The fourth patient (b)(6) was in hospital and there was an episode of VF detected. However, the device was interrogated before termination of the episode was detected. There was external intervention associated with the terminal event. The device was not interrogated again.

E.2.5 Spontaneous VF Episode Experience By Primary Indication

The primary indications for implant of the PCD® Transvene™ System were sudden cardiac death (**SCD**), recurrent sustained ventricular tachycardia (**VT**) and sudden cardiac death associated with recurrent sustained ventricular tachycardia (**SCD/VT**). Spontaneous VF episode efficacy by primary indication is provided in Table E-8. There is no difference in therapy efficacy among the patient's indications. The overall efficacy for spontaneous VF episodes is greater than 98% for each of the patient groups.

PCD® Transvene™ System
Spontaneous VF Episode Therapeutic Efficacy
By Primary Indication

Indication	# Episodes Successful	# Total Episodes	% Success
SCD	665	686	96.9%
VT	908	916	99.1%
SCD/VT	378	380	99.5%
TOTAL	1951	1982	98.4%

Table E-8: PCD® Transvene™ System - Spontaneous VF Episode Efficacy by Primary Indication -2/1/93

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E.2.6 Spontaneous VF Episode Experience By Therapy Type

The PCD® Device incorporates three programmable defibrillation pathways, SEQUENTIAL, SINGLE and SIMULTANEOUS, for the treatment of ventricular fibrillation. Spontaneous VF episode efficacy by programmed defibrillation pathway is provided in Table E-9.

PCD Transvene™ System
Spontaneous VF Episode Efficacy
By Programmed Therapy Type

VF Therapy Type	# Success	# Attempts	% Efficacy
Sequential	1525	1549	98.5%
Simultaneous	426	433	98.4%

Table E-9: PCD® Transvene™ System - Spontaneous VF Episode Efficacy by Therapy Type - 2/1/93

E.3 Overall Success Rate

Of the 757 patients who received a PCD® Transvene™ System, 597 patients (78.9% - 597/757) have either experienced a spontaneous VT/VF episode or had VT/VF induced during a post implant electrophysiology study. The performance of the PCD® Transvene™ System therapies have been thoroughly evaluated and been shown to be effective in detecting and terminating episodes of ventricular tachyarrhythmia.

There have been no reports of a patient death due to the PCD® Transvene™ System not detecting a spontaneous episode of VT or VF.

The overall success rate of the PCD® Transvene™ System in terminating spontaneous episodes of either VT or VF was 98.4% with a VT success rate of 98.4% and VF success rate of 98.4%. The incidence of unsuccessful termination of an apparent "true" episode of ventricular tachycardia despite delivery of all four therapies was 0.7% (68/10027).

The incidence of unsuccessful termination of an apparent "true" episode of ventricular fibrillation despite delivery of all four therapies was 0.3% (5/1982).

The evaluation of spontaneous episode experience indicates that the PCD® Transvene™ System's VT and VF detection and therapy functions have performed safely and effectively in the indicated patient population.

F. Complications and Observations

The use of a multiprogrammable implantable cardioverter defibrillator (ICD) device allows the physician to resolve most relevant medical events by noninvasively changing programmed parameters thus, avoiding invasive procedures. However, there will continue to be certain relevant medical events which will require invasive procedures for resolution.

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following definitions:

COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

As of February 1, 1993, there have been a total of 176 complications identified in 147 patients and 214 observations identified in 180 patients in the PCD® Transvene™ System patient population. Thus, 19.4% (147/757) of the patients have experienced a clinical event which was defined as a complication and 23.8% (180/757) of the patients have experienced a clinical event which was defined as an observation. Table F-1 summarizes how these events were reported with U.S versus International.

PCD® Transvene™ System Reported Complications/Observations U.S versus International		
	# of Complications	# of Observations
U.S.	104	93
International	72	121
Total	176	214

Table IG-1: PCD® Transvene™ System Complications/Observations U.S. versus International - 2/1/93

Table IG-2 summarizes the reported PCD® Transvene™ System complications and observations by category. The reported complications and observations are recognized clinical events that may occur with **any** of the current ICD devices. These complications and observations are discussed in the PCD® device and Transvene™ manual. **None of the reported complications or observations have resulted in a patient death.**

PCD® Transvene System Reported Complications/Observations By Category		
Category	Complications	Observations
	Num (% of Pts)	Num (% of Pts)
Increased Defibrillation Requirements	9 (1.2%)	8 (1.1%)
Inappropriate VF Therapy Delivery	-	14 (1.8%)
Inappropriate VT Therapy Delivery	-	59 (7.8%)
Loss of Capture	6 (0.8%)	14 (1.8%)
Oversensing	-	54 (7.1%)
Undersensing	-	-
Skin Erosion	5 (0.7%)	1 (0.1%)
Pocket Infection	24 (3.2%)	10 (1.3%)
Seroma	6 (0.8%)	14 (1.8%)
Hematoma	6 (0.8%)	17 (2.2%)
Pneumothorax	2 (0.3%)	1 (0.1%)
Pacemaker Syndrome	-	2 (0.3%)
Right Ventricle Perforation	6 (0.8%)	-
Subclavian Vein Thrombosis	1 (0.1%)	3 (0.4%)
Lead Fracture	9 (1.2%)	-
Subcutaneous Patch Crinkling	7 (0.9%)	5 (0.7%)
Early Device Explant	4 (0.5%)	-
Total Lead Dislodgement (n=757)	91 (12.0%)	12 (1.6%)
Total	176	214

Table IG-2: PCD® Transvene™ System: Reported Complications and Observations - 2/1/93

Table IG-3 contains a description of the lead dislodgements that have occurred in less than 30 days and in greater than 30 days.

PCD® Transvene System
Reported Complications/Observations
Lead Dislodgements <30 days and >30 days

Category	Complications		Observations	
	Num (% of Pts)		Num (% of Pts)	
	<30 days	>30 days	<30 days	>30 days
RV Lead Dislodgement n=741	14 (1.9%)	10 (1.3%)	0 (0%)	1 (0.1%)
CS Lead Dislodgement n= 261	12 (4.6%)	10 (3.8%)	2 (0.8%)	2 (0.8%)
SVC Lead Dislodgement n=535	16 (3.0%)	29 (5.4%)	1 (0.2%)	6 (1.1%)
Total Lead Dislodgement n=757	42 (5.6%)	49 (6.5%)	3 (0.4%)	9 (1.2%)

Table IG-3: PCD Transvene System: Lead Dislodgements <30 days and >30 days - 2/1/93

There have been a total of 49 lead dislodgements reported in patients at greater than 30 days. None of the lead dislodgements resulted in an ineffective therapy for a spontaneous VT of VF episode or patient death. Lead dislodgements were documented by fluoroscopic examination during electrophysiologic evaluation, chest x-ray obtained during routine follow-up, or during pacing/sensing threshold evaluation during routine follow-up. In all 48 cases, reoperation was required to reposition the lead and reestablish an effective defibrillation lead system.

Lead dislodgements are not specific to the PCD® Transvene™ System and have been reported with dual chamber pacemakers and the current market released implantable cardioverter defibrillator (ICD) system. The early history of dual chamber pacemakers witnessed a high lead dislodgement rate of at least 20% (Smyth, PND, et al. Permanent pervenous atrial sensing and pacing with a new J-shaped lead. J Thoracic Cardiovascular Surgery. 1976;72:565-570). Winkle, et al reported that the incidence of dislodgement of the superior vena cava spring leads with the current market release ICD system to be 6.3%. (Winkle, et al. Automatic Implantable Cardioverter-Defibrillator: Efficacy, Complications, and Survival in Patients with Malignant Ventricular Arrhythmias. JACC. June 1988; Vol.11, No.6:1278-86).

G. Inactive Patients

There are a total of 82 patients who had received a PCD® System and are no longer active in the study as of 2/1/93. Table G-1 shows the distribution of inactive patients by reason for no longer being active in the PCD® Transvene™ System clinical study.

PCD® Transvene™ System Inactive Patients	
Inactive Patients	**All Patients**
Patient Deaths	51
Infection (Explant)	22
Heart Transplant	9
Total	82

Table G-1: PCD® Transvene™ System - Inactive Patients - 2/1/93

H. Patient Deaths

The positive impact of implantable cardioverter defibrillator (ICD) therapy on sudden cardiac death mortality has been well documented in the medical literature. The use of device therapy for the treatment of recurrent ventricular arrhythmias has become an accepted and important clinical tool. An analysis of the sudden cardiac death survival in the PCD® Transvene™ System patient population was performed.

For purposes of the clinical study, each of the patient deaths was categorized using the following definitions:

Non-Cardiac: Deaths that occurred where the primary cause of death was determined to be non cardiac in nature, e.g. stroke, cancer, etc.

Cardiac: Deaths that occurred where the primary cause of death was determined to be cardiac in nature.

Non-Sudden: Deaths that occur greater than one hour after the onset of symptoms.

Sudden: Deaths that occur within one hour of the onset

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of symptoms or where the death is unwitnessed. Sudden cardiac deaths were also categorized as being **Witnessed** or **Unwitnessed**.

Perioperative: Deaths that occur within thirty days of implant.

System Related: A death which results from a malfunction (operation not according to design specification) of a PCD® System component, or as a result of a device induced arrhythmia, or an interaction between a PCD® System component and the patient.

Procedure Related: A death which occurs as a result of a procedure required to implant, follow or test a PCD® System.

All deaths and significant complications have been and will continue to be reviewed by a committee comprised of PCD® Transvene™ System investigators and other physicians. Two committees (Clinical Event Review Committees) have been formed, one to review North American deaths and complications, and the other to review European clinical events. The primary purpose of these reviews was to determine whether the PCD® System was related to the deaths or significant complications that have occurred and, if so, what changes may be required to prevent such events in the future.

There have been a total of 51 patient deaths reported in the PCD® Transvene™ System patient population. Table H-1 summarizes how these patient deaths have been classified.

PCD® Transvene™ System
Summary of Death Classifications
(n = 757)

Classifications	Number of Deaths
Sudden Cardiac	5
Non-Sudden Cardiac	30
Noncardiac	16
Total	51

Table H-1: PCD® Transvene™ System - Summary of Death Classifications - 2/1/93

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None of the patient deaths were attributed to a malfunction of the PCD® Transvene™ System.

Actuarial survival analysis on the PCD® Transvene™ System was done on all patients who were either evaluated for implantation or in whom the device was implanted. Thus, the analysis is done from the perspective of **intention to treat.** Those patients in whom the PCD® Device was OFF at the time of death or in whom no device was implanted **are** included in the survival analysis. Those patients that were screened for a PCD® Transvene™ System but failed to receive a Transvene™ system are not included in this analysis.

Projected one year survival calculations for the various death classifications are provided in Table H-2. **The actuarial projections include perioperative deaths only in the calculation of one year survival from death due to all causes (shown in the row labelled Overall).** The perioperative death rate defined as deaths which occurred within thirty days of implant was 0.7% (5/757) which is considerably less than the perioperative mortality for the PCD® System with Epicardial leads (5.3% - 39/742). Included in this table are the projected one year survival calculations for patients who ultimately received a PCD® Transvene™ System (n = 757) and all patients that were screened for a PCD® Transvene™ System (n = 854) regardless of implant outcome.

PCD® Transvene™ System One Year Actuarial Survival		
	Received PCD® Transvene™ System	**Screened for a PCD® Transvene™ System**
Sudden Cardiac Death	99.5%	99.4%
Non-Sudden Cardiac	96.2%	96.6%
All Cardiac	95.8%	96.1%
Noncardiac	98.1%	98.3%
Perioperative	0.7%	1.6%
Overall	93.3%	92.9%

Table H-2: PCD® Transvene™ System - One Year Actuarial Survival - 2/1/93

The positive impact of the PCD® Transvene™ System on patient mortality is clearly obvious from this analysis. The sudden cardiac death survival rate in this patient group is 99.5% in the patient group that received a Transvene™ System and 99.4% in those who were screened for a Transvene™ System. This is marked improvement when compared with the reported survival of similar patient groups treated with drug therapy alone of between 34% and 73% at one year.

I. Clinical Experience By Primary Indication

Medtronic is requesting approval for use of the PCD® Transvene™ System in the following patient population:

* Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or

* Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

Sudden cardiac death without recurrent VT (**SCD**) was the indication for implant in 37.1% of the patients, recurrent ventricular tachycardia without an episode of sudden cardiac death (**VT**) was the indication for implant in 49.8% of the patients, and sudden cardiac death and recurrent VT (**SCD/VT**) was the indication for implant in 13.1% of the patients.

The performance of the PCD® Transvene™ System in these three groups are summarized in Table I-1.

In all three patient groups, coronary artery disease was the predominant heart disease and the patients exhibited moderate left ventricular dysfunction as demonstrated by mean ejection fractions of less than 40%. The mean LED at the time of implant was similar among the patient groups as was the mean DFT.

The overall efficacy in terminating spontaneous VT/VF episodes in the SCD patient group was 98.4%, in the VT patient group 98.3%, and in the SCD/VT group 99.1%. Thus, independent of the indication for implant, the PCD® Transvene™ System was highly effective in terminating spontaneous episodes of VT/VF.

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The one year sudden cardiac death survival rates for all groups was greater than 98.6%

This analysis indicates that the PCD® Transvene™ System has performed safely and effectively in the indicated patient groups and should be approved for use in the indicated patient population.

PCD® Transvene™ System
Data Summary by Primary Indication

	SCD	VT	SCD/VT	All Patients
# of Patients	281 (37.1%)	377 (49.8%)	99 (13.1%)	757
Number, % Male Number, % Female	212 75.4% 69 24.6%	309 82.0% 68 18.0%	89 89.9% 10 10.1%	610 80.6% 147 19.4%
Mean Age	56.8 yrs	61.2 yrs	60.0 yrs	59.4 yrs
Coronary Artery Disease	191 68.0%	292 77.5%	78 78.8%	229 72.2%
Mean Ejection Fraction	39.1% (N=259)	33.7% (N=339)	32.5% (N=90)	35.6% (N=688)
Defibrillation Pathway: Sequential Simultaneous Single	 201 71.5% 74 26.3% 6 2.2%	 295 77.6% 82 21.6% 3 0.8%	 76 76.8% 22 22.2% 1 1.0%	 574 75.3% 178 23.4% 10 1.3%
Mean LED	15.3J (N=264)	16.2J (N=351)	17.3J (N=87)	16.0J (N=702)
Mean DFT	14.0J (N=117)	15.5J (N=155)	13.9J (N=44)	14.8J (N=316)
Spontaneous VT: # of Patients # of Episodes % Success	 58 1157 99.2%	 206 7591 98.1%	 52 1279 99.0%	 316 10027 98.4%
Spontaneous VF: # of Patients # of Episodes % Success	 107 686 96.9%	 162 916 99.1%	 48 380 99.5%	 317 1982 98.4%
1 Year SCD Survival	100.0%	99.4%	98.6%	99.5%

Table I-1: PCD® Transvene™ System Data Summary by Primary Indication - 2/1/93

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J. Patients Not Meeting Implant Criteria

J.1 Overview

The PCD® Transvene™ System offers a simpler and safer implantation technique for an implantable cardioverter defibrillator system. In addition, the PCD® Transvene™ System decreases the potential perioperative and long term mortality associated with current epicardial system implantation approaches.

There is a class of patients who cannot tolerate the thoracotomy required for the utilization of the epicardial patch lead defibrillation lead system and who are at high risk of sudden cardiac death. Because of the surgical risks and postsurgical complications associated with the implant of an epicardial lead system, implantation in the following patient groups may not be desirable or possible:

(1) patients in whom there is no indication for concomitant cardiovascular surgery at the time of ICD implant;

(2) patients with severe pulmonary disease who can not tolerate prolonged anesthesia or an open chest procedure;

(3) patients with severe congestive heart failure (ejection fraction < 40%) who are at increased risk for perioperative mortality following a thoracotomy procedure;

(4) patients who may eventually require open chest procedures for treatment of their coronary artery disease or cardiac transplant.

For these patients, a transvenous ICD System is the only therapy available. The PCD® Transvene™ System simplifies and greatly reduces the risk associated with lead introduction, making therapy available to these patient groups. Because there is no need to open the chest of these patients, more options for future therapy remain available; e.g. CABG is associated with increased morbidity and mortality if there has been prior open chest surgery.

However, it is expected that nonthoracotomy lead systems will have higher mean implant defibrillation thresholds as compared to traditional epicardial lead systems. In an

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epicardial lead system, the lead system has a larger electrode surface area theoretically decreasing defibrillation requirements.

The smaller electrode surface areas of the PCD® Transvene™ System defibrillation leads might reduce the proportion of patients in whom the implant criteria could be met. Not meeting the implant criteria may reduce the chronic effectiveness of the lead system. Recent studies indicated that 70% of patients evaluated may be candidates for a nonthoracotomy defibrillation lead system (Wilber, D, et al. Clinical Advances in Nonepicardial Implantable Defibrillator Lead Systems. The Journal of Invasive Cardiology. Vol.3, No.6,November/December 1991).

For purposes of the PCD® Transvene™ System, the implant criteria was defined as successful VF termination at least 3 times in 4 attempts with the final lead configuration with an output energy of 18 Joules or less. The determination of a defibrillation threshold was not required.

A defibrillation threshold (**DFT**) was defined as the energy at the lowest successful defibrillation attempt, provided the patient had a failure below the lowest success or a success at $\leq$ 5J. The lowest energy of defibrillation (**LED**) was defined as the lowest programmed energy that successfully defibrillated the patient. In both cases, conversion of ventricular tachycardia or ventricular flutter to sinus rhythm was **not** included in the determination of the DFT or LED.

(b)(4)

(b)(4)

System and are divided into the following groups - (1) Patients who received a PCD® Transvene™ System; and (2) Patients screened for a PCD® Transvene™ System and received a PCD® Epicardial System. Figure 1 provides an overview of the outcome of these patients.

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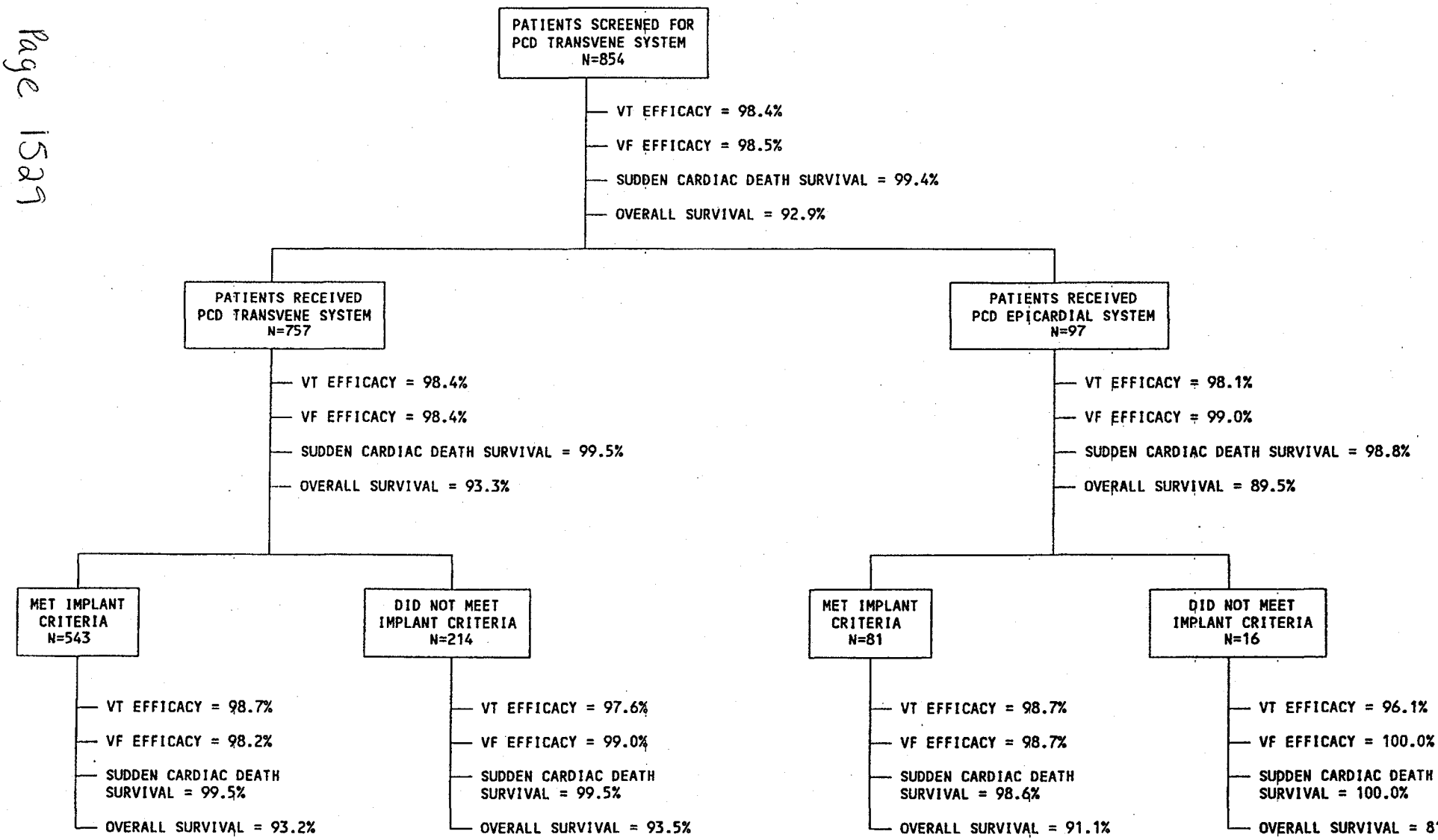
PCD® Transvene™ SYSTEM IMPLANT EVALUATION



ure 1: Patients Screened for a Transvene™ System

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As can be seen, 88.6% (b)(4) of the patients who were screened for a PCD® Transvene™ System ultimately received the system. Of these 757 patients, 71.7% (543 patients) met the recommended defibrillation implant criteria which compares favorably with the predicted success rates published in the literature (Wilber et al). However, 28.3% (214/757) of the patients did not meet the recommended defibrillation efficacy implant criteria and still received the PCD® Transvene™ System. It should be noted that 97.4% of the patients (737/757) received the PCD® Transvene™ System with at least a 10 Joule defibrillation safety margin between the lowest energy of success (24J) and the maximum output (34J) of the PCD® Device.

The investigators utilized this 10 Joule safety margin as a benchmark based on the clinical experience discussed in the article, Troup P., et al. The Implanted Defibrillator: Relation of Defibrillating Lead Configuration and Clinical Variables to Defibrillation Threshold. Journal of American College of Cardiology 1985; 6:1315-1321. Finally, and perhaps most importantly, the investigators also felt that for these patients the risk associated with not meeting the recommended implant criteria was outweighed by the risk of not implanting an ICD or implanting an epicardial system.

There were twenty patients (2.6%), who received a PCD® Transvene™ System, whose cardiovascular condition precluded further completion of the PCD® Transvene™ System and adequate definition of a defibrillation safety margin. In all cases, the physician felt that the benefit of the PCD® Transvene™ System outweighed the risk of further inductions or the risk of a thoracotomy and elected not to evaluate or implant a PCD® Epicardial System.

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J.2 Patients Receiving PCD® Transvene™ System & Did Not Meet Implant Criteria

For purposes of the PCD® Transvene™ System, the implant criteria was defined as successful VF termination at least 3 times in 4 attempts with the final lead configuration at an output energy of 18 Joules or less. Of the 757 patients who received a PCD® Transvene™ System, 214 patients (28.3%) did not meet the recommended defibrillation implant criteria and yet still received the PCD® Transvene™ System. The physicians justification for implanting the PCD® Transvene™ System despite not meeting the recommended defibrillation implant criteria are presented in Table J-1.

PCD® Transvene™ System
Reasons for Not Meeting Implant Criteria
Physician Justification

Reason	Number of Patients
Success at $\leq$ 24 Joules	170
Difficult/Unable to Induce VF	24
Patient Condition	20
Total	214

Table J-1: PCD® Transvene™ System: Physician Justification for Not Meeting Implant Criteria - 2/1/93

Further analysis of the patient who did not meet the recommended implant criteria indicates however, that 91% (194/214) had a 10 Joule safety margin between the lowest energy of successful defibrillation and the maximum output of the PCD Device (34J). Therefore, of the 757 patients who received a PCD® Transvene™ System, 97.4% (737/757) had at least a 10 Joule defibrillation safety with the implanted lead configuration.

There were 20 patients (2.6%) in whom the implant procedure was terminated due to poor patient condition. These patients received a PCD® Transvene™ System without at least a 10 Joule defibrillation safety margin. The

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implant circumstances of these patients is summarized as follows:

- At least one successful defibrillation was obtained at an energy level greater than 24 Joules and or equal to 34 Joules (N=11);
- Multiple inductions of VT were performed and successfully reverted with an energy level of 18 Joules or less. However, induced VF was not successfully reverted by an energy level of less than or equal to 34 Joules (N=6); and
- Physician elected to terminate the procedure due to the patient's condition before inductions with the final implanted lead configuration were performed (N=3).

Table J-2 provides a comparison of patient characteristics between patients who met the PCD® Transvene™ System implant criteria and those patients who did not meet the implant criteria but still received the PCD® Transvene™ System.

PCD® Transvene™ System
Patients Meeting Implant Criteria
versus
Patients Not Meeting Implant Criteria

Patient Characteristics

Data	Meeting Criteria	Not Meeting Criteria
Number of Patients	(b)(4) (b)(4)	214
Mean Follow-Up	12.3 months	10.1 months
Male* Female	(b)(4) (b)(4) 77.7%) (22.35)	(b)(4) (b)(4) (87.9%) (12.1%)
Mean Age	59.4 yrs	59.6 yrs
Indication* SCD VT SCD/VT	(b)(4) (b)(4) (38.5%) (51.2%) (10.3%)	(b)((33.6%) (46.3%) (20.1%) (b)(4)
Cardiovascular History CAD Cardiomyopathy	(b)(4) (b)(4) (72.9%) (31.9%)	(77.1%) (30.4%)
Mean EF*	6.3%	33.7%
NYHA Class I II III IV	(b)((b)(4) (30.9%) (52.4%) (15.4%) (1.3%)	(b)((b)(4) (25.8%) (56.6%) (16.6%) 2.0%)
Number ON Drugs at Implant Number ON Amiodarone	(41.1%) (14.4%)	(45.3%) (17.8%)

* (b)(4) (b)(4)

Table J-2: PCD® Transvene™ System: Patients Meeting Implant Criteria vs Not Meeting Implant Criteria - Comparison of Pt Characteristics - 2/1/93

Statistical analysis indicated three significant differences between these two patient groups - patient sex, indication for implant and mean ejection fraction.

Patients not meeting implant criteria had a statistically higher percentage of patients who were male (p = 0.002). This difference reflects that the majority of patients with

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coronary disease with concomitant life threatening ventricular arrhythmias are males.

Analysis indicated the patients not meeting the implant criteria had a statistically higher percentage of patients whose primary indication for implant was sudden cardiac death associated with recurrent ventricular tachycardia (b)(4) This difference reflects the physicians use of the PCD® Transvene™ System.

Finally, patients who did meet the implant criteria had a statistically lower mean ejection fraction (b)(4) which reflects a higher degree of underlying cardiovascular disease in these patients.

It should be noted, that none of these differences should be used as predictors for patients who should be screened for a PCD® Transvene™ System.

In order to determine if the patient's not meeting implant criteria had higher risk for morbidity and mortality, a comparison of their clinical outcome was made with those patients who did meet the implant criteria. This comparison is provided in Table J-3.

PCD® Transvene™ System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Implant Data		
Data	**Meeting Criteria**	**Not Meeting Criteria**
Number of Patients	543	214
Spontaneous VT Episode Efficacy	98.7%	97.6%
Spontaneous VF Episode Efficacy	98.7%	99.0%
Number of Patient Deaths	37	14
Perioperative Mortality	0.7%	0.5%
One Year Survival		
Sudden Cardiac	99.5%	99.5%
Non-Sudden Cardiac	95.8%	97.2%
All Cardiac	95.4%	96.7%
Noncardiac	98.5%	97.1%
Overall	93.2%	93.5%

Table J-3: PCD® Transvene™ System: Patients Not Meeting Implant Criteria versus Patients Meeting Implant Criteria - Comparison of Clinical Outcome - 2/1/93

The two patient groups had similar efficacy in the treatment of spontaneous VT/VF episodes. Importantly, in the patient population who did not meet the implant criteria there were no patients who experienced actual spontaneous VF episodes where all programmed PCD® Device therapies failed to terminate the episode.

Five patients experienced 7 episodes in which the PCD® Device was ineffective in terminating a spontaneous episode of VF despite delivery of all four programmed VF therapies. Three patients had 5 reported ineffective VF spontaneous episodes that were due to sinus tachycardia or atrial fibrillation with rapid ventricular response rather than VF. Reprogramming and pharmacologic intervention resolved these problems.

Two patients experienced 2 episodes in which the PCD® detected the episodes as VF but were actually episodes due to extraordinary circumstances. The first patient (b)(6) had incessant episodes of fast VT (cycle length 280 ms) that were eventually resolved by drugs. The second patient (b)(6) was in hospital and there was an episode of VF detected. However, the device was interrogated before termination of the episode was detected. There was external intervention associated with the terminal event. The device was not interrogated again.

Eighteen patients experienced 68 episodes in which the PCD® Device was ineffective in terminating a spontaneous episode of VT despite delivery of all four programmed VT therapies. Nine patients experienced 44 ineffective episodes that were due to sinus tachycardia or atrial fibrillation/flutter (SVT) with a rapid ventricular response that had been detected as VT. These episodes were resolved with either modification of programmed parameters or of antiarrhythmic drug therapy. It should be noted that the PCD® Device responded appropriately based on the programmed detection parameters.

The remaining 24 episodes occurred in 8 patients in which the programmed VT therapies were ineffective in terminating a spontaneous VT episode. **No patient deaths occurred as a result of ineffective VT therapy.** Reprogramming and pharmacologic intervention resolved these events.

There was no difference in the one year sudden cardiac survival or the overall survival in the two groups although follow-up was shorter for patients not meeting implant criteria (10.1 vs 12.3 months). This indicates, that despite not meeting the implant criteria these patients were not at higher risk of sudden cardiac death.

Finally, the survival of patients receiving a PCD® Transvene™ System without meeting implant criteria (N = 214) was compared to patients receiving a PCD® Epicardial System without meeting implant criteria (N = 92). This comparison is provided in Table J-4.

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PCD® Transvene™ System Patients Not Meeting Implant Criteria Survival Analysis versus PCD® Epicardial System Patients Not Meeting Implant Criteria Survival Analysis		
	PCD® Transvene System Not Meeting Implant Criteria	PCD® Epicardial System Not Meeting Implant Criteria
Number of Patients	214/757 (28.5%)	92/742 (12.4%)
Number of Deaths	14	17
Sudden Cardiac	99.5%	98.6%
Non-Sudden Cardiac	97.2%	98.8%
Noncardiac	97.1%	97.3%
Overall*	93.5%	87.6%

* Statistically Significant ($p \leq 0.05$)

Table J-4: PCD® Transvene™ System: Patients Not Meeting Implant Criteria - PCD Transvene System vs PCD® Epicardial System - 2/1/93

Though the PCD® Transvene™ System had a higher incidence of patients not meeting implant criteria (28.5%) compared to the PCD® Epicardial System (12.4%), there was no statistical difference in the sudden cardiac death patient survival. However, the overall survival of patients not meeting implant criteria with the Transvene™ System was significantly better ($p = 0.037$) when compared to the PCD® Epicardial System patients not meeting implant criteria, 93.5% and 87.6%, respectively.

The investigators felt in every case that the testing performed at the time of implant, though it did not meet the recommended implant criteria, did provide an adequate demonstration of device effectiveness and justified the implant of the PCD Transvene System. Finally, there have been no patients deaths secondary to unsuccessful termination of a spontaneous VT or VF episode in this patient population.

J.3 Description of Patients Not Meeting Implant Criteria

As noted previously, the patients not meeting implant criteria (N = 214) were divided into three groups (1) Successful defibrillation at an energy level of equal to or less than 24 Joules [79.4% of the patients]; (2) Difficult to induce VF [11.2% of the patients]; and (3) Implant procedure terminated due to poor patient condition [9.4% of the patients]. These patient groups are reviewed in the following discussion.

Lowest Energy of Defibrillation < 24 Joules

There were 170 patients in whom the PCD® Transvene™ System was implanted with a defibrillation safety margin of at least 10 Joules. Table J-5 provides an overview of these patients clinical experience.

These data indicate that the final implanted PCD® Transvene™ System was evaluated and significant attempts were made to meet the recommended implant criteria. In most of these patients (79.4%), a safety margin of 10 Joules was obtained between the successful defibrillation energy (24 J or less) for ventricular fibrillation and the maximum output of the PCD Device (34 J). The investigators decided in certain circumstances that this was appropriate demonstration of device effectiveness and that the PCD® Transvene™ System could be implanted.

Of these patients, 159 (93.5%) have had VT or VF induced at a chronic follow-up visit and in each case, VT or VF was successfully terminated by the PCD Transvene System (141 patients or 82.9% had only VF induced). In addition, 65 patients (38.2%) have experienced a spontaneous VF episode with an overall efficacy of 99.4%.

Thus, the clinical outcome in these patients was not adversely affected by not meeting implant criteria since their spontaneous VF episode efficacy was 99.4%% and the one year sudden cardiac death actuarial survival was also 99.4%. The duration of follow up, however, is limited to an average of 9.7 months.

PCD® Transvene™ System Patients Not Meeting Implant Criteria 10J Safety Margin Provided	
Number of Patients	170
Lowest Energy of Defibrillation:	
1 Success with 10J Safety Margin	87
2 Success with 10J Safety Margin	58
3 Success with 10J Safety Margin	18
> 3 Success with 10J Safety Margin	7
Overall Spontaneous VF Episode Efficacy	99.4%
One Year Survival:	
Sudden Cardiac	99.4%
Overall	93.8%

Table J-5: PCD® Transvene™ System: Patients Not Meeting Implant Criteria with 3/4 Successes at $\leq$ 24 Joules Clinical Experience - 2/1/93

Difficult to Induce VF

There were 24 patients who did not meet the recommended PCD® Transvene™ System implant criteria because at least three episodes of VF were not induced at the time of implant. Of these, 15 patients had ventricular tachycardia induced and successfully reverted. The remaining 9 patients had ventricular flutter induced and successfully reverted. In all 24 patients, the lowest successful energy was equal to or less than 18 Joules.

The indication for implant was sudden cardiac death (SCD) in 6 patients (25%), recurrent ventricular tachycardia (VT) in 13 patients (54.2%) and sudden cardiac death associated with recurrent ventricular tachycardia (SCD/VT) in 5 (20.8%) patients. Thus the majority of the patients, 75%, had documented recurrent ventricular tachycardia as part of their ventricular tachyarrhythmia history. Eight of the these patients (33.0%) were on Amiodarone therapy which may have contributed to the inability to induce VF.

Of the 24 patients who did not meet the recommended PCD® Transvene™ System implant criteria because at least

three episodes of VF were not induced at the time of implant, 13 patients (54.2%) have experienced a spontaneous VF episode and 21 patients (87.5%) have had VT or VF induced during a chronic follow-up. In all cases, VF was successfully reverted by the PCD® Transvene™ System.

There has been one reported patient death (b)(4), (b)(6) in the patient group with a resultant one year sudden cardiac death and overall actuarial survival of 100%.

Patient Condition

There were 20 patients in whom the implant procedure was terminated due to poor patient condition. These patients received a PCD® Transvene™ System without at least a 10 Joule defibrillation safety margin. The implant circumstances of these patients is summarized as follows:

- At least one successful defibrillation was obtained at an energy level greater than 24 Joules but less than 34 Joules (**N = 11 patients**);
- Multiple inductions of VT were performed and successfully reverted with an energy level of 18 Joules or less. However, induced VF was not successfully reverted by an energy level of less than or equal to 34 Joules (**N = 6 patients**); and
- Physician elected to terminate the procedure due to the patient's condition before inductions with the final implanted lead configuration were performed (**N = 3 patients**).

The mean ejection fraction of this group was 26.9%, indicating more severe underlying cardiovascular disease, and may have contributed to the physicians decision to terminate the implant procedure prior to meeting implant criteria. This group had a mean of 6.8 VF inductions, 2.2 lead configurations evaluated and a mean duration of VT/VF for the implant procedure of 220 total seconds. The circumstances of the implant procedures, mainly the duration of induced ventricular tachyarrhythmia and associated hemodynamic compromise, limited the number of inductions that could be performed and whether the recommended implant criteria could be met.

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Of these 20 patients, VT or VF has been induced at a chronic follow-up visit in 16 patients (80%) and in all cases successful defibrillation with the implanted PCD® Transvene™ System was documented.

The overall spontaneous VF episode efficacy for this patient group was 96.0%. However, further reviewed indicated that one patient experienced atrial fibrillation that was detected as VF and in whom all four programmed VF therapies were ineffective. This patient's antiarrhythmic drug therapy was modified and there were no further reports of ineffective therapies.

Thus, there have been no patients who have experienced an actual spontaneous VF episode where all four programmed VF therapies failed to terminate the episode.

There have been two reported patient deaths, Patient ID (b)(6) which was classified as non-sudden cardiac secondary to end stage heart failure and Patient ID (b)(6) which was also classified as non-sudden cardiac. The one year sudden cardiac death survival in this patient population is 100% while the overall one year survival was 85.5%. This lower overall one year survival may due to the lower mean ejection fraction of this patient group.

The clinical outcome in these twenty patients was not adversely affected by not meeting implant criteria since there was no reports of failure to terminate a spontaneous VF episode and the overall one year sudden cardiac death survival was 100%.

K. Comparison to AICD System Experience

K.1 Overview

The current AICD Epicardial System is implanted only with a defibrillation lead system requiring a thoracotomy. The PCD® Transvene™ System allows the implantation of an implantable cardioverter defibrillator (ICD) system without the potential increased perioperative morbidity and mortality associated with a thoracotomy. This allows the application of ICD therapy in patients who may not otherwise be candidates for this type of therapy. Though the PCD® Transvene™ System will have complications and observations that are specific to the lead system, the overall performance should be at least equivalent to that reported with the current AICD Epicardial System.

This section provides a comparison of the PCD® Transvene™ System clinical experience to that of the reported AICD Epicardial System clinical experience. The following areas will be discussed:

- Patient characteristics
- Clinical performance
- Survival analysis

For purposes of comparison, the Ventak-P Epicardial System patient population described in the Summary of Safety and Effectiveness Data (PMA Application Number P890061) dated May 2, 1991 will be used. A copy of this summary was obtained through the Freedom of Information Act.

K.2 Comparison of Patient Characteristics

In comparing the clinical experience with the PCD® Transvene™ System to the reported Ventak-P Epicardial System clinical experience, it is important to determine that the patients who received the device are comparable.

The characteristics of the patients receiving the PCD® Transvene™ System were compared to the characteristics of patients discussed in the Ventak-P Summary of Safety and Effectiveness Data and are presented in Table K-1.

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There were no differences between the two patient groups.

PCD® Transvene™ System Comparison of Patient Characteristics PCD® versus AICD		
	PCD®	Ventak-P
Number of Patients	757	292
Mean Follow-Up Time	11.7 months	6.8 months
% Males % Females	610 (81%) 147 (19%)	231 (79%) 61 (21%)
Mean Age	59.4 years	61.5 years
Primary Indication: SCD VT SCD/VT	 281 (37%) 377 (50%) 99 (13%)	 49 (16%) 169 (59%) 73 (25%)
Coronary Artery Disease	561 (74%)	228 (78%)
Mean Ejection Fraction	35.6%	34%
Drug Therapy at Implant	42%	45.0%
Concomitant Surgery	0%	18.0%

Table K-1: Comparison of Patient Characteristics, PCD® versus Ventak-P 2/1/93

The two patient groups are comparable in mean age and mean ejection fraction. Both groups had moderately depressed left ventricular function demonstrated by the mean ejection of 35.6% for the PCD® Transvene™ System patient group and 34% for the Ventak-P Epicardial System patient group.

Analysis indicated that no statistical differences between the PCD® Transvene™ System and Ventak-P Epicardial System patient populations except in the category of patient indication. There are more patients that had Sudden Cardiac Death as the primary indication in the PCD® Transvene™ population than in the AICD population ($p = 0.001$).

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K.3 Comparison of Clinical Performance

Areas of clinical performance that were compared were implant defibrillation thresholds, incidence of spontaneous VT/VF events, incidence of complications and patient survival. These specific areas were selected in order to evaluate the system performance in the two patient populations.

Implant Defibrillation Thresholds

For the purposes of the PCD® Transvene™ System clinical study, determination of defibrillation threshold was not mandatory. However, the preferred method of evaluating defibrillation efficacy was to determine the defibrillation threshold using a testing sequence of 18J, 15J, 10J, 5J with a failure at any level causing a return to 18 J for the remaining attempts. For the purposes of this report a defibrillation threshold was defined as the energy at the lowest successful defibrillation attempt, provided a patient had a failure below their lowest defibrillation success or a success at $\leq$ 5J. The rhythm treated must have been VF to be included in the analysis.

It should be noted, that it was expected that the PCD® Transvene™ System would have a higher mean defibrillation threshold as compared to a traditional epicardial defibrillation lead system. In a epicardial system, the increased electrode surface area would theoretically decrease defibrillation requirements.

A total of 316 patients had a defibrillation threshold determined at the time of PCD® device implant. The mean defibrillation threshold (DFT) for all lead systems was 14.8J. The recommendation for VF Therapy #1 is to program the stored energy to twice the implant DFT or 18 Joules, whichever is greater. Thus an adequate defibrillation safety margin was provided when following the VF therapy programming recommendations.

In the Ventak-P Epicardial System, the mean defibrillation threshold at implant was 13.4J. Thus the two systems had similar defibrillation thresholds at implant despite the fact that one system utilized an epicardial defibrillation lead

system while the other utilized a transvenous defibrillation lead system.

These data indicate that the PCD® Transvene™ System had comparable implant defibrillation threshold performance when compared to the reported Ventak-P Epicardial System clinical experience.

Incidence of Spontaneous VT/VF Episodes

The incidence of spontaneous VT/VF episodes in the Ventak-P Epicardial System and PCD® Transvene™ System patient population was evaluated by utilizing the stored episode information provided by both devices.

In the Ventak-P device, the total number of shocks delivered to the patient is provided via interrogation of the device. The PCD® device provides information on the total number of VT and VF episodes detected by the PCD® device and the total number of VT and VF episodes successfully treated by the PCD® device as well as the number of VT/VF episodes where the PCD® device was ineffective. In addition, the last 20 intervals of the last episode satisfying detection criteria along with the first 10 intervals after the last therapy delivered are recorded by the device. These data assist the physician in evaluating the frequency of VT/VF episodes, the efficacy of the PCD® device programmed parameters and the need for reprogramming.

In the Ventak-P Epicardial System experience of 292 patients with a mean follow-up of 6.8 months, 137 (46.9%) received a device countershock in response to a spontaneous ventricular tachyarrhythmia episode as defined by the Ventak-P Device detection criteria.

In the PCD® Transvene™ System experience of 757 patients with a mean follow-up of 11.7 months, 458 patients (60.5%) have received device therapy in response to a spontaneous ventricular tachyarrhythmia episode as defined by the PCD® Transvene™ System detection criteria.

A total of 10,027 spontaneous VT and 1982 spontaneous VF episodes have been recorded by the PCD® device

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episode counters. Of the 9864 successfully treated spontaneous VT episodes, 91.4% were treated with one of the programmed antitachycardia pacing therapies incorporated in the PCD® device. The clinical benefit of tiered therapy is the reduction of delivery of high energy shocks for the treatment of stable recurrent ventricular tachycardia that may be responsive to antitachycardia pacing.

Incidence of Complications

Table K-2 provides a comparison of reported complications and observations. The AICD clinical experience data is from the Winkle, et al Long Term Outcome with Automatic Implantable Cardioverter-Defibrillator; JACC, May 1989; 13(6); 135-161. This article was selected because it provides a detailed clinical complication experience on a large patient population, 270 patients. Note that the percentage reported in the PCD® Transvene™ System includes **both complications and observations.** In the following table, the complications are reported for the categories of Fail to Cardiovert/Defibrillate, Pocket Infection, and Erosion. Observations are reported in the Inappropriate/Problematic VT/VF Therapy Delivery category.

PCD® Transvene™ System
Comparison of Complication/Observation Rates
PCD® versus AICD

Category	PCD®%	AICD%
Fail to Cardiovert/Defibrillate	2.3%	4.1%
Inappropriate/Problematic VT/VF Therapy Delivery	9.6%*	20%
Pocket Infection	2.9%	2.2%
Erosion	0.8%	0.7%

* Includes Observations only; there were no Complications in this category.

Table K-2: Comparison of Complication/Observation Rates: PCD® Transvene™ System vs AICD Epicardial System - 2/1/93

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The incidence of failure to cardiovert and/or defibrillate was lower in the PCD® Transvene™ System patient population. The instances of failure to cardiovert and/or defibrillate in the PCD® Transvene™ System patient population were associated with increased defibrillation requirements during induced episodes, none of which resulted in patient death.

The failures to cardiovert/defibrillate reported in the Winkle, et al article were associated with patch dislodgement, patch crinkling, lead conductor fracture and elevated defibrillation thresholds.

The incidence of inappropriate/problematic VT/VF therapy delivery was lower in the PCD® Transvene™ System patient population. This is to be anticipated since the device incorporates independently programmable detection algorithms for VT and VF. The reasons for inappropriate VT/VF therapy delivery included sinus tachycardia being detected as VT or VF and atrial fibrillation with rapid ventricular response being detected as VT or VF.

The overdetection circumstances reported in Winkle, et al were nonsustained VT, VT, sinus tachycardia, atrial fibrillation with rapid ventricular response, sensing lead fracture and pacemaker interaction. The patients with VT complained of receiving multiple shocks with limited or no symptoms. The incorporation of antitachycardia pacing in the PCD® device decreases the need for delivery of cardioversion shocks for the termination of stable VT and increases patient acceptance of ICD therapy.

In the Winkle, et al experience all patients with pocket infection had the devices explanted. In the PCD Transvene System experience, the incidence of device explant secondary to pocket infection was 3.2% which was comparable to Winkle's article.

Thus, the incidence of complications and observations was similar to that of the AICD Epicardial System in the categories of ineffective VT/VF therapies, infection requiring explant and erosion. The incidence of inappropriate delivery of therapy is lower in the PCD Transvene System experience than in the AICD Epicardial System experience, which is clinically significant.

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This analysis indicates that the PCD® Transvene™ System offers clinical advantages in reducing the need for a thoracotomy for implantation and reducing the number of shocks due to successful antitachyarrhythmia pacing.

K.4 Comparison of One Year Actuarial Survival

The Ventak-P Epicardial System produced by Cardiac Pacemaker, Inc, has obtained market approval from the U.S. FDA to date. While there are important differences in the function of the Ventak-P Epicardial System and the PCD® Transvene™ System, there is a natural desire for comparison of the clinical outcome, particularly the impact of these devices on death rate.

A total of 51 deaths (6.7%) were reported in the PCD® Transvene™ System patient population. Of the 35 cardiac deaths, 30 were non-sudden cardiac and 5 were sudden cardiac. Sixteen deaths were classified as noncardiac. Five of the 51 total deaths occurred within the perioperative period (death less than 30 days post implant) with a resultant perioperative mortality of 0.7%.

In the Ventak-P Epicardial System patient population a total of 19 deaths (6.5%) were reported. Of the 12 cardiac deaths, 4 were classified as sudden cardiac and 8 were classified as non-sudden cardiac. Six of the deaths were classified as noncardiac and the cause of one was unknown. Eight of the deaths occurred within the perioperative period with a resultant perioperative mortality of 2.7%. The PCD® Transvene™ System population had a lower perioperative mortality, 0.7% vs 2.7% ($p = 0.006$).

For purposes of this comparison, only the **overall** actuarial survival rate includes perioperative deaths. All other calculations in both the PCD® Transvene™ System and Ventak-P Epicardial System group exclude perioperative deaths.

For the Ventak-P Epicardial System, patient deaths were **censored** if the Ventak-P device had been either electively deactivated for various reasons prior to the patient's death, thus preventing the device from attempting to convert the arrhythmia or if the pulse generators were known to be

nonfunctional and awaiting replacement. For purposes of this comparison, 7 patient deaths were **censored** in the PCD® Transvene™ System patient population because the devices were deactivated at the time of patient death.

This PCD® Transvene™ System sudden cardiac death survival of 99.7% at one year is comparable to that of the Ventak-P Epicardial System sudden cardiac death survival rate of 98.6%. More importantly, the overall one year actuarial survival for the PCD® Transvene™ System was 94.2% as compared to 90.8% for the Ventak-P Epicardial System. This difference was primarily due to the improvement in the reported perioperative mortality in the PCD® Transvene™ System patient population. [Note: Confidence interval analysis was performed indicating that there was a statistical difference in the reported **Overall** mortality.]

This comparison of actuarial survival rates indicates that the projected sudden cardiac death survival of patients receiving a PCD® System patient population is comparable to that reported for the Ventak-P Epicardial System. Thus, the incorporation of programmable VT/VF detection and therapy algorithms has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

In addition, the elimination of a surgical thoracotomy for implant in the PCD® Transvene™ System has improved the perioperative mortality and overall one year survival when compared to the Ventak-P Epicardial System.

L. Comparison to PCD® Epicardial System Clinical Results

The PCD® Epicardial System uses the same tiered therapy device that combines features of bradycardia support pacing, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. This system has incorporated programmability and multiple detection and therapeutic options that allows the titration of device therapy to a patient's specific clinical arrhythmia history.

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The PCD® Epicardial System requires a thoracotomy for implantation because of the need to insert epicardial patch leads. This exposes the patient to surgical risk and potentially limits the type of patient who may be considered for implant of the system. The need for a simpler and safer implantation technique is widely recognized. The incorporation of a nonthoracotomy lead system, such as the PCD® Transvene™ System, should decrease the potential perioperative and long term mortality and morbidity associated with current epicardial system implantation approaches.

The PCD® Epicardial System and PCD® Transvene System are identical except for the implanted defibrillation lead system. Thus, the performance of the PCD® device, associated support equipment, is similar in the two systems and therefore a comparison of clinical experience should focus on those areas where the implanted lead system may impact clinical outcome.

This section provides a comparison of the PCD® Transvene™ System clinical experience to the reported PCD® Epicardial System clinical experience. The following areas will be discussed:

- Patient characteristics
- Implant Data
- Spontaneous VT/VF Episode Efficacy
- Complications and Observations
- Survival analysis

This analysis will show that the incorporation of a nonthoracotomy defibrillation lead system has maintained the type of therapy available for the treatment of recurrent VT/VF and decreased the potential mortality and morbidity associated with epicardial implant approaches while maintaining the positive impact of ICD therapy on VT/VF episode efficacy and patient survival.

L.1 Comparison of Patient Characteristics

In comparing the clinical experience with the PCD® Transvene™ System to the PCD® Epicardial System clinical experience, it is important to determine that the patients who received the device are comparable.

Table L-1 contains the characteristics of the 757 patients receiving the PCD® Transvene™ System versus the

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characteristics of the 742 patients who received the PCD® Epicardial System as of 1/5/93.

PCD® Transvene™ System
Comparison of Patient Characteristics

	PCD® Transvene™ System	PCD® Epicardial System
Number of Patients	757	742
Mean Follow-Up Time	11.7 months	16.3 months
% Males*	610 80.6%	637 85.8%
% Females	147 19.4%	105 14.2%
Mean Age	59.4 years	59.6 years
Primary Indication*:		
SCD	281 37.1%	214 28.8%
VT	377 49.8%	405 54.6%
SCD/VT	99 13.2%	123 16.6%
Cardiovascular History:		
Coronary Artery Disease	561 74.1%	569 76.7%
Cardiomyopathy	238 13.1%	222 29.9%
Mean Ejection Fraction	35.6%	34.0%
Number of Drugs Failed*	2.3	3.0

* (b)(4) (b)(4)

Table L-1: Comparison of Patient Characteristics, PCD® Transvene™ System versus PCD® Epicardial System - 2/1/93

Both groups had moderately depressed left ventricular function demonstrated by the mean ejection of 35.6% for the PCD® Transvene™ System patient group and 34.0% for the PCD® Epicardial patient group.

Analysis indicated that the PCD® Transvene™ System patient population had a higher percentage of patients whose indication for implant was sudden cardiac death (p = (b)(4) (b)(4) and higher percentage of females (b)(4) (b)(4) It is not expected that these differences will result in a different clinical outcome in the PCD® Transvene™ System patient population as compared to the PCD® Epicardial System. This difference in patient indication is a reflection of the physicians use of the PCD® Transvene™ System.

It is interesting to note, that there was a statistical difference in the number of antiarrhythmic drugs tested between the two patient groups (b)(4) The PCD® Transvene™ System patient group failed a mean of 2.3 antiarrhythmic drugs prior to implant while the PCD® Epicardial System patient group failed a mean of 3.0 antiarrhythmic drugs. This difference is a reflection of the differences in the indications for implant between the two patient groups. The PCD® Transvene™ System patient group had a higher incidence of patients whose primary indication for implant was sudden cardiac death. These patients have a higher probability of having experienced a sudden cardiac death episode but were non-inducible during electrophysiologic testing so that drug testing was not feasible.

L.2 Spontaneous VT/VF Episodes Efficacy Comparison

The primary benefits from the use of the PCD® System center on the detection and termination of life-threatening ventricular tachyarrhythmias. An additional benefit of the PCD® Transvene™ System is the elimination of the need for a thoracotomy for implantation of the defibrillation lead system and the resultant decrease in potential patient morbidity and mortality associated with a thoracotomy. This clinical benefit should not be gained at the expense of providing effective termination of spontaneous VT and VF episodes. Table L-2 provides a comparison of the efficacy of the PCD® Transvene™ and PCD® Epicardial System in treating spontaneous episodes of VT and VF.

PCD® Transvene™ System Performance Comparison of Spontaneous VT/VF Efficacy PCD® Transvene™ vs Epicardial		
Spontaneous VT Episodes		
	PCD® Transvene™ System	**PCD® Epicardial System**
Mean Follow-Up	11.7 months	16.3 months
Number of Episodes	10,027	20,061
% Overall Efficacy	98.4%	98.3%
% Unsuccessful Termination	0.7%	1.0%
Spontaneous VF Episodes		
	PCD® Transvene System	**PCD® Epicardial System**
Mean Follow-Up	11.7 months	16.3 months
Number of Episodes	1092	2636
% Overall Efficacy	98.4%	98.7%
% Unsuccessful Termination	0.3%	0.5%

Table L-2: PCD® Transvene™ System: Comparison of Spontaneous VT/VF Episode Efficacy - 2/1/93

The overall success rate of the PCD® Transvene™ System in terminating spontaneous episodes of VT or VF is 98.5%. In addition, there have been no reported patient deaths due to ineffective termination of a spontaneous VT/VF episode. This success rate compares very favorably with the overall success rate of the PCD® Epicardial System which was 98.4%. Therefore, the PCD® Transvene™ System offers the potential of decreased patient morbidity and mortality without decreasing the treatment efficacy of spontaneous VT/VF episodes.

L.3 Incidence of Complications/Observations

A comparison of the reported complications and observations was made between the PCD® Transvene™ System and the PCD® Epicardial System. The PCD® Epicardial System patient population used for comparison included clinical experience as of January 5, 1992 with

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(b)(4) a mean implant duration of 16.3 months. These two patient groups are similar in the patient demographics and indication for implant of the PCD® System. In the PCD® Transvene™ System patient population, 19.4% of the patients experienced a clinical complication and 23.8% of the patients experienced a clinical observation. In the PCD® Epicardial System, 12.8% of the patients experienced a clinical complication and 25.7% of the patients experienced a clinical observation.

Table L-3 provides a comparison of the reported complications and the incidence in the two patient populations.

PCD® Transvene System
PCD® Transvene System versus PCD® Epicardial System
Reported Complications

Reported Complications	PCD® Transvene™ System	PCD® Epicardial System
	(b)(4)	
Increased Defibrillation Requirements	1.2%	0.5%
Inappropriate Therapy	-	2.2%
Pace/Sense Related	0.8%	3.5%
Infection Related - Explant	2.9%	2.3%
Lead Related	15.1%	2.8%
Device Related	0.5%	0.9%

Table L-3: Reported Complications: PCD® Transvene™ System versus PCD® Epicardial System - 2/1/93

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L.4 Survival Analysis Comparison

Despite their excellent clinical performance, epicardial defibrillation lead system have important limitations. The requirement for direct thoracic access contributes significantly to patient morbidity and mortality, patient discomfort and prolonged hospitalization. The availability of reliable nonthoracotomy lead systems should provide positive clinical impact on these issues while not negatively impacting patient survival. Therefore, a comparison of the one year actuarial survival rates for the PCD® Transvene™ and Epicardial System was performed.

Table L-4 provides a summary of the patient deaths reported in the two patient populations by classification. As a reference, the mean follow-up time for the PCD® Transvene™ System patient population was 11.7 months while for the PCD® Epicardial System it was 16.3 months.

PCD® Transvene™ System
Death Classifications
PCD® Transvene™ System versus PCD® Epicardial System

Death Classification	PCD® Transvene™ System (b)(4)	PCD® Epicardial System (b)(4)
Sudden Cardiac	5	24
Non-Sudden Cardiac	30	54
All Cardiac	35	78
Noncardiac	16	34
Total	51	112

Table L-4: Death Classifications: PCD® Transvene™ System versus PCD® Epicardial System - 2/1/93

Table L-5 provides a comparison of actuarial survival rates between the PCD® Transvene™ and PCD® Epicardial patient populations. The actuarial survival projections include perioperative deaths only in the calculation of survival from death due to all causes (shown in table row labelled **Overall**). Perioperative mortality includes those deaths

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which occur in the first thirty days post implant of the PCD® System.

PCD® Transvene™ System
Comparison of Actuarial Survival
PCD® Transvene™ System versus PCD® Epicardial System

One Year Survival	PCD® Transvene™ System	PCD® Epicardial® System	(b)(4)
Number of Patients	757	742	
Sudden Cardiac	99.5%	98.9%	
Non-Sudden Cardiac	96.2%	96.7%	(b)(4)
All Cardiac	95.8%	95.7%	
Noncardiac	98.1%	98.0%	
Overall*	93.3%	88.6%	

* (b)(4) (b)(4)

Table L-5: Comparison of Actuarial Survival: PCD® Transvene™ System versus PCD Epicardial System - 2/1/93

There was a significant increase in overall survival in the patients receiving a PCD® Transvene System®. As previously noted, the Overall one year actuarial survival includes death from all causes. The overall one year survival for patients receiving the PCD® Transvene™ System was 93.3%. This is significantly improved as compared to the overall one year actuarial survival for the PCD® Epicardial System (88.6%) (b)(4) (b)(4) This improvement in overall survival is primarily due to the marked improvement in perioperative mortality, the PCD® Transvene™ System having a 0.7% (5/757) perioperative mortality versus the a perioperative mortality of 5.3% (39/742) in the PCD® Epicardial System. This improvement in perioperative mortality is primarily due to the elimination of the need for a thoracotomy and its associated morbidity and mortality.

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M. PCD® System Performance

M.1 PCD® Device

Devices implanted for the treatment of recurrent ventricular tachyarrhythmias should perform safely and reliably in the indicated patient population. Device longevity, ventricular tachyarrhythmia detection, therapy performance, and analysis of explanted devices were evaluated to assess the performance of the PCD® Device.

Extended longevity of implantable cardioverter defibrillators should decrease the number of device replacements a given patient would experience over their lifetime and decrease unnecessary patient morbidity. Thus, the PCD® Device longevity, which is monitored utilizing battery voltage and charge time obtained via telemetry, was analyzed. The PCD® Device longevity data collected is consistent with the longevity projections.

The combined experience of induced and spontaneous VT/VF episode experience has shown that the PCD® Device VT/VF detection and therapies have performed safely and according to design specifications when required to treat induced and spontaneous VT/VF episodes.

There have been a total of 58 devices explanted. Reasons for explant were patient death (23), infection (22), cardiac transplant (9), low battery voltage (1) and PCD Device performance issues (3). The analysis of the device that was explanted due to lower than expected battery voltage indicated that the decreased battery voltage measurement was due to hermetic leakage at the input to one of the integrated circuits and this affected the battery indicator circuit only and did not affect the critical functions of the device. This leads to a voltage drop across a resistor where the voltage measurement is taken. Analysis indicated that the battery was performing to specifications and the hermetic leakage was a random event. Analysis of the other three devices indicated that two were due to random component failure and one due to shorting on Pulse 2 output. Thus, arcing occurred between the conductors inside the hermetically enclosed brazed ring of the high power hybrid. As a result, high voltage was momentarily

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applied to the low power circuitry, including the low power hybrid. This low power hybrid lost function including the capability to pace and transmit telemetry due to excessive voltage applied. Since this is the only device that exhibited this type of failure in the field and the hybrid manufacturing process has demonstrated that it will screen out infant mortality, this failure was assumed to be a random component failure.

Based on the clinical data collected, the PCD® Device has performed safely and reliably in the indicated patient population.

M.2 Transvene™ Lead Performance

The Transvene™ Lead System consists of a Right Ventricular Lead, a Coronary Sinus/Superior Vena Cava lead, and a Subcutaneous Patch lead. There have been a total of 757 Right Ventricular leads (15 with the SP2100 and 742 with the Model 6884/6966), 796 Coronary Sinus/Superior Vena Cava leads (Model 6881/6963), and 718 Subcutaneous Patch leads (Models 6895/10317/6999) implanted with a cumulative implant duration of 8894.8 months. The reported incidence of conductor coil fracture is 0.5% (4/757).

Based on the clinical data collected, the Transvene™ leads have performed safely and reliably.

N. Summary

The overall clinical experience with the PCD® Transvene™ System indicates that the system performed according to design and specification. The reported clinical complications and patient deaths are appropriately addressed in the required labelling for the system and the patient selection criteria for implant of the device is appropriate.

The following can be drawn from this analysis of the data collected in this clinical study:

Patient Deaths

- The projected one year survival probabilities for Sudden Cardiac Death, Non-Sudden Cardiac Death, all Cardiac Deaths and Noncardiac Death were found to be 99.5%, 96.2%, 95.8%, and 98.1%, respectively.

  The incorporation of programmable VT/VF detection and therapies has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

- The sudden cardiac death survival of 99.5% at one year is comparable to that of the AICD patient population 98.0%.

- There have been no deaths due to a PCD® Device malfunction.

Complications/Observations

- Complications were reported in 19.4% of the patient population and observations were reported in 23.8% of the patient population.

- The incidence of complications was comparable to that of the market released AICD system in the categories of ineffective VT/VF therapy, pocket infection, and pocket erosion and was lower than the AICD in the category of inappropriate delivery of VT/VF therapy.

Patient Indications

- All of the patients entered into this clinical evaluation met at least one of the primary indications. Sudden cardiac death (SCD) was the primary indication in 37.1% of the patients, recurrent ventricular tachycardia (VT) was the primary indication in 49.8 % of the patients and SCD/VT was the primary indication in 13.1% of the patients.

- The number of patients (60.5%) receiving VT/VF therapy for spontaneous episodes of ventricular arrhythmias supports the conclusion that the patient selection criteria are appropriate and that the PCD® Transvene™ System was implanted in patients who benefit from this therapy.

- The one year sudden cardiac death survival rates for the SCD patient group was 100.0%, for the VT patient group 99.4% and the SCD/VT patient group 98.6%.

VT/VF Detection and Therapy Performance

- The PCD® Transvene™ System properly detects and treats VT as demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VT was 98.4%.

- The PCD® Transvene™ System properly detects and treats VF as demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VF was 98.4%.

- There were no reported patient deaths due to the nondetection of a spontaneous VT or VF episode by the PCD® Transvene™ System.

PCD® Transvene™ System Performance

- The PCD® Transvene™ System components (Model 7216A/7217B and Model 6884/6966, 6881/6963, 6895/6999 Transvene™ leads) have performed according to design and specification and are, therefore, considered safe and effective in the indicated patient population.

5

O. Clinical Experience Summary Conclusions

The PCD® Transvene™ System is a tiered therapy device which combines features of bradycardia pacing support, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. The incorporation of these features has allowed the physician to titrate the ICD therapy to meet specific patient clinical needs, allowed fewer shocks to be delivered for recurrent ventricular tachycardia because of antitachycardia pacing features, allowed fewer cases of inappropriate therapy delivery due to programmable detection and allowed a sudden cardiac death survival rate identical to the Ventak-P Epicardial System.

The PCD® Transvene™ System, due to the elimination of the need for a thoracotomy, has provided a marked improvement in both the perioperative and overall patient mortality as compared to the PCD® Epicardial System. In addition, due to the decreased perioperative morbidity and mortality, the post implant hospital stay has been decreased to a mean of 7.6 days as opposed to a mean of 10.6 days (b)(4) for the PCD® Epicardial System.

Medtronic asserts and the PCD® Transvene™ investigators unanimously agree that the findings of the clinical study support the conclusion that the Medtronic Tachyarrhythmia Control System and the Transvene™ Cardioversion and Defibrillation Electrodes are safe and effective in the indicated patient population.

4

Summary of Clinical Experience

A. Introduction

The efficacy and safety of implantable cardioverter defibrillator (ICD) therapy for recurrent ventricular tachycardia (VT) and ventricular fibrillation (VF) has been well established. The current market released device (Medtronic Model 7217B with Epicardial Cardioversion/Defibrillation Leads) incorporates multiprogrammability, multiple detection and therapeutic options for the treatment of ventricular tachycardia and fibrillation. The current system, while providing lifesaving treatment of ventricular arrhythmias, requires a significant surgical procedure (thoracotomy, median sternotomy, etc.) for the placement of the epicardial lead system. The need to reduce the surgical mortality and morbidity associated with epicardial cardioversion/defibrillation lead systems has lead to the development of the PCD® Transvene™ System.

This report represents a full report of Medtronic's clinical experience with the Medtronic PCD® Model 7217B Multiprogrammable Tachyarrhythmia Control System with Transvene™ Cardioversion and Defibrillation Electrodes (Reference IDE G870102). The data included in this analysis is all data that was received by Medtronic and entered onto the clinical database as of **February 1, 1993.**

The PCD® Model 7217B Multiprogrammable Tachyarrhythmia Control System described in this submission is identical to the system which was recommended for approval by the FDA advisory panel on February 3, 1992, with the addition of Transvene™ leads.

The data analysis is organized in functional rather than chronological categories in order to present a complete picture of each of the PCD® Device's various functions. The sections included in this summary are:

- Name, Intended Use of System
- Tachyarrhythmia Control System Features
- Indicated Patient Population
- Study Objectives and Protocol Summary
- Overview of Clinical Experience
  - Implant Data
  - Spontaneous VT/VF Episode Experience

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Overall Success Rate
- Complications and Observations
- Inactive Patients
- Patient Deaths
- Clinical Experience by Primary Indication
- Patients not Meeting Implant Criteria
- Comparison to AICD Clinical Experience
- Comparison to PCD® Epicardial Clinical Experience
- PCD® Transvene™ System Performance

This summary provides an overview of the clinical experience which verifies that the PCD® Transvene™ System is safe and effective in the indicated patient population.

B. Name and Intended Use of the System

The Pacer-Cardioverter-Defibrillator (PCD®) device is an implantable, multiprogrammable, automatic tachyarrhythmia control device. The PCD® Device is used in conjunction with appropriate lead systems for the treatment of patients with ventricular tachycardia (VT) and/or ventricular fibrillation (VF). The PCD® Device also provides backup pacing in the VVI mode and noninvasive electrophysiologic (EP) study capabilities.

The PCD® Device is programmed with the market released Medtronic programmer and a unique MemoryMod™ Cartridge. The PCD® Device incorporates a two-way telemetry system which receives operational instructions from the programmer and transmits status, electrogram and event information back to the programmer for display and/or printout.

The External Tachyarrhythmia Control Device (ETCD) is an external, multiprogrammable, tachyarrhythmia control device. Its operation is similar to the PCD® Device except that cardioversion and defibrillation therapies are delivered manually. In addition, it displays measurements of cardioversion and defibrillation therapy parameters. The ETCD is used for making defibrillation threshold measurements during the PCD® Device implantation procedure.

Components

The Medtronic PCD® Transvene™ System, which is represented in Figures 1A and 1B, for which market release approval is being requested, consists of the following components:

S1

Implanted Device and Related Programming System
Pacer-Cardioverter-Defibrillator (PCD®) Device
Model 7217B

Programmer
Model 9710 programmer and related accessories (currently market released), plus
Model 9788 MemoryMod™ Software Cartridge
Lead System
Electrode Leads:
Model 6966
Model 6963
Model 6999

Implant Measurements System
Model 5355 ETCD™ External Tachyarrhythmia Control Device
Model 5418 Patient Cable
Model 5414 Test Load
Model 5417 EGM Cable
Model 5419 Jumper Cable

The physical characteristics of the Model 7217B are summarized in Table IB-1:

PCD® Model 7217B Physical Characteristics	
Feature	**Model 7217B**
Volume	113 cc
Weight	198 grams
Connector Module	Four connector ports
Power Source	Wilson Greatbatch Model 8830 Lithium Silver Vanadium Oxide
Sensing Configuration	Standard Bipolar
Pacing Configuration	Integrated Bipolar

Table IB-1: Features: Model 7217B - 2/1/93

The Model 7217B PCD® Device uses the pace/sense leads for sensing, thus providing **standard bipolar** sensing. Pacing is delivered in the integrated bipolar configuration.

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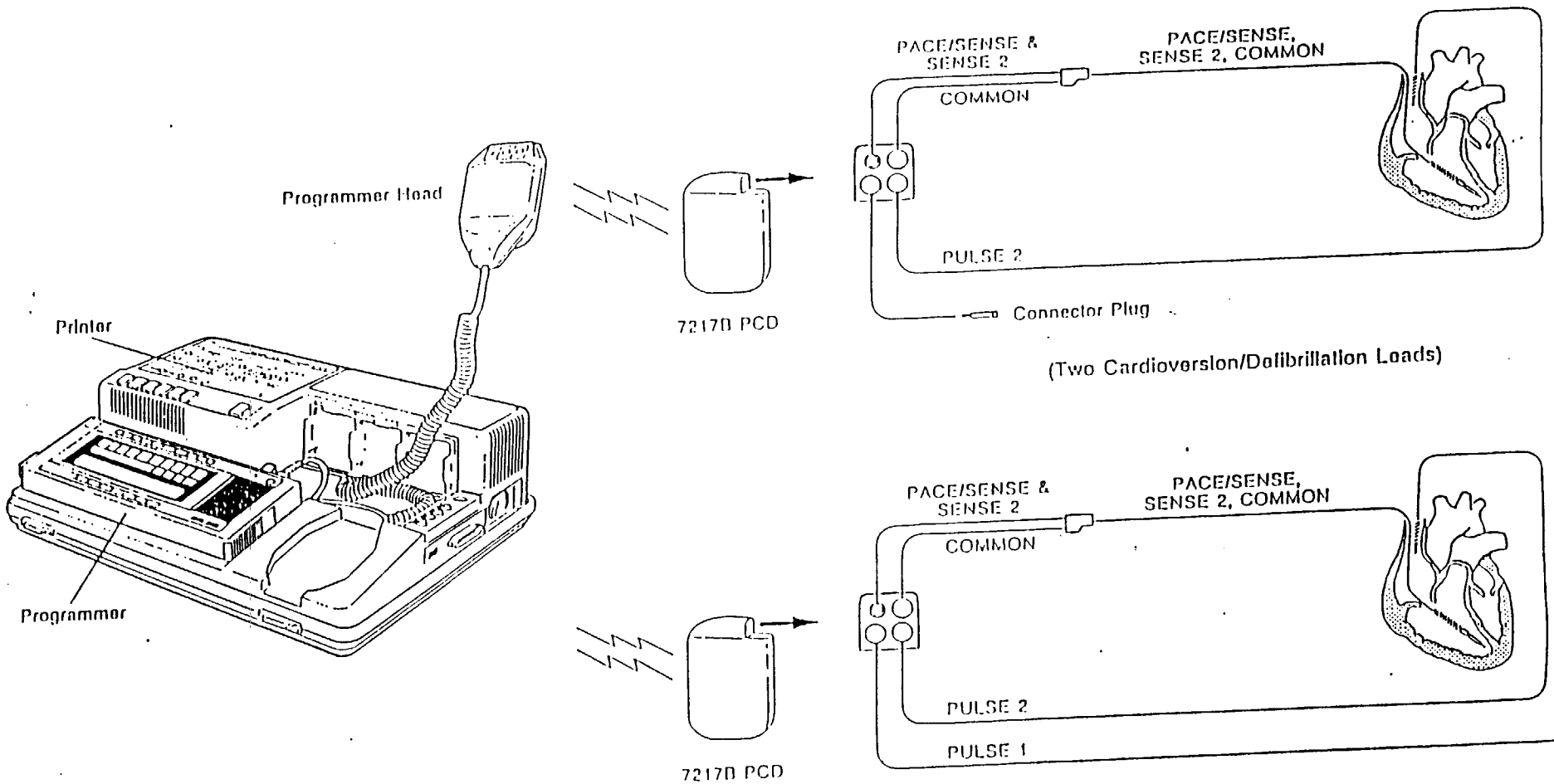

7217B PCD Device and Nonthoracotomy Lead System

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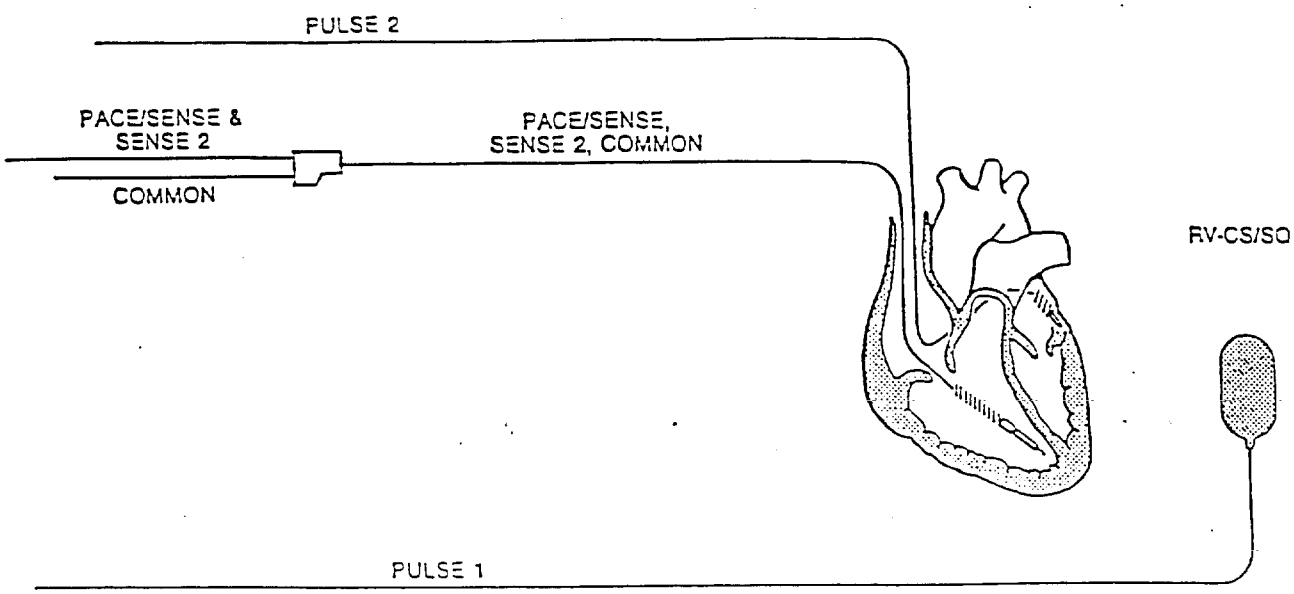
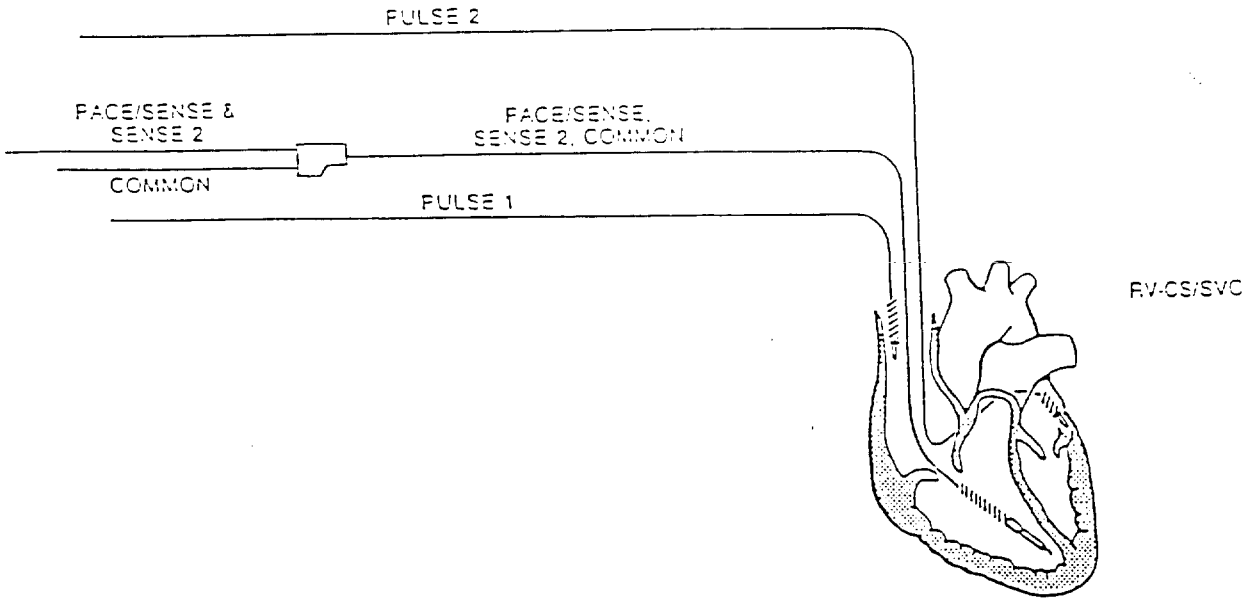
FIGURE 1B



Example of Lead Placement for Simultaneous or Sequential Path (RV-CS/SQ).



Example of Lead Placement for Simultaneous or Sequential Path (RV-CS/SVC).

C. Tachyarrhythmia Control System Features

C.1 PCD® Device

The PCD® Device is an implantable device designed to detect episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF), and upon detection, automatically deliver the appropriate therapy or progression of therapies programmed by the physician for each patient. The available therapy types that can be programmed are overdrive pacing, cardioversion, and defibrillation.

The main features of the PCD® Device include the detection and treatment of recurrent ventricular tachycardia (VT) and/or ventricular fibrillation (VF). The device has two independently programmable detection and therapy algorithms, one for VT and a second for VF. A series of up to four tiered therapies can be delivered after detection of VT and a separately programmed series of up to four therapies after the detection of VF. If a therapy does not convert the arrhythmia, the next programmed therapy is delivered.

Other features of the device include VVI back-up pacing, flexible programming, noninvasive electrophysiology study capabilities, and information reports.

VT Detection and Therapy

The VT detection algorithm includes up to three separately programmable criteria to identify the presence of a tachycardia.

The PCD® Device employs a feature that automatically adjusts signal detection sensitivity to assure proper detection while minimizing sensing of T-waves following intrinsic cardiac events. This function, **Auto-Adjusting Sensitivity**, is active during any sensing period, including VT and VF detection. It allows use of sensitive settings required for VF detection without oversensing during normal sinus rhythm.

The device utilizes interval length as the primary VT detection criterion; it also provides two additional detection

criteria to add specificity in detecting pathological VT. The two programmable parameters of the Interval Criterion are:

- **Tachycardia Detection Interval (TDI):** Intervals shorter than this value (and longer than FDI are classified as VT intervals.

- **Number of Intervals to Detect (VT NID):** This parameter determines how many consecutive VT intervals must be sensed for therapy to be delivered.

The two additional criteria are:

- **Onset Criterion:** Used to determine when the rate of change in cycle length is sufficiently abrupt to qualify as the onset of paroxysmal VT and not sinus tachycardia.

- **Stability Criterion:** Used to determine when the intervals vary sufficiently on a beat to beat basis to differentiate VT from a rapid ventricular response due to atrial fibrillation.

After a VT episode has fulfilled the programmed detection criteria, the system treats the arrhythmia by delivering one of the three types of VT therapies: Burst, Ramp, or Cardioversion Therapy. Therapy delivery is highly programmable and is "tiered" to allow progression through different therapies selected by the physician to match a patient's particular clinical needs. Up to four separate therapies may be programmed in any combination of the three types to treat each arrhythmia episode. The three therapies are detailed below:

Burst Therapy treats the VT episode by pacing the heart with a "burst" of pulses at a rate greater than that of the VT episode but adapted to the VT rate. The rate adaptive pulse intervals are a programmed percentage of actual tachycardia cycle length. If a pacing sequence is ineffective and the episode is redetected, the pulse interval of the next sequence can be decremented further resulting in a higher pacing rate.

Ramp Therapy decrements each pulse interval within a single sequence of multiple pulses with the first pulse to pulse interval adapted to the VT cycle length. Each subsequent pulse interval in the Ramp sequence is shortened from the preceding interval by a programmed value. If the pacing sequence is ineffective and the VT is redected, Ramp Therapy adds an additional stimulus in each subsequent sequence.

Cardioversion Therapy: delivers synchronized, high-energy pulses in one of the following configurations:

- A **single** pulse delivered over one pathway.
- A **simultaneous** pulse delivered over two pathways.
- Two **sequential** pulses separated by a very short interval delivered over two different pathways.

VF Detection and Therapy

In order to ensure appropriate sensing and detection of VF, the device uses a probabilistic detection algorithm that allows for missed detections due to variations in ventricular depolarization amplitudes and intervals during VF.

Similar to the VT detection algorithm, the PCD® Device detects VF by monitoring the cardiac cycle length and comparing it to the programmed VF detection criteria, which is called the VF Interval Criterion.

The two programmable parameters of this criterion are:

- **Fibrillation Detection Interval (FDI)**: Intervals equal to or shorter than this value are classified as VF intervals.
- **Number of Intervals to Detect (VF NID)**: This parameter determines how many VF intervals must be sensed for therapy to be delivered.

After a VF episode has fulfilled the programmed detection

criteria, the system treats the arrhythmia by delivering up to four defibrillation therapies.

Defibrillation Therapy delivers high-energy pulses in one of the following configurations:

- A **single** pulse delivered over one pathway.
- A **simultaneous** pulse delivered over two pathways.
- Two **sequential** pulses separated by a very short interval delivered over two different pathways.

Bradycardia Therapy

The PCD® Device delivers bradycardia pacing in the VVI mode.

Other Capabilities

The PCD® Device can be used to conduct noninvasive electrophysiologic studies (EPS) via the programmer with the Model 9788 MemoryMod™ software cartridge. The physician can also manually deliver various therapies via the programmer to manage an induced or spontaneous tachyarrhythmia episode.

The PCD® Device will provide the physician with information, via the Programmer about its present programmed status and data on its operation. This information may be printed and retained in the patient's file.

A programmer-generated set of symbols, termed Marker Channel, allows real-time visualization of sensing, pacing, detection, and therapy events occurring within the device.

Figure 2 provides an ECG example of an induced episode of VT detected and terminated by antitachycardia pacing and Figure 3 shows an induced episode of VF detected and terminated by a defibrillation therapy delivered by the PCD® Device.

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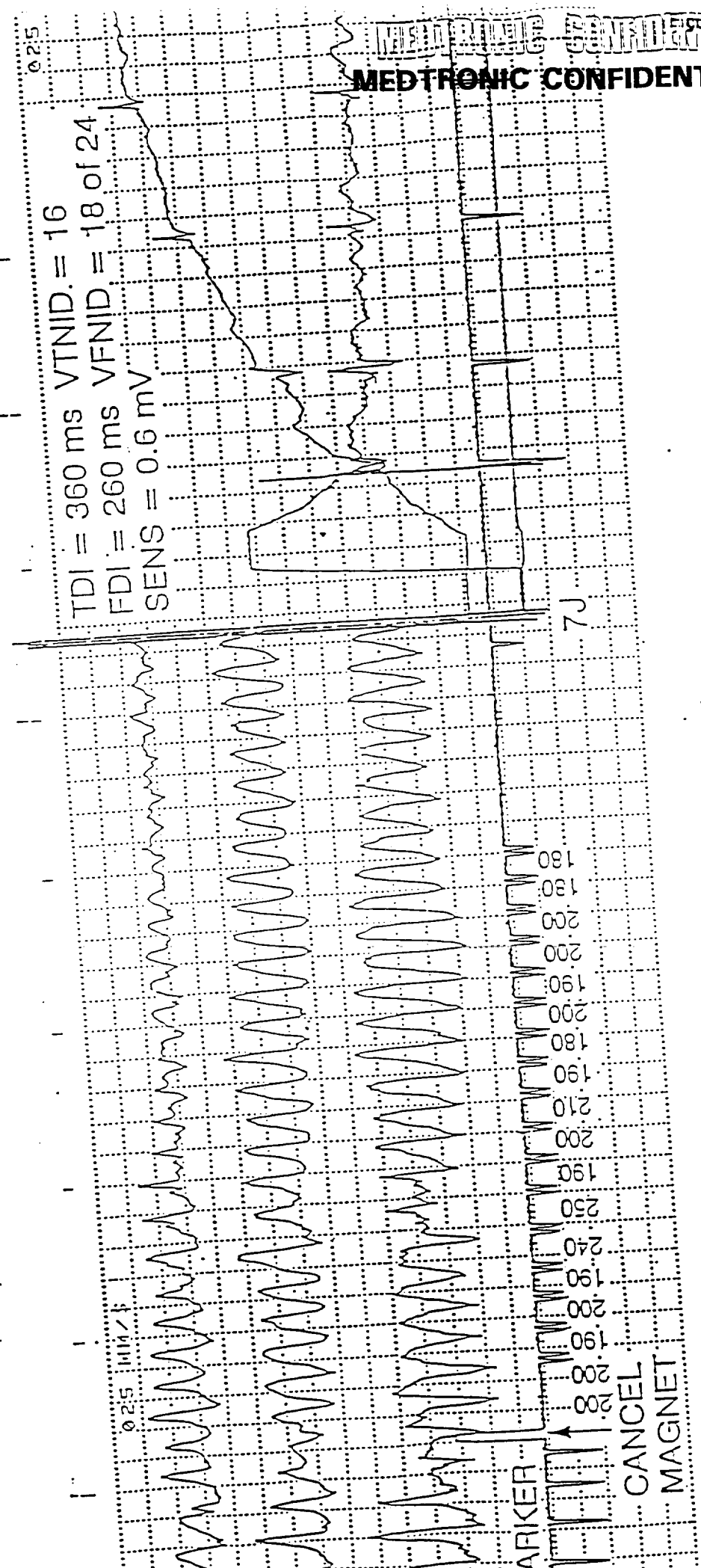
Figure 3


TDI = 360 ms VTNID = 16
FDI = 260 ms VFNID = 18 of 24
SENS = 0.6 mV
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ARKER

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C.2 Transvene™ Lead Systems

The PCD® Transvene™ System uses leads which do not require open-chest surgery to implant. Multiple configurations involving either two or three leads may be used to deliver cardioversion and defibrillation pulses. These configurations are based on a tri-polar, Right Ventricular (RV) lead (Model 6966), and either a Coronary Sinus (CS)/Superior Vena Cava (SVC) lead (Model 6963) or a Subcutaneous (SQ) lead (Model 6999) or all three of these leads (e.g. RV/CS/SQ, RV/SVC/SQ or RV/SQ, RV/SVC). The Model 6963 lead can be placed in either the Coronary Sinus/Great Cardiac vein or the Superior Vena Cava (SVC).

A system using two leads delivers cardioversion and defibrillation pulses between two electrodes. A system using three leads delivers cardioversion and defibrillation pulses either simultaneously or sequentially from the anode electrodes (PULSE1 and PULSE2) to the COMMON defibrillation electrode.

In these systems, the retractable, helical tip and ring of the RV lead are used for sensing, thus providing standard, bipolar sensing. The tip electrode is termed PACE/SENSE and the ring electrode is termed SENSE2. Bradycardia pacing takes place between the tip (PACE/SENSE) and the COMMON defibrillation electrode.

To detect VT/VF, the PCD® device monitors the cardiac cycle length for fulfillment of the programmed VT/VF detection criteria. When the programmed criteria are fulfilled, the PCD® device detects the VT or VF episode and delivers the first programmed therapy. If this therapy is ineffective and the VT/VF is again detected, the next programmed therapy is delivered. This progression continues until the PCD® confirms termination or delivers all programmed therapies.

The performance of the Models 6966, 6963, and 6999 are evaluated at the following times:

1) At implant by evaluating the pacing and sensing thresholds and the defibrillation efficacy in treating

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induced VF;

2) Chronically by evaluating (1) the defibrillation efficacy in terminating induced episodes of VT or VF; (2) the efficacy of VT and VF therapies in treating spontaneous episodes; (3) the evaluation of pace/sense characteristics of the implanted lead system and (4) the incidence of lead complications or observations such as dislodgement or fracture.

C.3 Model 9788 MemoryMod™ Software Cartridge and 9710 Programmer

Programming and interrogation of the PCD® Device is performed using the Model 9788 MemoryMod™ software cartridge in conjunction with the Model 9710 programmer. The use of the programmer allows the modification of VT and VF detection, therapy, and bradycardia support therapy parameters. It allows the physician the ability to review and record programmed device settings, perform noninvasive EP procedures and deliver emergency therapy and review other non-programmable information including charge time, battery voltage and event recording. In addition, it allows the user to evaluate the battery status of the PCD® Device as well as determine if the device has delivered therapy for spontaneous episodes of VT and VF.

C.4 Model 5355 External Tachyarrhythmia Control Device (ETCD)

The Model 5355 ETCD is intended for use in conjunction with an antitachycardia/defibrillation lead system to evaluate VT and VF sensing and therapy efficacy for terminating ventricular tachycardia and ventricular fibrillation prior to the implantation of the PCD® system.

Testing the lead system for permanent implantation, including VF sensing and defibrillation efficacy, is done using the Model 5355 ETCD™ or Model 2394 ECVD. The 5355 is an external, multiprogrammable, tachyarrhythmia control device, which can automatically deliver bradycardia and tachycardia pacing therapies and can deliver manually initiated cardioversion or defibrillation therapies. Its operation is similar to the PCD® Device except that

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cardioversion and defibrillation therapies are delivered manually. In addition, it measures and displays parameters, e.g., pathway impedance of cardioversion and defibrillation therapies. The Model 2394 ECVD is also an external cardioverter defibrillator. However, its functions are limited to only manual cardioversion and defibrillation. The output pulses are equivalent to the Model 5355 and Model 7217B PCD®. Additionally, the Model 2394 ECVD does not have the capability to deliver either bradycardia or tachycardia pacing therapies.

The Model 5355 ETCD™ is controlled via the Model 9710 programmer and the MemoryMod™ software cartridge, Model 9788. The Model 2394 ECVD is controlled manually.

D. Indicated Patient Population

The PCD® System is intended to treat patients at risk of sudden cardiac death due to ventricular tachyarrhythmias which have been shown to be reliably terminated, and in the case of VF, terminated at an energy level below the maximum output of the PCD® Device.

Results provided in this application will support Medtronic's request for market release of the PCD® System for use in the following patient population:

> Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or
>
> Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

For this patient population the primary benefits from the use of the PCD® System center on the detection and termination of life-threatening ventricular arrhythmias. The use of pacing therapies for the treatment of ventricular tachycardia reduces patient trauma associated with higher energy cardioversion pulses and extends the longevity of the PCD® pulse generator.

The PCD® System allows the titration of therapies for patients

with ventricular tachycardia while providing the critical defibrillation backup. Defibrillation backup is important in the event that an episode of VT accelerates to VF whether spontaneously or as a result of a delivered therapy. The capacity to provide programmable extrastimuli pacing allows noninvasive electrophysiologic studies to be performed. The potential benefits from permanent cardiac pacing provide support for chronic and transient episodes of bradycardia. Finally, the benefits of programmability of tachyarrhythmia detection and therapy parameters, VVI parameters and stored telemetry data on the delivery of therapy may avert the need for reoperation in the event of changing patient conditions or complications.

E. Study Objectives and Protocol Summary

The clinical study was designed to evaluate the operation, safety and effectiveness of the PCD® System components in detecting and treating episodes of ventricular tachycardia and ventricular fibrillation.

The analysis focuses on data supporting the safety and effectiveness of the PCD® system, including the implantable pulse generator and associated transvenous lead system and its therapy in this patient population. The analysis includes the clinical experience with the PCD® system, pace/sense, detection and therapy functions in both the acute and chronic implant settings. In addition, data is provided on clinical observations, clinical complications and deaths in this patient population. The analysis will also provide data demonstrating the safety and effectiveness of the Model 5355 ETCD.

The objectives of the clinical study were:

* to evaluate the sensitivity and specificity of the PCD® Device with Transvene™ lead systems to detect episodes of VT and VF, and to evaluate the ability of the system to appropriately discriminate between VT/VF and other potentially nonmalignant rhythms;

* to monitor the efficacy of the PCD® Device with Transvene™ lead systems in treating VT and VF episodes. VT/VF therapy efficacy is determined as the ratio of successful termination of episodes detected to the total number of episodes detected in which one or more therapies were delivered (Successful Termination/Number of Detected Episodes with Therapy Delivered). Investigators were free to choose from any of the available leads and VT/VF therapies that the efficacy was first evaluated acutely;

* to evaluate the performance of the Model 6966, 6963 and 6999 Transvene™ leads;

* to monitor the patient selection criteria and patient management methods required by the PCD® Device and Transvene™ leads.

* to evaluate the safety and effectiveness of the Model 5355 ETCD™ when used during the implant procedure. Specifically, tachyarrhythmia episode induction, detection, termination and ease of use were analyzed.

* to evaluate the safety and performance of the Model 9710 Programmer and the 9788 MemoryMod™ Software Cartridges in programming sensing and therapy parameters and the appropriate delivery of noninvasive electrophysiologic stimulation.

Clinical data was collected at the following study points to support the safety and efficacy of the PCD® System:

Pre-implant Patient Assessment
Lead System Testing at Implant
Implantable Pulse Generator Testing at Implant
Pre-hospital Discharge Testing
Follow-up Evaluation 1 and 3 months post implant then at 3 month intervals

Specific data was collected at each of these points to meet the objectives of the clinical study. This included:

Pre-implant Patient Assessment - extensive pre-implant testing was performed to ensure that the general patient selection criteria were met. This testing included at least an electrophysiologic evaluation, measurement of ejection fraction, and assessment of the patient's New York Heart Association (NYHA) classification of their cardiovascular status. Depending on the patient history, cardiac catheterization and exercise testing were also conducted.

Lead System Testing - implant evaluation was performed to verify that one of the specified lead systems was capable of properly detecting and treating episodes of ventricular fibrillation and, when appropriate, ventricular tachycardia. The Model 5355 ETCD™ or the 2394 External Cardioverter Defibrillator (ECVD) was used for testing.

This testing included pacing and sensing thresholds during sinus rhythm, evaluation of VF electrogram amplitudes and defibrillation efficacy evaluation. The PCD® Device implant criteria were:

1) successful VF termination at least 3 times in 4 attempts with an output energy of 18 Joules or less and

2) a 2:1 VF sensing safety margin.

Implanted Pulse Generator Testing - this implant evaluation was performed to demonstrate proper detection and termination of ventricular fibrillation by the implanted PCD® System with VF Therapy #1 programmed to 34 Joules in addition to pacing and sensing thresholds.

Pre-hospital Discharge Testing - testing performed at the pre-hospital discharge included proper detection and termination of induced ventricular tachycardia. Final sensing and therapy parameters are programmed at the PHD.

Follow-up Evaluation - regular testing was performed to evaluate the chronic stability of detection and therapy parameters of the PCD® System. This testing included an assessment of the relative stability of the energy required to defibrillate a patient and efficacy and acceleration rate assessment of the VT therapies. The number of spontaneous VT/VF episodes treated by the PCD® Device were evaluated. Complication rates and patient mortality data were also evaluated.

Patients were evaluated prior to hospital discharge and/or one (1) month post implant, three months post-implant and then at intervals of every three months. In some cases additional testing was performed at physician discretion to evaluate spontaneous events and/or potential clinical complications.

Medtronic collected all clinical data on the PCD® System and its components under the clinical protocol outlined in the Investigational Plan. A common protocol was used on all study patients on a worldwide basis.

Clinical data presented in this summary includes experience with the Model 7216A and 7217B PCD® Devices with the Model 6966, 6963 and 6999 Transvene™ Leads. This report presents the clinical evaluation of the safety and efficacy of the PCD® Device with Transvene™ Leads implanted in 757 patients of which 657 have implant durations equal to or greater than six months.

International centers were subject to the appropriate requirements (e.g., the Declaration of Helsinki) in order that the data met the statutory requirements of the FDA. All clinical data, U.S. and International, obtained with the PCD® System with Transvene™ Leads is included in this report.

F. Overview of Clinical Experience

This report covers a total of 762 implants in (b)(4) of the PCD® Device with the Transvene™ Defibrillation Lead System. A total of 78 investigative centers participated in the clinical trial with 35 centers in the U.S. and 43 Internationally. The first implant occurred internationally on October 20, 1989, and the first implant in the U.S. occurred on October 16, 1990. Table IF-1 shows the distribution of Model 7216A and Model 7217B patients between U.S. and International investigators.

PCD® Transvene™ System
Implant Distribution

	Total	U.S.	Int'l
7216A	18 (2.4%)	3 (0.7%)	15 (4.8%)
7217B	744 (97.6%)	444 (99.3%)	300 (95.2%)

Table IF-1: PCD® Transvene™ System - Implant Distributions - 2/1/93

The mean documented implant duration for this patient population is 11.7 months and ranged from implant to 37.4 months. The cumulative implant duration is 8894.8 months. There are 657 patients with implant durations equal to or greater than 6 months and 393 patients with implant durations equal to or greater than 1 year.

The patient population enrolled in the clinical trial was predominately male (80.6%) with a mean age of 59.4 years. In half of the patients (49.8%), the primary indication for implant was recurrent, sustained ventricular tachycardia without an episode of sudden cardiac death. Sudden Cardiac Death was the primary indication for 37.1% of the patients and SCD in combination with recurrent, sustained VT was the primary indication in 13.1%. Coronary artery disease was the primary heart disease in 74.1% of the patient population with a mean reported ejection fraction of 35.6% Table IF-2 provides a data summary on these patients. Also included is the data summary of the patients with 6 months and 12 months of follow-up.

PCD® Transvene™ System Data Summary	All Patients (3 Electrode Systems)	Patients with **6** months of Follow-up	Patients with **12** months of Follow-up
Number of Patients	757	657	393
Device Months Follow-up	8894.8	8602.6	6454.6
Mean Follow-up Time	11.7 mo	13.0 mo	16.3 mo
Maximum Follow-up Time	37.4 mo	37.4 mo	37.4 mo
Number, % Male **Number, % Female**	610 80.6% 147 19.4%	527 80.2% 130 19.8%	310 78.9% 83 21.1%
Mean Age	59.4 yrs	59.1 yrs	58.8 yrs
Primary Indication: **SCD** **VT** **SCD/VT**	 281 37.1% 377 49.8% 99 13.1%	 249 37.9% 326 49.6% 82 12.5%	 150 38.2% 191 48.6% 52 13.2%
Coronary Artery Disease	561 74.1%	483 73.5%	272 69.2%
Mean Ejection Fraction	688 35.6%	595 36.6%	357 38.0%
Defibrillation Pathway: **Sequential** **Simultaneous** **Single**	 574 75.3% 178 23.4% 10 1.3%	 496 74.9% 156 23.6% 10 1.5%	 296 74.9% 93 23.6% 6 1.5%
Mean LED	16.0J (N=702)	16.0J (N=609)	15.6J (N=365)
Mean DFT	14.8J (N=316)	14.8J (N=277)	14.3J (N=184)
Spontaneous VT: **Number of Patients** **Number of Episodes** **% Success**	 316 10027 98.4%	 288 8820 98.3%	 186 6338 99.0%
Spontaneous VF: **Number of Patients** **Number of Episodes** **% Success**	 317 1982 98.4%	 292 1742 98.3%	 176 1105 98.6%
One Year SCD Survival	99.5%	99.7%	100.0%

Table IF-2: PCD® System Data Summary - All Transvene™ Patients versus Transvene™ Patients with 6 mo Follow-up - 2/1/93

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F.1 Implant Data

Implants of the PCD® Device may use two or three Transvene™ leads. The physician has the flexibility to use whichever lead system best meets the patient's needs.

Two terms were developed to accurately report defibrillation efficacy, Lowest Energy of Defibrillation (LED) and Defibrillation Threshold (DFT). They are defined as follows:

> Lowest Energy of Defibrillation (LED): The lowest programmed energy that successfully defibrillated the patient with the implanted lead system.
>
> Defibrillation Threshold (DFT): The lowest programmed energy which successfully defibrillated the heart provided there is a failure at an energy below the lowest success or a success at less than or equal to 5J.

Table IF-3 illustrates the lowest energy of defibrillation (LED) and defibrillation threshold (DFT) for the implanted lead systems. The implant criteria for the PCD® Device was 3 of 4 episodes of VF successfully terminated at 18 Joules or less with a given lead configuration. Some patients did not have a LED at implant. The LED is only identified if the investigator reported the induced rhythm as VF. Conversion of VT or V Flutter (as defined by the physician) to sinus rhythm was not included in the determination of the LED. In addition, it is not a protocol requirement to obtain a DFT at implant. However, recommendations have been provided to those institutions that prefer to obtain DFT's during the implant procedure.

PCD® Transvene™ System Mean LED and DFT Values				
Lead System	Implant Frequency	Mean LED	Implant Frequency	Mean DFT
All Systems	702	16.0J	316	14.8J
RV-SVC-SQ	455	16.7J	187	15.8J
RV-CS-SQ	210	14.6J	110	12.8J
RV-CS-SVC	37	15.2J	19	16.0J

Table IF-3: PCD® Transvene™ System - LED and DFT Values - 2/1/93

The mean implant Lowest Energy of Defibrillation (LED) for all lead systems was 16.0J and mean implant Defibrillation threshold (DFT) for all lead systems was 14.8J. As the mean DFT's and LED's indicate, VF was reliably terminated at an energy value below the maximum output (34 Joules) of the PCD® Device.

F.2 Spontaneous VT and VF Episode Experience

A total of 458 patients (60.5%) have experienced a spontaneous ventricular tachyarrhythmia episode that has been detected and treated by the PCD® Device. A total of 141 (18.6%) experienced VT only, 142 patients (18.8%) experienced VF only and 175 patients (23.1%) experienced both an episode of VT and VF.

There have been a total of 12,009 episodes of spontaneous VT or VF as detected by the PCD®. The overall PCD® Device success rate in terminating spontaneous VT/VF episodes as detected by the PCD® is presented in Table IF-4.

PCD® Transvene™ System Success Rate in Terminating Spontaneous VT/VF Episodes			
	Number of Episodes Successful	Total Number of Episodes	Efficacy Rate
VT	9864	10,027	98.4%
VF	1951	1982	98.4%
Total	11,815	12,009	98.4%

Table IF-4: PCD® Transvene™ System - Success Rate for Spontaneous VT/VF Episodes - 2/1/93

F.2.1 Spontaneous VT

For the purposes of this clinical trial, spontaneous VT was defined as those episodes that satisfied the programmed VT detection criteria. Specifically, all programmed VT detection criteria must be fulfilled to detect a VT episode. Successful termination of the episode was defined as satisfying the VT episode termination criteria.

To date, 10,027 spontaneous episodes of VT have been detected by the PCD® Device in 316 patients. The mean number of episodes per patient with VT was 31.7 and ranged from 1 - 531 episodes.

Most spontaneous VT episodes (90.7%) were successfully treated with VT Therapy #1 and 98.4% were successfully treated with one of the four programmable VT therapies.

Of the 9864 successfully terminated spontaneous VT episodes, 91.4% were treated with one of the programmed antitachycardia pacing therapies incorporated in the PCD® Transvene™ System. The clinical benefit of tiered therapy is the reduction of delivery of high energy shocks for the treatment of stable recurrent ventricular tachycardia. This greatly enhances the patient acceptance of ICD therapy since antitachycardia pacing is usually not perceived by the patient.

Sixty patients experienced 163 (1.6%) episodes in which

the PCD® Device was ineffective in terminating a spontaneous episode of VT despite delivery of all four programmed VT therapies. Thirty-nine patients experienced 95 ineffective episodes that were due to sinus tachycardia or atrial fibrillation/flutter (SVT) with a rapid ventricular response that had been detected as VT. These episodes were resolved with either modification of programmed parameters or of antiarrhythmic drug therapy. It should be noted that the PCD® Device responded appropriately based on the programmed detection parameters.

The remaining 68 episodes occurred in 21 patients in which the programmed VT therapies were ineffective in terminating a spontaneous VT episode. **No patient deaths occurred as a result of ineffective VT therapy.** Reprogramming and pharmacologic intervention resolved these events.

F.2.2 Spontaneous VF

For purposes of this clinical trial, VF is defined as those episodes that satisfy the programmed VF detection criteria. Specifically, all programmed VF detection criteria must be fulfilled to detect a VF episode. Successful termination of the episode is defined as satisfying the VF detection criterion for episode termination.

To date, 1982 spontaneous episodes of VF have been detected by the PCD® Device in 317 patients. The mean number of episodes per patient was 4.3 and ranged from 1 - 77 episodes. A review of the chart per investigator for this patient that experienced the 77 episodes of VF revealed that 75 were most likely due to atrial fibrillation. VF detection parameters were modified in this patient.

Most (89.1%) spontaneous VF episodes were successfully treated with VF Therapy #1 and 98.4% were successfully treated with one of the four programmable VF therapies.

Sixteen patients experienced 31 episodes (1.3%) in which the PCD® Device was ineffective in terminating a spontaneous episode of VF despite delivery of all four programmed VF therapies. Nine patients had 22 reported ineffective VF spontaneous episodes that were due to sinus

tachycardia or atrial fibrillation with rapid ventricular response rather than VF. Reprogramming and pharmacologic intervention resolved these problems.

Four patients experienced 5 ineffective episodes that were detected as VF by the PCD® System. One of these patients (b)(6) required external defibrillation to convert the VF episode. This patient's antiarrhythmic drug regimen was modified to improve defibrillation efficacy. Another patient (b)(6) had an episode recorded as ineffective on the event counters but presented in sinus rhythm. Subsequent evaluation demonstrated appropriate PCD® function. Another of these patients (b)(6) had two spontaneous episodes of VT that were detected as VF by the PCD® while in the hospital for progressive CHF. These episodes required external cardioversion. The patient requested the PCD® be turned OFF. Patients was alive at the last known follow-up. The last of these four patients (b)(6) experienced cardiac arrest at home and was found by the paramedics to be in sinus rhythm. While on a monitor the patient developed VF. The PCD® delivered the programmed therapy which terminated the episode but the patients developed EMD, arrived at the ER comatose and died.

Four patients (one patient (b)(6) experienced 2 episodes due to AF but is described below again) experienced 4 episodes in which the PCD® detected the episodes as VF but were actually episodes due to extraordinary circumstances. One patient (b)(6) experienced an episode where all four therapies failed secondary to RV lead fracture. The patient had Twiddlers Syndrome. Reoperation was required. It appears that the inappropriate therapy was not due to VT/VF but due to noise. Another patient (b)(6) had a surgical procedure (CABG) where the CS lead dislodged post surgery. The episode that was detected was due to the lead dislodgement. The third patient (b)(6) had incessant episodes of fast VT (cycle length 280 ms) that were eventually resolved by drugs. The fourth patient (b)(6) was in hospital and there was an episode of VF detected. However, the device was interrogated before termination of the episode was detected. There was external intervention associated with the terminal event. The device was not interrogated again.

B

F.3 Overall Success Rate

Of the 757 patients who received a PCD® Transvene™ System, 597 patients (78.9% - 597/757) have either experienced a spontaneous VT/VF episode or had VT/VF induced during a post implant electrophysiology study. The performance of the PCD® Transvene™ System therapies have been thoroughly evaluated and been shown to be effective in detecting and terminating episodes of ventricular tachyarrhythmia.

There have been no reports of a patient death due to the PCD® Transvene™ System not detecting a spontaneous episode of VT or VF.

The overall success rate of the PCD® Transvene™ System in terminating spontaneous episodes of either VT or VF was 98.4% with a VT success rate of 98.4% and VF success rate of 98.4%. The incidence of unsuccessful termination of an apparent "true" episode of ventricular tachycardia despite delivery of all four therapies was 0.7% (68/10027). The incidence of unsuccessful termination of an apparent "true" episode of ventricular fibrillation despite delivery of all four therapies was 0.3% (5/1982).

The evaluation of spontaneous episode experience indicates that the PCD® Transvene™ System's VT and VF detection and therapy functions have performed safely and effectively in the indicated patient population.

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G. Complications and Observations

The use of a multiprogrammable implantable cardioverter defibrillator (ICD) device allows the physician to resolve most relevant medical events by noninvasively changing programmed parameters thus, avoiding invasive procedures. However, there will continue to be certain relevant medical events which will require invasive procedures for resolution.

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following definitions:

COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

As of February 1, 1993, there have been a total of 176 complications reported in 147 patients and 214 observations reported in 180 patients in the PCD® Transvene™ System patient population. Thus, 19.4% (147/757) of the patients had reported a clinical event which was categorized as a complication and 23.8% (180/757) of the patients had reported a clinical event which was categorized as an observation. Table IG-1 summarizes how these events were reported with U.S versus International.

PCD® Transvene™ System
Reported Complications/Observations
U.S versus International

	# of Complications	# of Observations
U.S.	104	93
International	72	121
Total	176	214

Table IG-1: PCD® Transvene™ System Complications/Observations U.S. versus International - 2/1/93

Table IG-2 summarizes the reported PCD® Transvene™ System complications and observations by category. The reported complications and observations are recognized clinical events that may occur with **any** of the current ICD devices. These complications and observations are discussed in the PCD® device and Transvene™ manual. **None of the reported complications or observations have resulted in a patient death.**

PCD® Transvene System
Reported Complications/Observations
By Category

Category	Complications	Observations
Increased Defibrillation Requirements	9 (1.2%)	8 (1.1%)
Inappropriate VF Therapy Delivery	-	14 (1.8%)
Inappropriate VT Therapy Delivery	-	59 (7.8%)
Loss of Capture	6 (0.8%)	14 (1.8%)
Oversensing	-	54 (7.1%)
Undersensing	-	-
Skin Erosion	5 (0.7%)	1 (0.1%)
Pocket Infection	24 (3.2%)	10 (1.3%)
Seroma	6 (0.8%)	14 (1.8%)
Hematoma	6 (0.8%)	17 (2.2%)
Pneumothorax	2 (0.3%)	1 (0.1%)
Pacemaker Syndrome	-	2 (0.3%)
Perforation	6 (0.8%)	-
Subclavian Vein Thrombosis	1 (0.1%)	3 (0.4%)
Lead Fracture	9 (1.2%)	-
Subcutaneous Patch Crinkling	7 (0.9%)	5 (0.7%)
Early Device Explant	4 (0.5%)	-
Total Lead Dislodgement	91 (12.0%)	12 (1.6%)
Total	**176**	**214**

Table IG-2: PCD Transvene System: Reported Complications and Observations - 2/1/93

Table IG-3 contains a description of the lead dislodgements that have occurred in less than 30 days and in greater than 30 days.

PCD® Transvene System
Reported Complications/Observations
Lead Dislodgements <30 days and >30 days

Category	Complications		Observations	
	Num (% of Pts)		Num (% of Pts)	
	<30 days	>30 days	<30 days	>30 days
RV Lead Dislodgement n=741	14 (1.9%)	10 (1.3%)	0 (0)	1 (0.1%)
CS Lead Dislodgement n= 261	12 (4.6%)	10 (3.8%)	2 (0.8%)	2 (0.8%)
SVC Lead Dislodgement n=535	16 (3.0%)	29 (5.4%)	1 (0.2%)	6 (1.1%)
Total Dislodgement n=757	42 (5.6%)	49 (6.5%)	3 (0.4%)	9 (1.2%)

Table IG-3: PCD Transvene System: Lead Dislodgements <30/>30 days - 2/1/93

There have been a total of 49 lead dislodgements reported in patients at greater than 30 days. None of the lead dislodgements resulted in an ineffective therapy for a spontaneous VT of VF episode or patient death. Lead dislodgements were documented by fluoroscopic examination during electrophysiologic evaluation, chest x-ray obtained during routine follow-up, or during pacing/sensing threshold evaluation during routine follow-up. In all 49 cases, reoperation was required to reposition the lead and reestablish an effective defibrillation lead system.

Lead dislodgements are not specific to the PCD® Transvene™ System and have been reported with dual chamber pacemakers and the current market released implantable cardioverter defibrillator (ICD) system. The early history of dual chamber pacemakers witnessed a high lead dislodgement rate of at least 20% (Smyth, PND, et al. Permanent perivenous atrial sensing and pacing with a new J-shaped lead. J Thoracic Cardiovascular Surgery. 1976;72:565-570). Winkle, et al reported that the incidence of dislodgement of the superior vena cava spring leads with the current market release ICD system to be 6.3%. (Winkle, et al. Automatic Implantable Cardioverter-Defibrillator: Efficacy, Complications, and Survival in Patients with Malignant Ventricular Arrhythmias. JACC. June 1988; Vol.11, No.6:1278-86).

H. Inactive Patients

There are a total of 82 patients who had received a PCD® System and are no longer active in the study as of 2/1/93. Table IH-1 shows the distribution of inactive patients by reason for no longer being active in the PCD® Transvene™ System clinical study.

PCD® Transvene™ System Inactive Patients	
Reason for Inactivity	**# of Patients**
Patient Deaths	51
Infection (Explant)	22
Heart Transplant	9
Total	82

Table IH-1: Inactive Patients - 2/1/93

I. Patient Deaths

The positive impact of implantable cardioverter defibrillator (ICD) therapy on sudden cardiac death mortality has been well documented in the medical literature. The use of device therapy for the treatment of recurrent ventricular arrhythmias has become an accepted and important clinical tool. An analysis of the sudden cardiac death survival in the PCD® Transvene™ System patient population was performed.

For purposes of the clinical study, each of the patient deaths was categorized using the following definitions:

Non-Cardiac: Deaths that occurred where the primary cause of death was determined to be non cardiac in nature, e.g. stroke, cancer, etc.

Cardiac: Deaths that occurred where the primary cause of death was determined to be cardiac in nature.

Non-Sudden: Deaths that occur greater than one hour after the onset of symptoms.

Sudden: Deaths that occur within one hour of the onset of symptoms or where the death is

unwitnessed. Sudden cardiac deaths were also categorized as being **Witnessed** or **Unwitnessed.**

Perioperative: Deaths that occur within thirty days of implant.

System Related: A death which results from a malfunction (operation not according to design specification) of a PCD® System component, or as a result of a device induced arrhythmia, or an interaction between a PCD® System component and the patient.

Procedure Related: A death which occurs as a result of a procedure required to implant, follow or test a PCD® System.

All deaths and significant complications have been and will continue to be reviewed by a committee comprised of PCD® Transvene™ System investigators and other physicians. Two committees (Clinical Event Review Committees) have been formed, one to review North American deaths and complications, and the other to review European clinical events. The primary purpose of these reviews was to determine whether the PCD® System was related to the deaths or significant complications that have occurred and, if so, what changes may be required to prevent such events in the future.

There have been a total of 51 patient deaths reported in the PCD® Transvene™ System patient population. Table II-1 summarizes how these patient deaths have been classified.

PCD® Transvene™ System
Summary of Death Classifications
(n = 757)

Classifications	Number of Deaths
Sudden Cardiac	5
Non-Sudden Cardiac	30
Noncardiac	16
Total	51

Table II-1: PCD® Transvene™ System - Summary of Death Classifications - 2/1/93

None of the patient deaths were attributed to a malfunction of the PCD® Transvene™ System.

Actuarial survival analysis on the PCD® Transvene™ System was done on all patients who were either evaluated for implantation or in whom the device was implanted. Thus, the analysis is done from the perspective of **intention to treat.** Those patients in whom the PCD® Device was OFF at the time of death or in whom no device was implanted **are** included in the survival analysis. Those patients that were screened for a PCD® Transvene™ System but failed to receive a Transvene™ system are not included in this analysis.

Projected one year survival calculations for the various death classifications are provided in Table II-2. **The actuarial projections include perioperative deaths only in the calculation of one year survival from death due to all causes (shown in the row labelled Overall).** The perioperative death rate defined as deaths which occurred within thirty days of implant was 0.7% (5/757) which is considerably less than the perioperative mortality for the PCD® System with Epicardial leads (5.3% - 39/742). Included in this table are the projected one year survival calculations for patients who ultimately received a PCD® Transvene™ System (n = 757) and all patients that were screened for a PCD® Transvene™ System (n = 854) regardless of implant outcome.

PCD® Transvene™ System One Year Actuarial Survival		
	Received PCD® Transvene™ System	**Screened for a PCD® Transvene™ System**
Sudden Cardiac Death	99.5%	99.4%
Non-Sudden Cardiac	96.2%	96.6%
All Cardiac	95.8%	96.1%
Noncardiac	98.1%	98.3%
Perioperative	0.7%	1.6%
Overall	93.3%	92.9%

Table II-2: PCD® Transvene™ System - One Year Actuarial Survival - 2/1/93

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The positive impact of the PCD® Transvene™ System on patient mortality is clearly obvious from this analysis. The sudden cardiac death survival rate in this patient group is 99.5% for those in the patient group that received a Transvene™ System and 99.4% for those who were screened for a Transvene™ System. This is marked improvement when compared with the reported survival of similar patient groups treated with drug therapy alone of between 34% and 73% at one year.

J. Clinical Experience By Primary Indication

Medtronic is requesting approval for use of the PCD® Transvene™ System in the following patient population:

* Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or

* Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

Sudden cardiac death without recurrent VT (**SCD**) was the indication for implant in 37.1% of the patients, recurrent ventricular tachycardia without an episode of sudden cardiac death (**VT**) was the indication for implant in 49.8% of the patients, and sudden cardiac death and recurrent VT (**SCD/VT**) was the indication for implant in 13.1% of the patients.

The performance of the PCD® Transvene™ System in these three groups are summarized in Table IJ-1.

In all three patient groups, coronary artery disease was the predominant heart disease and the patients exhibited moderate left ventricular dysfunction as demonstrated by mean ejection fractions of less than 40%. The mean LED at the time of implant was similar among the patient groups as was the mean DFT.

The overall efficacy in terminating spontaneous VT/VF episodes in the SCD patient group was 98.4%, in the VT patient group 98.3%, and in the SCD/VT group 99.1%. Thus, independent of the indication for implant, the PCD® Transvene™ System was highly effective in terminating spontaneous episodes of VT/VF.

The one year sudden cardiac death survival rates for all groups was greater than 98.6%

This analysis indicates that the PCD® Transvene™ System has performed safely and effectively in the indicated patient groups and should be approved for use in the indicated patient population.

PCD® Transvene™ System
Data Summary by Primary Indication

	SCD	VT	SCD/VT	All Patients
# of Patients	281 (37.1%)	377 (49.8%)	99 (13.1%)	757
Number, % Male Number, % Female	212 75.4% 69 24.6%	309 82.0% 68 18.0%	89 89.9% 10 10.1%	610 80.6% 147 19.4%
Mean Age	56.8 yrs	61.2 yrs	60.0 yrs	59.4 yrs
Coronary Artery Disease	191 68.0%	292 77.5%	78 78.8%	229 72.2%
Mean Ejection Fraction	39.1% (N=259)	33.7% (N=339)	32.5% (N=90)	35.6% (N=688)
Defibrillation Pathway: Sequential Simultaneous Single	 201 71.5% 74 26.3% 6 2.2%	 295 77.6% 82 21.6% 3 0.8%	 76 76.8% 22 22.2% 1 1.0%	 574 75.3% 178 23.4% 10 1.3%
Mean LED	15.3J (N=264)	16.2J (N=351)	17.3J (N=87)	16.0J (N=702)
Mean DFT	14.0J (N=117)	15.5J (N=155)	13.9J (N=44)	14.8J (N=316)
Spontaneous VT: # of Patients # of Episodes % Success	 58 1157 99.2%	 206 7591 98.1%	 52 1279 99.0%	 316 10027 98.4%
Spontaneous VF: # of Patients # of Episodes % Success	 107 686 96.9%	 162 916 99.1%	 48 380 99.5%	 317 1982 98.4%
1 Year SCD Survival	100.0%	99.4%	98.6%	99.5%

Table IJ-1: PCD® Transvene™ System Data Summary by Primary Indication - 2/1/93

K. Patients Not Meeting Implant Criteria

K.1 Overview

The PCD® Transvene™ System offers a simpler and safer implantation technique for an implantable cardioverter defibrillator system. In addition, the PCD® Transvene™ System decreases the potential perioperative and long term mortality associated with current epicardial system implantation approaches.

There is a class of patients who cannot tolerate the thoracotomy required for the utilization of the epicardial patch lead defibrillation lead system and who are at high risk of sudden cardiac death. Because of the surgical risks and postsurgical complications associated with the implant of an epicardial lead system, implantation in the following patient groups may not be desirable or possible:

(1) patients in whom there is no indication for concomitant cardiovascular surgery at the time of ICD implant;

(2) patients with severe pulmonary disease who can not tolerate prolonged anesthesia or an open chest procedure;

(3) patients with severe congestive heart failure (ejection fraction < 40%) who are at increased risk for perioperative mortality following a thoracotomy procedure;

(4) patients who may eventually require open chest procedures for treatment of their coronary artery disease or cardiac transplant.

For these patients, a transvenous ICD System is the only therapy available. The PCD® Transvene™ System simplifies and greatly reduces the risk associated with lead introduction, making therapy available to these patient groups. Because there is no need to open the chest of these patients, more options for future therapy remain available; e.g. CABG is associated with increased morbidity and mortality if there has been prior open chest surgery.

However, it is expected that nonthoracotomy lead systems will have higher mean implant defibrillation thresholds as compared to traditional epicardial lead systems. In an epicardial lead system, the lead system has a larger

electrode surface area theoretically decreasing defibrillation requirements.

The smaller electrode surface areas of the PCD® Transvene™ System defibrillation leads might reduce the proportion of patients in whom the implant criteria could be met. Not meeting the implant criteria may reduce the chronic effectiveness of the lead system. Recent studies indicated that 70% of patients evaluated may be candidates for a nonthoracotomy defibrillation lead system (Wilber, D, et al. Clinical Advances in Nonepicardial Implantable Defibrillator Lead Systems. The Journal of Invasive Cardiology. Vol.3, No.6,November/December 1991).

For purposes of the PCD® Transvene™ System, the implant criteria was defined as successful VF termination at least 3 times in 4 attempts with the final lead configuration with an output energy of 18 Joules or less. The determination of a defibrillation threshold was not required.

A defibrillation threshold (**DFT**) was defined as the energy at the lowest successful defibrillation attempt, provided the patient had a failure below the lowest success or a success at $\leq$ 5J. The lowest energy of defibrillation (**LED**) was defined as the lowest programmed energy that successfully defibrillated the patient. In both cases, conversion of ventricular tachycardia or ventricular flutter to sinus rhythm was **not** included in the determination of the DFT or LED.

A total of 854 patients had an evaluation of a PCD® Transvene™ System and are divided into the following groups - (1) Patients who received a PCD® Transvene™ System; and (2) Patients screened for a PCD® Transvene™ System and received a PCD® Epicardial System. Figure 1 provides an overview of the outcome of these patients.

(b)(4)

As can be seen, 88.6% (757/854) of the patients who were screened for a PCD® Transvene™ System ultimately received the system. Of these 757 patients, 71.7% (543 patients) met the recommended defibrillation implant criteria which compares favorably with the predicted success rates published in the literature (Wilber et al). However, 28.3% (214/757) of the patients did not meet the recommended defibrillation efficacy implant criteria and still received the PCD® Transvene™ System. It should be noted that 97.4% of the patients (737/757) received the PCD® Transvene™ System with at least a 10 Joule defibrillation safety margin between the lowest energy of success (24J) and the maximum output (34J) of the PCD® Device.

The investigators utilized this 10 Joule safety margin as a benchmark based on the clinical experience discussed in the article, Troup P., et al. The Implanted Defibrillator: Relation of Defibrillating Lead Configuration and Clinical Variables to Defibrillation Threshold. Journal of American College of Cardiology 1985; 6:1315-1321. Finally, and perhaps most importantly, the investigators also felt that for these patients the risk associated with not meeting the recommended implant criteria was outweighed by the risk of not implanting an ICD or implanting an epicardial system.

There were twenty patients (2.6%), who received a PCD® Transvene™ System, whose cardiovascular condition precluded further completion of the PCD® Transvene™ System and adequate definition of a defibrillation safety margin. In all cases, the physician felt that the benefit of the PCD® Transvene™ System outweighed the risk of further inductions or the risk of a thoracotomy and elected not to evaluate or implant a PCD® Epicardial System.

K.2 Patients Receiving PCD® Transvene™ System & Did Not Meet Implant Criteria

For purposes of the PCD® Transvene™ System, the implant criteria was defined as successful VF termination at least 3 times in 4 attempts with the final lead configuration at an output energy of 18 Joules or less. Of the 757 patients who **received** a PCD® Transvene™ System, 214 patients (28.3%) did not meet the recommended defibrillation implant criteria and yet still received the PCD® Transvene™ System. The physicians justification for implanting the PCD® Transvene™ System despite not meeting the recommended defibrillation implant criteria are presented in Table IK-1.

PCD® Transvene™ System
Reasons for Not Meeting Implant Criteria
Physician Justification

Reason	Number of Patients
Success at $\leq$ 24 Joules	170
Difficult/Unable to Induce VF	24
Patient Condition	20
Total	214

Table IK-1: PCD® Transvene™ System: Physician Justification for Not Meeting Implant Criteria - 2/1/93

Further analysis of the patient who did not meet the recommended implant criteria indicates however, that 91% (194/214) had a 10 Joule safety margin between the lowest energy of successful defibrillation and the maximum output of the PCD Device (34J). Therefore, of the 757 patients who received a PCD® Transvene™ System, 97.4% (737/757) had at least a 10 Joule defibrillation safety with the implanted lead configuration.

There were 20 patients (2.6%) in whom the implant procedure was terminated due to poor patient condition. These patients received a PCD® Transvene™ System without at least a 10 Joule defibrillation safety margin. The implant circumstances of these patients is summarized as

follows:

- At least one successful defibrillation was obtained at an energy level greater than 24 Joules and or equal to 34 Joules (**N = 11**);
- Multiple inductions of VT were performed and successfully reverted with an energy level of 18 Joules or less. However, induced VF was not successfully reverted by an energy level of less than or equal to 34 Joules (**N = 6**); and
- Physician elected to terminate the procedure due to the patient's condition before inductions with the final implanted lead configuration were performed (**N = 3**).

Table IK-2 provides a comparison of patient characteristics between patients who met the PCD® Transvene™ System implant criteria and those patients who did not meet the implant criteria but still received the PCD® Transvene™ System.

PCD® Transvene™ System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Patient Characteristics		
Data	**Meeting Criteria**	**Not Meeting Criteria**
Number of Patients	543	214
Mean Follow-Up	12.3 months	10.1 months
Male*	422 (77.7%)	188 (87.9%)
Female	121 (22.35)	26 (12.1%)
Mean Age	59.4 yrs	59.6 yrs
Indication*		
SCD	209 (38.5%)	72 (33.6%)
VT	278 (51.2%)	99 (46.3%)
SCD/VT	56 (10.3%)	43 (20.1%)
Cardiovascular History		
CAD	396 (72.9%)	165 (77.1%)
Cardiomyopathy	173 (31.9%)	65 (30.4%)
Mean EF*	36.3%	33.7%
NYHA Class		
I	164 (30.9%)	53 (25.8%)
II	278 (52.4%)	114 (56.6%)
III	82 (15.4%)	34 (16.6%)
IV	7 (1.3%)	4 (2.0%)
Number ON Drugs at Implant	223 (41.1%)	97 (45.3%)
Number ON Amiodarone	78 (14.4%)	38 (17.8%)

* Statistically Significant ($p \leq 0.05$)

Table IK-2: PCD® Transvene™ System: Patients Meeting Implant Criteria vs Not Meeting Implant Criteria - Comparison of Pt Characteristics - 2/1/93

Statistical analysis indicated three significant differences between these two patient groups - patient sex, indication for implant and mean ejection fraction.

Patients not meeting implant criteria had a statistically higher percentage of patients who were male ($p = 0.002$). This difference reflects that the majority of patients with coronary disease with concomitant life threatening

ventricular arrhythmias are males.

Analysis indicated the patients not meeting the implant criteria had a statistically higher percentage of patients whose primary indication for implant was sudden cardiac death associated with recurrent ventricular tachycardia ($p = 0.002$). This difference reflects the physicians use of the PCD® Transvene™ System.

Finally, patients who did meet the implant criteria had a statistically lower mean ejection fraction ($p = 0.0342$) which reflects a higher degree of underlying cardiovascular disease in these patients.

It should be noted, that none of these differences should be used as predictors for patients who should be screened for a PCD® Transvene™ System.

Implant data obtained in these two patient groups is presented in Table IK-3. As would be expected the patients not meeting the implant criteria had higher mean DFT and LED values when compared to the patients who did meet the implant criteria. However, the mean DFT (18.8J) and LED (19.5J) values obtained in patients not meeting implant criteria provided at least a 10 Joule defibrillation safety margin between the successful energy and the maximum output of the PCD® Device (34J) in nearly all (97.4%) of the patients.

PCD® Transvene™ System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Implant Data		
Data	**Meeting Criteria**	**Not Meeting Criteria**
Number of Patients	543	214
Mean Number of Inductions	7.0	8.2
Number of Configurations	2.0	2.7
Mean DFT	13.4J	18.8J
Mean LED	14.8J	19.5J
Implanted Lead System		
RV-SVC-SQ	351 (64.6%)	145 (67.8%)
RV-CS-SQ	159 (29.3%)	63 (29.4%)
RV-CS-SVC	33 (6.1%)	6 (2.8%)
Efficacy of 1st Lead System	396 (72.9%)	137 (64.0%)
Defibrillation Pathway		
Sequential	414 (75.7%)	160 (74.4%)
Simultaneous	127 (23.2%)	51 (23.7%)
Single	6 (1.1%)	4 (1.9%)

Table IK-3: PCD® Transvene™ System: Patients Not Meeting Implant Criteria versus Patients Meeting Implant Criteria - Comparison of Implant Data - 2/1/93

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In order to determine if the patient's not meeting implant criteria had higher risk for morbidity and mortality, a comparison of their clinical outcome was made with those patients who did meet the implant criteria. This comparison is provided in Table IK-4.

PCD® Transvene™ System
Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria

Implant Data		
Data	**Meeting Criteria**	**Not Meeting Criteria**
Number of Patients	543	214
Spontaneous VT Episode Efficacy	98.7%	97.6%
Spontaneous VF Episode Efficacy	98.2%	99.0%
Number of Patient Deaths	37	14
Perioperative Mortality	0.7%	0.5%
One Year Survival		
Sudden Cardiac	99.5%	99.5%
Non-Sudden Cardiac	95.8%	97.2%
All Cardiac	95.4%	96.7%
Noncardiac	98.5%	97.1%
Overall	93.2%	93.5%

Table IK-4: PCD® Transvene™ System: Patients Not Meeting Implant Criteria versus Patients Meeting Implant Criteria - Comparison of Clinical Outcome - 2/1/93

The two patient groups had similar efficacy in the treatment of spontaneous VT/VF episodes. Importantly, in the patient population who did not meet the implant criteria there were no patients who experienced actual spontaneous VF episodes where all programmed PCD® Device therapies failed to terminate the episode.

Five patients experienced 7 episodes in which the PCD® Device was ineffective in terminating a spontaneous episode of VF despite delivery of all four programmed VF therapies. Three patients had 5 reported ineffective VF

spontaneous episodes that were due to sinus tachycardia or atrial fibrillation with rapid ventricular response rather than VF. Reprogramming and pharmacologic intervention resolved these problems.

Two patients experienced 2 episodes in which the PCD® detected the episodes as VF but were actually episodes due to extraordinary circumstances. The first patient (b)(6) had incessant episodes of fast VT (cycle length 280 ms) that were eventually resolved by drugs. The second patient (b)(6) was in hospital and there was an episode of VF detected. However, the device was interrogated before termination of the episode was detected. There was external intervention associated with the terminal event. The device was not interrogated again.

Eighteen patients experienced 68 episodes in which the PCD® Device was ineffective in terminating a spontaneous episode of VT despite delivery of all four programmed VT therapies. Nine patients experienced 44 ineffective episodes that were due to sinus tachycardia or atrial fibrillation/flutter (SVT) with a rapid ventricular response that had been detected as VT. These episodes were resolved with either modification of programmed parameters or of antiarrhythmic drug therapy. It should be noted that the PCD® Device responded appropriately based on the programmed detection parameters.

The remaining 24 episodes occurred in 8 patients in which the programmed VT therapies were ineffective in terminating a spontaneous VT episode. **No patient deaths occurred as a result of ineffective VT therapy.** Reprogramming and pharmacologic intervention resolved these events.

There was no difference in the one year sudden cardiac survival or the overall survival in the two groups although follow-up was shorter for patients not meeting implant criteria (10.1 vs 12.3 months). This indicates, that despite not meeting the implant criteria these patients were not at higher risk of sudden cardiac death.

Finally, the survival of patients receiving a PCD® Transvene™ System without meeting implant criteria

(N = 214) was compared to patients receiving a PCD® Epicardial System without meeting implant criteria (N = 92). This comparison is provided in Table IK-5.

PCD® Transvene™ System Patients Not Meeting Implant Criteria Survival Analysis versus PCD Epicardial System Patients Not Meeting Implant Criteria Survival Analysis		
	PCD Transvene System Not Meeting Implant Criteria	PCD Epicardial System Not Meeting Implant Criteria
Number of Patients	214/757 (28.5%)	92/742 (12.4%)
Number of Deaths	14	17
Sudden Cardiac	99.5%	98.6%
Non-Sudden Cardiac	97.2%	98.8%
Noncardiac	97.1%	97.3%
Overall*	93.5%	87.6%

* Statistically Significant ($p \leq 0.05$)

Table IK-5: PCD® Transvene™ System: Patients Not Meeting Implant Criteria - PCD Transvene System vs PCD® Epicardial System - 2/1/93

Though the PCD® Transvene™ System had a higher incidence of patients not meeting implant criteria (28.5%) compared to the PCD® Epicardial System (12.4%), there was no statistical difference in the sudden cardiac death patient survival. However, the overall survival of patients not meeting implant criteria with the Transvene™ System was significantly better ($p = 0.037$) when compared to the PCD® Epicardial System patients not meeting implant criteria, 93.5% and 87.6%, respectively.

The investigators felt in every case that the testing performed at the time of implant, though it did not meet the recommended implant criteria, did provide an adequate demonstration of device effectiveness and justified the implant of the PCD Transvene System. Finally, there have been no patients deaths secondary to unsuccessful termination of a spontaneous VT or VF episode in this patient population.

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K.3 Description of Patients Not Meeting Implant Criteria

As noted previously, the patients not meeting implant criteria (N=214) were divided into three groups (1) Successful defibrillation at an energy level of equal to or less than 24 Joules [79.4% of the patients]; (2) Difficult to induce VF [11.2% of the patients]; and (3) Implant procedure terminated due to poor patient condition [9.4% of the patients]. These patient groups are reviewed in the following discussion.

Lowest Energy of Defibrillation < 24 Joules

There were 170 patients in whom the PCD® Transvene™ System was implanted with a defibrillation safety margin of at least 10 Joules. Table IK-6 provides an overview of these patients clinical experience.

These data indicate that the final implanted PCD® Transvene™ System was evaluated and significant attempts were made to meet the recommended implant criteria. In most of these patients (79.4%), a safety margin of 10 Joules was obtained between the successful defibrillation energy (24 J or less) for ventricular fibrillation and the maximum output of the PCD Device (34 J). The investigators decided in certain circumstances that this was appropriate demonstration of device effectiveness and that the PCD® Transvene™ System could be implanted.

Of these patients, 159 (93.5%) have had VT or VF induced at a chronic follow-up visit and in each case, VT or VF was successfully terminated by the PCD Transvene System. In addition, 65 patients (38.2%) have experienced a spontaneous VF episode with an overall efficacy of 99.4%.

Thus, the clinical outcome in these patients was not adversely affected by not meeting implant criteria since their spontaneous VF episode efficacy was 99.4% and the one year sudden cardiac death actuarial survival was also 99.4%. The duration of follow up, however, is limited to an average of 9.7 months.

PCD® Transvene™ System Patients Not Meeting Implant Criteria 10J Safety Margin Provided	
Number of Patients	170
Lowest Energy of Defibrillation **1 Success with 10J Safety Margin** **2 Success with 10J Safety Margin** **3 Success with 10J Safety Margin** **> 3 Success with 10J Safety Margin**	 87 58 18 7
Overall Spontaneous VF Episode Efficacy	99.4%
One Year Survival: **Sudden Cardiac** **Overall**	 99.4% 93.8%

Table IK-6: PCD® Transvene™ System: Patients Not Meeting Implant Criteria with 3/4 Successes at ≤ 24 Joules Clinical Experience - 2/1/93

Difficult to Induce VF

There were 24 patients who did not meet the recommended PCD® Transvene™ System implant criteria because at least three episodes of VF were not induced at the time of implant. Of these, 15 patients had ventricular tachycardia induced and successfully reverted. The remaining 9 patients had ventricular flutter induced and successfully reverted. In all 24 patients, the lowest successful energy was equal to or less than 18 Joules.

The indication for implant was sudden cardiac death (SCD) in 6 patients (25%), recurrent ventricular tachycardia (VT) in 13 patients (54.2%) and sudden cardiac death associated with recurrent ventricular tachycardia (SCD/VT) in 5 (20.8%) patients. Thus the majority of the patients, 75%, had documented recurrent ventricular tachycardia as part of their ventricular tachyarrhythmia history. Eight of the these patients (33.0%) were on (b)(4) (b)(4) therapy which may have contributed to the inability to induce VF.

Of the 24 patients who did not meet the recommended PCD® Transvene™ System implant criteria because at least three episodes of VF were not induced at the time of

implant, 13 patients (54.2%) have experienced a spontaneous VF episode and 21 patients (87.5%) have had VT or VF induced during a chronic follow-up. In all cases, VF was successfully reverted by the PCD® Transvene™ System.

There has been one reported patient death (b)(6) in this patient group. Since this patient died after one year, the one year sudden cardiac death and overall actuarial survival remains 100%.

Patient Condition

There were 20 patients in whom the implant procedure was terminated due to poor patient condition. These patients received a PCD® Transvene™ System without at least a 10 Joule defibrillation safety margin. The implant circumstances of these patients is summarized as follows:

- At least one successful defibrillation was obtained at an energy level greater than 24 Joules but less than 34 Joules (**N = 11 patients**);
- Multiple inductions of VT were performed and successfully reverted with an energy level of 18 Joules or less. However, induced VF was not successfully reverted by an energy level of less than or equal to 34 Joules (**N = 6 patients**); and
- Physician elected to terminate the procedure due to the patient's condition before inductions with the final implanted lead configuration were performed (**N = 3 patients**).

The mean ejection fraction of this group was 26.9%, indicating more severe underlying cardiovascular disease, and may have contributed to the physicians decision to terminate the implant procedure prior to meeting implant criteria. This group had a mean of 6.8 VF inductions, 2.2 lead configurations evaluated and a mean duration of VT/VF for the implant procedure of 220 total seconds. The circumstances of the implant procedures, mainly the duration of induced ventricular tachyarrhythmia and associated hemodynamic compromise, limited the number of inductions that could be performed and whether the recommended implant criteria could be met.

Of these 20 patients, VT or VF has been induced at a

chronic follow-up visit in 16 patients (80%) and in all cases successful defibrillation with the implanted PCD® Transvene™ System was documented.

The overall spontaneous VF episode efficacy for this patient group was 96.0%. However, examination of events indicated that one patient experienced atrial fibrillation that was detected as VF and in whom all four programmed VF therapies were ineffective. This patient's antiarrhythmic drug therapy was modified and there were no further reports of ineffective therapies.

Thus there have been no patients who have experienced an actual spontaneous VF episode where all four programmed VF therapies failed to terminate the episode.

There have been two reported patient deaths, Patient ID (b)(6) which was classified as non-sudden cardiac secondary to end stage heart failure and Patient ID (b)(6) which was also classified as non-sudden cardiac. The one year sudden cardiac death survival in this patient population is 100% while the overall one year survival was 85.5%. This lower overall one year survival may due to the lower mean ejection fraction of this patient group.

The clinical outcome in these twenty patients was not adversely affected by not meeting implant criteria since there was no reports of failure to terminate a spontaneous VF episode and the overall one year sudden cardiac death survival was 100%.

Conclusion

In conclusion, 214 patients received the PCD® Transvene™ System despite not meeting the recommended implant criteria. These 214 patients are divided into the following groups:

- successful defibrillation of VF at 24 Joules or less (170/214),
- difficult to induce at least three episodes of VF at implant (24/214), and
- worsening patient condition which prevented further inductions (20/214).

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It should be noted that 91 % (194/214) of the patients not meeting the recommended implant criteria had at least one successful termination of induced ventricular tachyarrhythmia (VT, VFlutter or VF) at 24 Joules or less.

L. Comparison to AICD System Experience

L.1 Overview

The current AICD Epicardial System is implanted only with a defibrillation lead system requiring a thoracotomy. The PCD® Transvene™ System allows the implantation of an implantable cardioverter defibrillator (ICD) system without the potential increased perioperative morbidity and mortality associated with a thoracotomy. This allows the application of ICD therapy in patients who may not otherwise be candidates for this type of therapy. Though the PCD® Transvene™ System will have complications and observations that are specific to the lead system, the overall performance should be at least equivalent to that reported with the current AICD Epicardial System.

This section provides a comparison of the PCD® Transvene™ System clinical experience to that of the reported AICD Epicardial System clinical experience. The following areas will be discussed:

- Patient characteristics
- Clinical performance
- Survival analysis

For purposes of comparison, the Ventak-P Epicardial System patient population described in the Summary of Safety and Effectiveness Data (PMA Application Number P890061) dated May 2, 1991 will be used. A copy of this summary was obtained through the Freedom of Information Act.

L.2 Comparison of Patient Characteristics

In comparing the clinical experience with the PCD® Transvene™ System to the reported Ventak-P Epicardial System clinical experience, it is important to determine that the patients who received the device are comparable.

The characteristics of the patients receiving the PCD® Transvene™ System were compared to the characteristics of patients discussed in the Ventak-P Summary of Safety and Effectiveness Data and are presented in Table IL-1. There were no differences between the two patient groups.

PCD® Transvene™ System
Comparison of Patient Characteristics
PCD® versus AICD

	PCD®	Ventak-P
Number of Patients	757	292
Mean Follow-Up Time	11.7 months	6.8 months
% Males **% Females**	610 (81%) 147 (19%)	231 (79%) 61 (21%)
Mean Age	59.4 years	61.5 years
Primary Indication: **SCD** **VT** **SCD/VT**	 281 (37%) 377 (50%) 99 (13%)	 49 (16%) 169 (59%) 73 (25%)
Coronary Artery Disease	561 (74%)	228 (78%)
Mean Ejection Fraction	35.6%	34%
Drug Therapy at Implant	42%	45.0%
Concomitant Surgery	0%	18.0%

Table IL-1: Comparison of Patient Characteristics, PCD® versus Ventak-P 2/1/93

The two patient groups are comparable in mean age and mean ejection fraction. Both groups had moderately depressed left ventricular function demonstrated by the mean ejection of 35.6% for the PCD® Transvene™ System patient group and 34% for the Ventak-P Epicardial System patient group.

Analysis indicated that no statistical differences between the PCD® Transvene™ System and Ventak-P Epicardial System patient populations except in the category of patient indication. There are more patients that had Sudden Cardiac Death as the primary indication in the PCD® Transvene™ population than in the AICD population ($p = 0.001$).

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L.3 Comparison of Clinical Performance

Areas of clinical performance that were compared were implant defibrillation thresholds, incidence of spontaneous VT/VF events, incidence of complications and patient survival. These specific areas were selected in order to evaluate the system performance in the two patient populations.

Implant Defibrillation Thresholds

For the purposes of the PCD® Transvene™ System clinical study, determination of defibrillation threshold was not mandatory. However, the preferred method of evaluating defibrillation efficacy was to determine the defibrillation threshold using a testing sequence of 18J, 15J, 10J, 5J with a failure at any level causing a return to 18 J for the remaining attempts. For the purposes of this report a defibrillation threshold was defined as the energy at the lowest successful defibrillation attempt, provided a patient had a failure below their lowest defibrillation success or a success at $\leq$ 5J. The rhythm treated must have been VF to be included in the analysis.

It should be noted, that it was expected that the PCD® Transvene™ System would have a higher mean defibrillation threshold as compared to a traditional epicardial defibrillation lead system. In a epicardial system, the increased electrode surface area would theoretically decrease defibrillation requirements.

A total of 316 patients had a defibrillation threshold determined at the time of PCD® device implant. The mean defibrillation threshold (DFT) for all lead systems was 14.8J. The recommendation for VF Therapy #1 is to program the stored energy to twice the implant DFT or 18 Joules, whichever is greater. Thus an adequate defibrillation safety margin was provided when following the VF therapy programming recommendations.

In the Ventak-P Epicardial System, the mean defibrillation threshold at implant was 13.4J. Thus the two systems had similar defibrillation thresholds at implant despite the fact that one system utilized an epicardial defibrillation lead

system while the other utilized a transvenous defibrillation lead system.

These data indicate that the PCD® Transvene™ System had comparable implant defibrillation threshold performance when compared to the reported Ventak-P Epicardial System clinical experience.

Incidence of Spontaneous VT/VF Episodes

The incidence of spontaneous VT/VF episodes in the Ventak-P Epicardial System and PCD® Transvene™ System patient population was evaluated by utilizing the stored episode information provided by both devices.

In the Ventak-P device, the total number of shocks delivered to the patient is provided via interrogation of the device. The PCD® device provides information on the total number of VT and VF episodes detected by the PCD® device and the total number of VT and VF episodes successfully treated by the PCD® device as well as the number of VT/VF episodes where the PCD® device was ineffective. In addition, the last 20 intervals of the last episode satisfying detection criteria along with the first 10 intervals after the last therapy delivered are recorded by the device. These data assist the physician in evaluating the frequency of VT/VF episodes, the efficacy of the PCD® device programmed parameters and the need for reprogramming.

In the Ventak-P Epicardial System experience of 292 patients with a mean follow-up of 6.8 months, 137 (46.9%) received a device countershock in response to a spontaneous ventricular tachyarrhythmia episode as defined by the Ventak-P Device detection criteria.

In the PCD® Transvene™ System experience of 757 patients with a mean follow-up of 11.7 months, 458 patients (60.5%) have received device therapy in response to a spontaneous ventricular tachyarrhythmia episode as defined by the PCD® Transvene™ System detection criteria.

A total of 10027 spontaneous VT and 1982 spontaneous VF episodes have been recorded by the PCD® device

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episode counters. Of the 9864 successfully treated spontaneous VT episodes, 91.4% were treated with one of the programmed antitachycardia pacing therapies incorporated in the PCD® device. The clinical benefit of tiered therapy is the reduction of delivery of high energy shocks for the treatment of stable recurrent ventricular tachycardia that may be responsive to antitachycardia pacing.

Incidence of Complications

Table IL-2 provides a comparison of reported complications and observations. The AICD clinical experience data is from the Winkle, et al Long Term Outcome with Automatic Implantable Cardioverter-Defibrillator; JACC, May 1989; 13(6); 135-161. This article was selected because it provides a detailed clinical complication experience on a large patient population, 270 patients. Note that the percentage reported in the PCD® Transvene™ System includes **both complications and observations.** In the following table, the complications are reported for the categories of Fail to Cardiovert/Defibrillate, Pocket Infection, and Erosion. Observations are reported in the Inappropriate/Problematic VT/VF Therapy Delivery category.

PCD® Transvene™ System
Comparison of Complication/Observation Rates
PCD® versus AICD

Category	PCD®%	AICD%
Fail to Cardiovert/Defibrillate	2.3%	4.1%
Inappropriate/Problematic VT/VF Therapy Delivery	9.6%*	20%
Pocket Infection (explant)	2.9%	2.2%
Erosion	0.8%	0.7%

* Includes Observations only; there were no Complications in this category.

Table IL-2: Comparison of Complication/Observation Rates: PCD® Transvene™ System vs AICD Epicardial System - 2/1/93

The incidence of failure to cardiovert and/or defibrillate was lower in the PCD® Transvene™ System patient population. The instances of failure to cardiovert and/or defibrillate in

the PCD® Transvene™ System patient population were associated with increased defibrillation requirements during induced episodes, none of which resulted in patient death.

The failures to cardiovert/defibrillate reported in the Winkle, et al article were associated with patch dislodgement, patch crinkling, lead conductor fracture and elevated defibrillation thresholds.

The incidence of inappropriate/problematic VT/VF therapy delivery was lower in the PCD® Transvene™ System patient population. This is to be anticipated since the device incorporates independently programmable detection algorithms for VT and VF. The reasons for inappropriate VT/VF therapy delivery included sinus tachycardia being detected as VT or VF and atrial fibrillation with rapid ventricular response being detected as VT or VF.

The overdetection circumstances reported in Winkle, et al were nonsustained VT, VT, sinus tachycardia, atrial fibrillation with rapid ventricular response, sensing lead fracture and pacemaker interaction. The patients with VT complained of receiving multiple shocks with limited or no symptoms. The incorporation of antitachycardia pacing in the PCD® device decreases the need for delivery of cardioversion shocks for the termination of stable VT and increases patient acceptance of ICD therapy.

In the Winkle, et al experience all patients with pocket infection had the devices explanted. In the PCD Transvene System experience, the incidence of device explant secondary to pocket infection was 3.2% which was comparable to Winkle's article.

Thus, the incidence of complications and observations was similar to that of the AICD Epicardial System in the categories of ineffective VT/VF therapies, infection requiring explant and erosion. The incidence of inappropriate delivery of therapy is lower in the PCD Transvene System experience than in the AICD Epicardial System experience, which is clinically significant.

This analysis indicates that the PCD® Transvene™ System offers clinical advantages in reducing the need for a

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thoracotomy for implantation and reducing the number of shocks due to successful antitachyarrhythmia pacing.

L.4 Comparison of One Year Actuarial Survival

The Ventak-P Epicardial System produced by Cardiac Pacemaker, Inc, has obtained market approval from the U.S. FDA to date. While there are important differences in the function of the Ventak-P Epicardial System and the PCD® Transvene™ System, there is a natural desire for comparison of the clinical outcome, particularly the impact of these devices on death rate.

A total of 51 deaths (6.7%) were reported in the PCD® Transvene™ System patient population. Of the 35 cardiac deaths, 30 were non-sudden cardiac and 5 were sudden cardiac. Sixteen deaths were classified as noncardiac. Five of the 51 total deaths occurred within the perioperative period (death less than 30 days post implant) with a resultant perioperative mortality of 0.7%.

In the Ventak-P Epicardial System patient population a total of 19 deaths (6.5%) were reported. Of the 12 cardiac deaths, 4 were classified as sudden cardiac and 8 were classified as non-sudden cardiac. Six of the deaths were classified as noncardiac and the cause of one was unknown. Eight of the deaths occurred within the perioperative period with a resultant perioperative mortality of 2.7%. The PCD® Transvene™ System population had a lower perioperative mortality, 0.7% vs 2.7% ($p = 0.006$).

For purposes of this comparison, only the **overall** actuarial survival rate includes perioperative deaths. All other calculations in both the PCD® Transvene™ System and Ventak-P Epicardial System group exclude perioperative deaths.

For the Ventak-P Epicardial System, patient deaths were **censored** if the Ventak-P device had been either electively deactivated for various reasons prior to the patient's death, thus preventing the device from attempting to convert the arrhythmia or if the pulse generators were known to be nonfunctional and awaiting replacement. For purposes of this comparison, seven patient deaths were **censored** in the

PCD® Transvene™ System patient population because the devices were deactivated at the time of patient death.

This PCD® Transvene™ System sudden cardiac death survival of 99.7% at one year is comparable to that of the Ventak-P Epicardial System sudden cardiac death survival rate of 98.6%. More importantly, the overall one year actuarial survival for the PCD® Transvene™ System was 94.2% as compared to 90.8% for the Ventak-P Epicardial System. This difference was primarily due to the improvement in the reported perioperative mortality in the PCD® Transvene™ System patient population. [Note: Confidence interval analysis was performed indicating that there was a statistical difference in the reported **Overall** mortality.]

This comparison of actuarial survival rates indicates that the projected sudden cardiac death survival of patients receiving a PCD® System patient population is comparable to that reported for the Ventak-P Epicardial System. Thus, the incorporation of programmable VT/VF detection and therapy algorithms has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

In addition, the elimination of a surgical thoracotomy for implant in the PCD® Transvene™ System has improved the perioperative mortality and overall one year survival when compared to the Ventak-P Epicardial System.

M. Comparison to PCD® Epicardial System Clinical Results

The PCD® Epicardial System uses the same tiered therapy device that combines features of bradycardia support pacing, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. This system has incorporated programmability and multiple detection and therapeutic options that allows the titration of device therapy to a patient's specific clinical arrhythmia history.

The PCD® Epicardial System requires a thoracotomy for implantation because of the need to insert epicardial patch leads. This exposes the patient to surgical risk and potentially limits the

type of patient who may be considered for implant of the system. The need for a simpler and safer implantation technique is widely recognized. The incorporation of a nonthoracotomy lead system, such as the PCD® Transvene™ System, should decrease the potential perioperative and long term mortality and morbidity associated with current epicardial system implantation approaches.

The PCD® Epicardial System and PCD® Transvene System are identical except for the implanted defibrillation lead system. Thus, the performance of the PCD® device, associated support equipment, is similar in the two systems and therefore a comparison of clinical experience should focus on those areas where the implanted lead system may impact clinical outcome.

This section provides a comparison of the PCD® Transvene™ System clinical experience to the reported PCD® Epicardial System clinical experience. The following areas will be discussed:

- Patient characteristics
- Implant Data
- Spontaneous VT/VF Episode Efficacy
- Complications and Observations
- Survival analysis

This analysis will show that the incorporation of a nonthoracotomy defibrillation lead system has maintained the type of therapy available for the treatment of recurrent VT/VF and decreased the potential mortality and morbidity associated with epicardial implant approaches while maintaining the positive impact of ICD therapy on VT/VF episode efficacy and patient survival.

M.1 Comparison of Patient Characteristics

In comparing the clinical experience with the PCD® Transvene™ System to the PCD® Epicardial System clinical experience, it is important to determine that the patients who received the device are comparable.

Table IM-1 contains the characteristics of the 757 patients receiving the PCD® Transvene™ System versus the characteristics of the 742 patients who received the PCD® Epicardial System as of 1/5/93.

PCD® Transvene™ System Comparison of Patient Characteristics		
	PCD® Transvene System	**PCD® Epicardial System**
Number of Patients	757	742
Mean Follow-Up Time	11.7 months	16.3 months
% Males*	610 80.6%	637 85.8%
% Females	147 19.4%	105 14.2%
Mean Age	59.4 years	59.6 years
Primary Indication*		
SCD	281 37.1%	214 28.8%
VT	377 49.8%	405 54.6%
SCD/VT	99 13.2%	123 16.6%
Cardiovascular History		
Coronary Artery Disease	561 74.1%	569 76.7%
Cardiomyopathy	238 13.1%	222 29.9%
Mean Ejection Fraction	35.6%	34.0%
Number of Drugs Failed*	2.3	3.0

* **Statistically Significant**

Table IM-1: Comparison of Patient Characteristics, PCD® Transvene™ System versus PCD® Epicardial System - 2/1/93

Both groups had moderately depressed left ventricular function demonstrated by the mean ejection of 35.6% for the PCD® Transvene™ System patient group and 34.0% for the PCD® Epicardial patient group.

Analysis indicated that the PCD® Transvene™ System patient population had a higher percentage of patients whose indication for implant was sudden cardiac death ($p = 0.002$) and higher percentage of females ($p = 0.007$). It is not expected that these differences will result in a different clinical outcome in the PCD® Transvene™ System patient population as compared to the PCD® Epicardial System. This difference in patient indication is a reflection of the physicians use of the PCD® Transvene™ System.

It is interesting to note, that there was a statistical difference in the number of antiarrhythmic drugs tested

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between the two patient groups (p = 0.001). The PCD® Transvene™ System patient group failed a mean of 2.3 antiarrhythmic drugs prior to implant while the PCD® Epicardial System patient group failed a mean of 3.0 antiarrhythmic drugs. This difference is a reflection of the differences in the indications for implant between the two patient groups. The PCD® Transvene™ System patient group had a higher incidence of patients whose primary indication for implant was sudden cardiac death. These patients have a higher probability of having experienced a sudden cardiac death episode but were non-inducible during electrophysiologic testing so that drug testing was not feasible.

M.2 Implant Data Comparison

In both systems, lead system testing was performed to verify that one of the specified lead systems was capable of properly detecting and treating episodes of ventricular fibrillation and, when appropriate ventricular tachycardia. This testing included pacing and sensing thresholds during sinus rhythm, evaluation of VF electrogram amplitudes and defibrillation efficacy evaluation. The implant criteria for both systems was identical and were:

1. Successful VF termination at least 3 times in 4 attempts with an output energy of 18 Joules or less and

2. At least a 2:1 VF sensing safety margin

Pace/Sense Performance

In both the PCD® Transvene™ and PCD® Epicardial Systems, sensing is performed in a standard bipolar configuration and pacing is performed in the integrated bipolar configuration. The pace/sense implant criteria for both systems was:

Pacing Threshold:	$\leq$ 1.5V @ 0.5 ms
R-Wave Amplitude:	$\geq$ 5 mV
Slew Rate:	$\geq$ 0.75 volt/sec
Resistance:	200 - 880 ohms

Table IM-2 provides a comparison of the mean pace/sense values obtained at the time of implant for the PCD® Transvene™ and Epicardial Systems. It should be noted

that the pace/sense values presented for the PCD® Epicardial System are for the Model 7217B PCD® Device.

PCD® Transvene™ System Performance Comparison Implant Pace/Sense Parameters		
Parameter	**PCD® Transvene System**	**PCD® Epicardial System**
Pacing Threshold*	0.87 V (0.1-3.6V)	0.98 V (0.2-5.3 V)
R Wave Amplitude*	14.2 mV (1.3-32 mV)	13.5 mV (2.2-37.2 mV)
Slew Rate*	1.66 v/S (0.25-9.8 v/S)	1.38 v/S (0.15-7.2 v/S)
Resistance*	575 ohms (264-1381 ohms)	438 ohms (157-1206)

* **Statistically Significant**

Table IM-2: PCD® Transvene™ System: Comparison of Implant Pace/Sense Parameters - 2/1/93

The implant pace/sense parameters obtained for the PCD® Transvene™ System indicates that the lead system provided adequate pacing and safety margins. There was a statistically significant difference in all of the implant pace/sense parameters ($p = 0.001$). This is anticipated because endocardial pace/sense parameters are better than epicardial values for bradycardia pacing electrode systems. This difference has no clinical impact on the pacing and sensing performance of the PCD® Transvene™ System.

Electrogram amplitudes were evaluated at follow-up evaluations of both systems to evaluate the performance of the pace/sense lead system and assure adequate safety margin for detection of both baseline rhythms and ventricular tachyarrhythmias. In addition, pacing thresholds were also evaluated at follow-up evaluations to assure an adequate safety margin for capture during both bradycardia and antitachycardia pacing therapies. A comparison of the chronic pace/sense performance for the two systems is presented in Table IM-3. It should be noted that there was no statistical difference in the chronic pace/sense performance of the two systems.

4D

PCD® Transvene™ System Performance Comparison Chronic Pace/Sense Parameters		
Parameter	**PCD® Transvene System**	**PCD® Epicardial System**
Electrogram Amplitude	10.0 mV (0.5 - 25 mV)	9.5 mV (0.5 - 40 mV)
Pulse Width Threshold	0.24 ms (0.03-1.59 ms)	0.24 ms (0.03-1.59 ms)

Table IM-3: PCD® Transvene™ System: Comparison of Chronic Pace/Sense Parameters - 2/1/93

The incidence of loss of capture requiring lead system modification in the PCD® Transvene™ System was 0.8% while the incidence in the PCD® Epicardial System was 2.0%. There were no reports of undersensing requiring lead modification in the PCD® Transvene™ System while the incidence in the PCD® Epicardial System was 0.8%.

This comparison of implant and chronic pace/sense data performance indicates that the performance of the PCD® Transvene™ System is similar to that reported with the PCD® Epicardial System. The PCD® Transvene™ System provides appropriate acute and chronic safety margins for sensing of sinus rhythm and ventricular tachyarrhythmia as well as appropriate safety margins for pacing therapy.

Implant Defibrillation Thresholds

For the purposes of both systems, determination of defibrillation threshold was not mandatory. However, the preferred method of evaluating defibrillation efficacy was to determine the defibrillation threshold using a testing sequence of 18J, 15J, 10J, 5J with a failure at any level causing a return to 18 J for the remaining attempts.

A defibrillation threshold was defined as the energy at the lowest successful defibrillation attempt, provided a patient had a failure below their lowest defibrillation success or a success at $\leq$ 5J. The rhythm treated must have been VF to be included in the analysis.

Table IM-4 provides a comparison of defibrillation thresholds determined at implant for the PCD® Transvene™ and PCD® Epicardial Systems.

PCD® Transvene™ System Performance Comparison Implant Defibrillation Thresholds	
System	**Mean DFT**
PCD® Transvene™ System*	14.8J
PCD® Epicardial System	9.8J

* **Statistically Significant ($p \leq 0.05$)**

Table IM-4: PCD® Transvene™ System: Comparison of Implant DFT - 2/1/93

The PCD® Transvene™ System did have a significantly higher mean implant defibrillation threshold ($p = 0.0001$). It should be noted, that it was expected that the PCD® Transvene™ System would have a higher mean defibrillation threshold as compared to a traditional epicardial defibrillation lead system. In a traditional epicardial system, the increased electrode surface area would theoretically decrease defibrillation requirements.

The programmed defibrillation pathways for the two patient populations is presented in Table IM-5. The implanted PCD® Transvene™ Systems are almost exclusively three lead systems and this explains the decreased use of SINGLE pathway. The use of SIMULTANEOUS pathway is higher in the PCD® Transvene™ System and indicates that in a group of patients the incorporation of multiple defibrillation pathways allowed an increase in the ability to meet the PCD® Transvene™ System implant criteria. Most of the PCD® Epicardial System implants used a two patch system resulting in the increased use of the SINGLE pathway.

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PCD® Transvene System Performance Comparison Programmed Defibrillation Pathway		
Defibrillation Pathway	**PCD® Transvene System**	**PCD® Epicardial System**
Sequential	574 (75.3%)	251 (33.0%)
Simultaneous	178 (23.4%)	14 (1.8%)
Single	10 (1.3%)	496 (65.2%)

Table IM-5: PCD® Transvene™ System: Comparison of Programmed Defibrillation Pathway - 2/1/93

The differences in the programmed status of the PCD® device in the PCD® Transvene™ System are a reflection of the type of patients who received the device and the defibrillation energy requirements for each lead system. It is important to note that the PCD® device performed safely and effectively in both patient populations.

M.3 Spontaneous VT/VF Episodes Efficacy Comparison

The primary benefits from the use of the PCD® System center on the detection and termination of life-threatening ventricular tachyarrhythmias. An additional benefit of the PCD® Transvene™ System is the elimination of the need for a thoracotomy for implantation of the defibrillation lead system and the resultant decrease in potential patient morbidity and mortality associated with a thoracotomy. This clinical benefit should not be gained at the expense of providing effective termination of spontaneous VT and VF episodes. Table IM-6 provides a comparison of the efficacy of the PCD® Transvene™ and PCD® Epicardial System in treating spontaneous episodes of VT and VF.

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PCD® Transvene™ System Performance Comparison		
Spontaneous VT Episodes		
	PCD® Transvene™ System	**PCD® Epicardial System**
Mean Follow-Up	11.7 months	16.3 months
Number of Episodes	10,027	20,061
% Overall Efficacy	98.4%	98.3%
% Unsuccessful Termination	0.7%	1.0%
Spontaneous VF Episodes		
	PCD® Transvene System	**PCD® Epicardial System**
Mean Follow-Up	11.7 months	16.3 months
Number of Episodes	1982	2636
% Overall Efficacy	98.4%	98.7%
% Unsuccessful Termination	0.3%	0.5%

Table IM-6: PCD® Transvene™ System: Comparison of Spontaneous VT/VF Episode Efficacy - 2/1/93

The overall success rate of the PCD® Transvene™ System in terminating spontaneous episodes of VT or VF is 98.5%. In addition, there have been no reported patient deaths due to ineffective termination of a spontaneous VT/VF episode. This success rate compares very favorably with the overall success rate of the PCD® Epicardial System which was 98.4%. Therefore, the PCD® Transvene™ System offers the potential of decreased patient morbidity and mortality without decreasing the treatment efficacy of spontaneous VT/VF episodes.

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M.4 Incidence of Complications/Observations

A comparison of the reported complications and observations was made between the PCD® Transvene™ System and the PCD® Epicardial System. The PCD® Epicardial System patient population used for comparison included clinical experience as of January 5, 1992 with 742 patients and a mean implant duration of 16.3 months. These two patient groups are similar in the patient demographics and indication for implant of the PCD® System. In the PCD® Transvene™ System patient population, 19.4% of the patients experienced a clinical complication and 23.8% of the patients experienced a clinical observation. In the PCD® Epicardial System, 14.2% of the patients experienced a clinical complication and 32.9% of the patients experienced a clinical observation.

Table IM-7 and IM-8 provide a comparison of the reported complications/observations and their incidence in the two patient populations.

PCD® Transvene System
PCD® Transvene System versus PCD® Epicardial System Reported Complications

Reported Complications	PCD® Transvene™ System (N = 757)	PCD® Epicardial System (N = 742)
Increased Defibrillation Requirements	1.2%	0.5%
Inappropriate Therapy	-	2.2%
Pace/Sense Related	0.8%	3.5%
Infection Related - Explant	2.9%	2.3%
Lead Related	15.1%	2.8%
Device Related	0.5%	0.9%

Table IM-7: Reported Complications: PCD® Transvene™ System versus PCD® Epicardial System - 2/1/93

PCD® Transvene™ System PCD® Transvene System versus PCD® Epicardial System Reported Observations		
Reported Observations	**PCD® Transvene™ System (N=757)**	**PCD® Epicardial System (N=742)**
Ineffective Therapy	1.1%	1.1%
Inappropriate Therapy	9.6%	13.6%
Pace/Sense Related	9.0%	14.0%
Infection Related	5.3%	2.5%
Lead Related	2.3%	1.2%
Device Related	-	-

Table IM-8: Reported Observations: PCD® Transvene System versus PCD® Epicardial System - 2/1/93

M.5 Survival Analysis Comparison

Despite their excellent clinical performance, epicardial defibrillation lead system have important limitations. The requirement for direct thoracic access contributes significantly to patient morbidity and mortality, patient discomfort and prolonged hospitalization. The availability of reliable nonthoracotomy lead systems should provide positive clinical impact on these issues while not negatively impacting patient survival. Therefore, a comparison of the one year actuarial survival rates for the PCD® Transvene™ and Epicardial System was performed.

Table IM-9 provides a summary of the patient deaths reported in the two patient populations by classification. As a reference, the mean follow-up time for the PCD® Transvene™ System patient population was 11.7 months while for the PCD® Epicardial System it was 16.3 months.

PCD® Transvene™ System Death Classifications PCD® Transvene™ System versus PCD® Epicardial System		
Death Classification	**PCD® Transvene™ System (N=757)**	**PCD® Epicardial System (N=742)**
Sudden Cardiac	5	24
Non-Sudden Cardiac	30	54
All Cardiac	35	78
Noncardiac	16	34
TOTAL	51	112

Table IM-9: Death Classifications: PCD® Transvene™ System versus PCD® Epicardial System - 2/1/93

Table IM-10 provides a comparison of actuarial survival rates between the PCD® Transvene™ and PCD® Epicardial patient populations. The actuarial survival projections include perioperative deaths only in the calculation of survival from death due to all causes (shown in table row labelled **Overall**). Perioperative mortality includes those deaths which occur in the first thirty days post implant of the PCD® System.

PCD® Transvene™ System Comparison of Actuarial Survival PCD® Transvene™ System versus PCD® Epicardial System			(b)(4)
One Year Survival	**PCD® Transvene™ System**	**PCD® Epicardial System**	
Number of Patients	757	742	(b)(4)
Sudden Cardiac	99.5%	98.9%	
Non-Sudden Cardiac	96.2%	96.7%	
All Cardiac	95.8%	95.7%	
Noncardiac	98.1%	98.0%	
Overall*	93.3%	88.6%	

* (b)(4) (b)(4)

Table IM-10: Comparison of Actuarial Survival: PCD® Transvene™ System versus PCD Epicardial System - 2/1/93

There was a significant increase in overall survival in the patients receiving a PCD® Transvene System™. As previously noted, the Overall one year actuarial survival includes death from all causes. The overall one year survival for patients receiving the PCD® Transvene™ System was 93.3%. This is significantly improved as compared to the overall one year actuarial survival for the PCD® Epicardial System (88.6%) (b)(4) This improvement in overall survival is primarily due to the marked improvement in perioperative mortality, the PCD® Transvene™ System having a 0.7% (5/757) perioperative mortality versus the a perioperative mortality of 5.3% (39/742) in the PCD® Epicardial System. This improvement in perioperative mortality is primarily due to the elimination of the need for a thoracotomy and its associated morbidity and mortality.

N. PCD® System Performance

N.1 PCD® Device

Devices implanted for the treatment of recurrent ventricular tachyarrhythmias should perform safely and reliably in the indicated patient population. Device longevity, ventricular tachyarrhythmia detection, therapy performance, and analysis of explanted devices were evaluated to assess the performance of the PCD® Device.

Extended longevity of implantable cardioverter defibrillators should decrease the number of device replacements a given patient would experience over their lifetime and decrease unnecessary patient morbidity. Thus, the PCD® Device longevity, which is monitored utilizing battery voltage and charge time obtained via telemetry, was analyzed. The PCD® Device longevity data collected is consistent with the longevity projections.

The combined experience of induced and spontaneous VT/VF episode experience has shown that the PCD® Device VT/VF detection and therapies have performed safely and according to design specifications when required to treat induced and spontaneous VT/VF episodes.

There have been a total of 58 devices explanted. Reasons

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for explant were patient death (23), infection (22), cardiac transplant (9), low battery voltage (1) and PCD Device performance issues (3). The analysis of the device that was explanted due to lower than expected battery voltage indicated that the decreased battery voltage measurement was due to hermetic leakage at the input to one of the integrated circuits and this affected the battery indicator circuit only and did not affect the critical functions of the device. This leads to a voltage drop across a resistor where the voltage measurement is taken. Analysis indicated that the battery was performing to specifications and the hermetic leakage was a random event. Analysis of the other three devices indicated that two were due to random component failure and one due to shorting on Pulse 2 output. Thus, arcing occurred between the conductors inside the hermetically enclosed brazed ring of the high power hybrid. As a result, high voltage was momentarily applied to the low power circuitry, including the low power hybrid. This low power hybrid lost function including the capability to pace and transmit telemetry due to excessive voltage applied. Since this is the only device that exhibited this type of failure in the field and the hybrid manufacturing process has demonstrated that it will screen out infant mortality, this failure was assumed to be a random component failure.

Based on the clinical data collected, the PCD® Device has performed safely and reliably in the indicated patient population.

N.2 Transvene™ Lead Performance

The Transvene™ Lead System consists of a Right Ventricular Lead, a Coronary Sinus/Superior Vena Cava lead, and a Subcutaneous Patch lead. There have been a total of 757 Right Ventricular leads (15 with the SP2100 and 742 with the Model 6884/6966), 796 Coronary Sinus/Superior Vena Cava leads (Model 6881/6963), and 718 Subcutaneous Patch leads (Models 6895/10317/6999) implanted with a cumulative implant duration of 8894.8 months. The reported incidence of conductor coil fracture is 0.5% (4/757).

Based on the clinical data collected, the Transvene™ leads

have performed safely and reliably.

O. Summary

The overall clinical experience with the PCD® Transvene™ System indicates that the system performed according to design and specification. The reported clinical complications and patient deaths are appropriately addressed in the required labelling for the system and the patient selection criteria for implant of the device is appropriate.

The following can be drawn from this analysis of the data collected in this clinical study:

Patient Deaths

- The projected one year survival probabilities for Sudden Cardiac Death, Non-Sudden Cardiac Death, all Cardiac Deaths and Noncardiac Death were found to be 99.5%, 96.2%, 95.8%, and 98.1%, respectively.

  The incorporation of programmable VT/VF detection and therapies has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

- The sudden cardiac death survival of 99.5% at one year is comparable to that of the AICD patient population 98.0%.

- There have been no deaths due to a PCD® Device malfunction.

Complications/Observations

- Complications were reported in 19.4% of the patient population and observations were reported in 23.8% of the patient population.

- The incidence of complications was comparable to that of the market released AICD system in the categories of ineffective VT/VF therapy, pocket infection, and pocket erosion and was lower than the AICD in the category of inappropriate delivery of VT/VF therapy.

Patient Indications

- All of the patients entered into this clinical evaluation met at least one of the primary indications. Sudden cardiac death (SCD) was the primary indication in 37.1% of the patients, recurrent ventricular tachycardia (VT) was the primary indication in 49.8 % of the patients and SCD/VT was the primary indication in 13.1% of the patients.

- The number of patients (60.5%) receiving VT/VF therapy for spontaneous episodes of ventricular arrhythmias supports the conclusion that the patient selection criteria are appropriate and that the PCD® Transvene™ System was implanted in patients who benefit from this therapy.

- The one year sudden cardiac death survival rates for the SCD patient group was 100.0%, for the VT patient group 99.4% and the SCD/VT patient group 98.6%.

VT/VF Detection and Therapy Performance

- The PCD® Transvene™ System properly detects and treats VT as demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VT was 98.4%.

- The PCD® Transvene™ System properly detects and treats VF as demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VF was 98.4%.

- There were no reported patient deaths due to the nondetection of a spontaneous VT or VF episode by the PCD® Transvene™ System.

PCD® Transvene™ System Performance

- The PCD® Transvene™ System components (Model 7216A/7217B and Model 6884/6966, 6881/6963, 6895/6999 Transvene™ leads) have performed according to design and specification and are, therefore, considered safe and effective in the indicated patient population.

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P. Clinical Experience Summary Conclusions

The PCD® Transvene™ System is a tiered therapy device which combines features of bradycardia pacing support, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. The incorporation of these features has allowed the physician to titrate the ICD therapy to meet specific patient clinical needs, allowed fewer shocks to be delivered for recurrent ventricular tachycardia because of antitachycardia pacing features, allowed fewer cases of inappropriate therapy delivery due to programmable detection and allowed a sudden cardiac death survival rate identical to the Ventak-P Epicardial System.

The PCD® Transvene™ System, due to the elimination of the need for a thoracotomy, has provided a marked improvement in both the perioperative and overall patient mortality as compared to the PCD® Epicardial System. In addition, due to the decreased perioperative morbidity and mortality, the post implant hospital stay has been decreased to a mean of 7.6 days as opposed to a mean of 10.6 days ($p = 0.001$) for the PCD® Epicardial System.

Medtronic asserts and the PCD® Transvene™ investigators unanimously agree that the findings of the clinical study support the conclusion that the Medtronic Tachyarrhythmia Control System and the Transvene™ Cardioversion and Defibrillation Electrodes are safe and effective in the indicated patient population.

MJ
ICDD
DLRND

P 015/S000

2-Jun-1993

FROM:	LETTER DATE	LOGIN DATE	DUE DATE
MEDTRONIC INC. ATTN: JENNIFER M. MARRONE 7000 CENTRAL AVENUE, N.E. MINNEAPOLIS,, MN 554323576	06/01/93	06/02/93	/ /
	DOCUMENT: PMA	CONTROL # P920015/S000 AMENDMENT	

SUBJECT:
MEDTRONIC(R) TRANSVENE LEAD SYSTEM

	OFFICE	DATE REFERRED
3 COPIES OF VOLUME 1	CK	6/3/93
____ COPIES OF VOLUME ____	DCRND	
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MEMORANDUM

From: Doris Terry (HFZ-450)
To: File # P920015/Amendment
Subject: Transvene Lead System
Date: June 3, 1993
Office: DCRND/ODE

The manufacturer submitted the referenced amendment to inform us of a case of "cosmetic" metal ion oxidation (MIO). The MIO was found on the Model 6884 (comparable to Model 6966) Transvene RV lead explanted from a patient who underwent a heart transplant.

According to the manufacturer, the presence of MIO on the middle insulation is not entirely unexpected. It was stated that if the middle insulation completely degrades (shorting the sensing ring), then an integrated bipolar sensing system would result (sensing would occur between the unipolar pacing tip and the common defibrillation electrode instead of true bipolar (sensing between the pace/sense tip and the ring electrodes). However, if the innermost insulation degrades and the pacing tip electrode is shorted, intermittent sensing could result. This type of behavior such as intermittent sensing, oversensing, undersensing, etc. could be detected at the follow-up intervals.

Consultation and the review of the issue in the referenced amendment, as well as previous IDE supplements, have taken place with (b)(6) Due to the failure of the Medtronic, Inc. brady leads which employ the platinum sputtering process as the Model 6966 and 6884 leads, she is very concerned. In past reviews, we have requested that the manufacturer institute long term testing to asses the MIO problem.

The monthly report of all observations and complications, as referenced in our letter regarding the IDE expansion, was requested. In addition, the following concerns were conveyed to the manufacturer:

1. The differences between the Model 6884 and the Model 6966 Transvene leads. (The Model 6884 (b)(4) connector size and the Model 6966 -(b)(4) connector size). The number of leads explanted to date and the MIO and environmental stress cracking (ESC) noted. (As of 150 explants, there was no evidence of MIO).

2. To date, how many patients have received the Transvene lead System? How many patients have been implanted for 2 years and greater? (at least 50) What is the compliance to follow-up of these patients. (Compliance to follow-up 98 to 99 percent). Update on clinical experience: lead related complications, first shock VT/VF efficacy, survival rates,

etc. Are there patients with a dilated RV counted in the group followed for 2 years or more? At what intervals were the complications noted?

3. A description of the expected failure mechanism of the leads. In the referenced case, evidence of MIO was noted at 2 years (MIO visible on the innermost insulation and the middle insulation). What is considered the life expectancy of the leads void of signs of MIO? What is the projected rate of progression. Are their studies to confirm these speculations?

4. Based upon the review of the requested data, the protocol and testing at follow-up might need to be modified to include the following: x-rays or fluoroscopy when there are recurring and/or suspect lead complications or observations and periodically at preset intervals.

5. Regarding the patient whose lead was explanted:

   a. When were the 6 spontaneous VT/VF shocks delivered? Was the system interrogated after explant? [This was the implant history].

   b. Was there more damage noted on the innermost or middle insulation?

   c. What were the lead impedance and threshold measurements?

   d. Explain how the patient's dilated RV contributed to the MIO noted.

The occurrence of MIO noted upon explant of the Model 6966 leads and its significance will be brought to the attention of the Panel.

The manufacturer agreed to provide answers to the above questions and additional supporting data in the Panel volumes.

Medtronic

Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576
Telephone: (612) 574-4000
Cable: Medtronic Telex: 29-0598
FAX: (612) 574-4879

June 1, 1993

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Office of Device Evaluation
PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

Re: Transvene® Lead System, PMA Amendment
(Document Control Number P920015) Ac 2/1

The purpose of this submission is to provide a follow-up report detailing the analysis of an explanted Model 6884 right ventricular, transvenous lead, as described in the March 26, 1993 PMA amendment. The follow-up analysis is provided in Attachment 1. For reference, a copy of the relevant information provided on March 26 is also enclosed in this submission as Appendix A.

The existence of the PMA Amendment and the data and other information it contains are confidential, and the protection afforded to such confidential information by 18 USC 1905 and other applicable laws is hereby claimed.

Three copies of this PMA amendment are provided. Should additional information be required by the Agency, please contact the undersigned.

Sincerely yours,

MEDTRONIC, INC.

Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
(612) 574-4688
(612) 574-6424 FAX

Attachment

4

ATTACHMENT 1

A Model 6884, screw-in, right ventricular, pace/sense, cardioversion/ defibrillation lead was returned to Medtronic 27 months post implant. The lead was returned to Medtronic following explant from a patient that was undergoing a heart/lung transplant. Note that the lead had been fully functional while implanted and was found to be fully functional upon explant.

Upon undergoing further analysis at Medtronic, some MIO (metal ion oxidation) was observed on the lumen of the middle insulation approximately 20 cm proximal of the pacing tip electrode, and on the outside of the inner insulation. The MIO was further characterized to be "cosmetic" in that it had not functionally affected the lead in any way. Cosmetic MIO is defined as any crack that has not breached the insulation.

Initial analysis indicated that the presence of the MIO was in the clavicular region of the body; i.e., the location, 20 cm proximal of the tip, would be in the first rib clavicle region of a small adult. There was no evidence, however, of conductor coil fracture and the lead was fully functional. Given the Model 6884 lead is generally implanted via subclavian vein insertion, this type of observation may occasionally be expected. However, subsequent analysis of the patient X-rays showed that the area of MIO was actually in the right ventricle. The patient's right ventricle was extremely dilated, secondary to pulmonary hypertension. Therefore, 20 cm from the proximal tip electrode located the area of MIO at the point of maximum curvature of the lead, in the right ventricle, rather than in the clavicular region.

Detailed Analysis Results

Visual/Microscopic

Shallow (cosmetic) environmental stress cracking (ESC) was visible. No coil deformation was visible in the first rib/clavicle region. Possible MIO was visible 20 cm proximal of the electrode tip extending approximately 0.5 cm on the middle insulation. Possible MIO was also visible on the innermost insulation starting at 19.3 cm proximal of the electrode tip and extending 5.4 cm proximally.

Scanning Electron Microscopy

MIO was observed on the lumen of the middle insulation and on the outside of the innermost insulation. The MIO penetration was less than five percent of the insulation wall thickness. In addition to the insulation, both the middle and inner coils were evaluated up to 2500 times magnification. There were no

anomalies apparent on the inside or outside of the middle coil in the region of the MIO. The innermost coil showed no signs of crush or fatigue in the region of the MIO.

FTIR-ATR

FTIR spectra were obtained for a control area (no MIO) of the inner tubing and the cracked area of the tubing. Relative ratios of key bonds were calculated using the absorption intensities. These ratios indicated that the ether segments were oxidized in the polyurethane, which is characteristic of MIO. In addition, peaks appeared, indicative of carboxylic acids or esters (oxidation byproducts).

Discussion

Contrary to the initial dimensional analysis of this lead that indicated the area of MIO was located to the clavicular region of implant, review of the patient's X-rays revealed that the heart was significantly enlarged due to the advanced disease state. Subsequently, a significant portion of the insulated lead body was located in the heart, including the portion with cosmetic MIO. Typically, 20 cm proximal of the tip electrode approximates the clavicular region.

Consistent with our previous analysis of MIO relative to the 6884/6966 lead, the observed MIO did not, in any way, affect the clinical performance of this lead. Patient data analysis shows that the implanted lead system, inclusive of the 6884 lead, performed appropriately. Of six spontaneous VT/VF episodes reported (4VT/2VF), all were appropriately detected and treated via the implanted PCD Transvene system.

In addition, the presence of MIO on the middle insulation is not entirely unexpected (reference February 18, 1993, Medtronic/FDA meeting). If the middle insulation had been degraded to the point of electrically shorting the sensing ring (middle conductor coil) to the common defibrillation electrode (middle coil), an integrated bipolar sensing system would, in essence, be created. In this type of system, sensing occurs between the unipolar pacing tip and the common defibrillation electrode, versus standard, or true, bipolar sensing between the pace/sense tip and the ring electrodes. This type of sensing system is identical to the (b)(4) (b)(4) as well as Medtronic's earlier design of a Transvene RV lead, i.e., the Model SP2100. These types of integrated systems have been shown to be clinically acceptable. Note that canine testing of a shorted, RV cardioversion/defibrillation lead, indicated that this type of failure does not result in the lack of therapy delivery.

If the innermost insulation had degraded such that the pacing tip electrode shorted, this could manifest as intermittent sensing of the brady pace/sense function of the lead. This type of anomalous system performance is expected to be observed at follow-up sessions, given the frequent monitoring of patients

(every three months) or as necessary when the patient experiences VT/VF episodes or anything unusual. Similar to brady pacing patients, problems related to pace/sense performance are typically observed at the time of follow-up (pace/sense threshold measurements are standard follow-up procedure for both brady and tachy lead systems) and/or when the patient reports to his/her physician for any unusual events, e.g., intermittent pacing/sensing.

The extensive dilatation of the right ventricle in which this lead was implanted resulted in a large portion of insulated lead body being in the right ventricle, as opposed to primarily just the cardioversion/defibrillation electrode coil. Subsequently, this lead may have been subject to more flexing in the heart than what is typical for the RV lead. Note: this was demonstrated in the videotape that was presented to FDA at the February 18, 1993, Medtronic/FDA meeting.

Clinical data from brady pacing leads indicates that the portion of the lead subject to the flexing motion in the heart may be related to the occurrence of MIO in brady lead bodies. Brady pacing leads, proximal to the tip/ring electrodes are subject to more flexing motion, relative to a cardioversion/defibrillation RV lead, while contained in the heart. On the other hand, cardioversion/defibrillation leads, like the 6884/6966, are comprised of a comparatively stiff portion proximal to the tip/ring electrode. This length of defibrillation electrode, 5 cm, appears to flex less than a typical brady pacing lead while in the heart, as a result of greater stiffness. However, in the extremely hypertrophic heart, as was the case with this particular RV lead, the lead may be subject to more flexing, similar to that of a brady pacing lead.

Conclusions

As noted, Medtronic cannot assure that MIO, or other lead failure mechanisms will not occur in the 6884/6966 lead. However, one should consider the actual benefits of the lead versus the **potential** for MIO occurrence. Specifically, clinical data to date for the Transvene system show that one year actuarial survival from SCD is 99.5 percent and the average hospital stay for Transvene implant is only seven days (versus ten for an epicardial system)*. Regarding the potential for MIO occurrence, analysis shows this would result in a bipolar integrated sensing system, or in an intermittent pace/sense system. Integrated sensing has been shown to be clinically acceptable, and intermittent pacing/sensing is assessed as part of standard follow-up procedures. Additionally, with postmarket surveillance mechanisms in place, such as returned product analysis and chronic lead monitoring, Medtronic is well positioned to appropriately evaluate and manage potential failure mechanisms of implantable cardiac leads. We are committed to these surveillance mechanisms in the interest of delivering optimal implantable technology products to the health care market.

*Values are lower than those reported February 1993 due to increased follow-up data.

APPENDIX A

(from March 26, 1993 PMA Amendment,
Response to deficiency #36)

36. **In light of the failure of your platinum sputtered polyurethane bradycardia pacing leads, and since the Transvene™ lead Model 6966 is also a platinum sputtered polyurethane lead, please provide documentation regarding the failure mechanism of the pacing leads and all relevant information pertaining to these cases. How can we be assured that the failure may be restricted to the bradycardia pacing leads? Based on your testing to date regarding the pacing leads and the testing of the Model 6966 lead, discuss the potential and the probability of failure of the Model 6966 lead. A side by side comparison of the Model 6966 and the 4,000 series bradycardia pacing leads must be provided. The comparison must include material, design, dimensions, function, tests performed and a schematic drawing.**

RESPONSE:

Background on Brady Pacing Lead Experiences

Medtronic utilizes two systems to monitor performance of its brady pacing leads. The analysis of returned product is used to identify lead failure mechanisms. However, it cannot be used to estimate clinical performance since all leads/lead segments are not explanted or returned. Clinical performance is monitored through our Chronic Lead Study (CLS), a multi-center study currently involving eleven representative U.S. Clinical centers and over 20,000 leads. Lead performance in the CLS is presented as actuarial survival from clinical complications resulting in lead explants or abandonment. Specific complication criteria have been established (reference Medtronic Product Performance Report, February 1993, in Appendix C). Since all leads are not explanted it is not always possible to relate a clinical complication to a specific failure mechanism and not all complications are associated with lead failure.

The primary failure mechanisms for brady pacing leads are conductor fracture and insulation failure. Conductor fractures are primarily associated with the widely accepted "Subclavian Stick" implant procedure using percutaneous lead introducers. Leads implanted by this procedure can be clamped and crushed between the first rib and clavicle, leading to fracture of the conductor, and sometimes, insulation failures as well. Bipolar leads are more susceptible to this failure mechanism than unipolar leads because of their larger lead body diameter. Crush fractures tend to occur primarily during the first two years post implant.

For leads with polyurethane insulation, the primary insulation failure mechanisms are Environmental Stress Cracking (ESC) and Metal Ion

Oxidation (MIO); both tend to occur starting about 2 years post implant. Bipolar leads tend to be more susceptible to insulation failure than unipolar leads.

ESC is associated with stress on the lead either induced during manufacture or via implant procedure. Newer generation Medtronic leads have greater ESC resistance due to improvements in design, manufacturing processes and materials.

MIO is an oxidative degradation of polyurethane insulation. The reaction is catalyzed by metal ions released by the corrosion of the conductor coils. To reduce the potential for MIO, newer Medtronic lead designs have applied a sputtered coating of platinum to the conductor coils. Also, (b)(4) polyurethane tends to be more resistant to MIO than (b)(4) Medtronic has used an accelerated oxidation environment, (b)(4) to evaluate MIO and potential factors that can minimize its occurrence.

A table depicting the frequency of these failure mechanisms (conductor fractures, MIO and ESC) for brady leads, Models 4004/M and 4058/M, follows this response. As shown, conductor fracture due to crush is the predominate failure mode. See table, Failure Mechanisms, following this response.

The Model 4004/M is a bipolar lead incorporating (b)(4) polyurethane and platinum coating. As of February 28, 1993, survival probability of the Models 4004/4004M is 97.0 ± 1.7% at 36 months (reference the February 1993 Product Performance Report in Appendix C). Crush fracture is the primary source of lead failures to date, with rates comparable to that of earlier bipolar lead designs.

Over the past several months Medtronic and FDA have had numerous discussions about the occurrences of failure associated with MIO in the Model 4004/M lead. As of February 28, 1993, Returned Product Analyses has identified 22 MIO failures out of approximately 74,000 leads implanted (.030%). MIO failures in previous lead designs tend to predominate in 3 areas: proximally in the pacemaker pocket, medially in the clavicular region, and distally near the ring electrode. With Models 4004/M, platinum sputter coating appears to reduce the occurrence of MIO proximally and medially. The majority of the MIO failures (20 of 22) occurred distally. Distal failure occurs between the ring electrode and the AV valve and appear to be related to flexing of the lead associated with ventricular contractions.

Initial (b)(4) testing was conducted under static conditions and gave no indication of this failure mechanism. Currently testing is underway to develop a dynamic (b)(4) test to study factors affecting this

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failure mechanism and potential corrective actions. To date, we have been able to induce failures and are conducting experiments to understand contributing factors.

In order to illustrate the similarities and differences between the brady and tachy leads, a side-by-side comparison of the Model 6966 to the 4,000 series brady leads is presented in a table following this response. Note that only bipolar, polyurethane, brady leads from the 4,000 series are presented (includes Models 4016A, 4058/M, 4024, 4004/M and 4012/4082). This is due to their similarity of design characteristics to the 6966, and also because these brady leads are being, or were, widely used in the field, and therefore present with comprehensive data from the Chronic Lead Study and Medtronic's returned product analysis. Tests performed to qualify the brady leads were the same as those used for the tachy leads (except for high voltage system and crush testing). All tests are consistent with Medtronic standards and requirements for implantable cardiac leads (reference response to #34). Drawings of these brady leads are also presented following the comparative tables.

Some common features to all the leads in the table are the (b)(4) conductor coil, coaxial coil design, polyurethane insulation (b)(4) and/or (b)(4) and platinum alloy electrode material. Like the 6966 lead, the Models 4016A, 4058/M and 4024 also have platinum coating on the conductor coil and (b)(4) as the inner insulation. Individual lead differences include the electrode fixation mechanisms, i.e., screw-in helix versus tines and the (b)(4) versus (b)(4) insulation usage. Using (b)(4) insulation provides more stiffness, and greater resistance to insulation failure, whereas (b)(4) provides for greater ease of handling.

As presented in the lead comparison table, the brady lead most similar to the 6966 lead is the 4016A. Both have (b)(4) polyurethane as the inner(most) insulation, (b)(4) for the middle/outer insulations, distal screw-in fixation mechanisms, similar French (introduction) sizes and virtually identical insulation dimensions. Only the coil dimensions vary slightly. Note that the 4058/M lead is also very similar to the 4016A; the only substantive change is the introduction size, (b)(4) Model 4016A and 4058/M leads have shown excellent clinical performance; for the 4016A actuarial survival is 98.2% at three years (3,800 implants) and for the 4058/M actuarial survival is 99.7% at three years (37,000 implants), reference the CLS and returned product analysis as presented in the Medtronic Product Performance Report, Appendix C.

As previously presented, the 6966 lead has a larger body diameter than the brady leads. This is to be expected given the tripolar coaxial design of the lead. Given the larger French size of the 6966, it is more susceptible to crush between the clavicle and rib than the smaller French

leads. Lead fracture due to crush in this area is, however, a recognized failure mechanism for all transvenous leads implanted via subclavian insertion, (brady or tachy leads). This is vigorously addressed in product labeling (lead technical manuals) and includes appropriate cautions about the use of the procedure.

Also, the larger diameter of the 6966 lead body and presence of a defibrillation coil electrode proximal to the distal pace/sense ring of the 6966 lead imparts more stiffness to it than the brady leads. Hence, there is less lead body movement below the valve when the 6966 is implanted in the right ventricle as compared to a brady lead. This was clearly evident in the videotape comparing the in-vivo flexing of both a brady and tachy lead (presented in FDA/Medtronic meeting of February 18, 1993). Decreased flexing of the 6966 lead below the valve is our basis for expecting flex-related MIO will not be a significant failure mechanism of the 6966 lead.

Analysis of Transvene Model 6966 Lead and Clinical Presentation

The Model 6966 tripolar tachy lead is comparatively less flexible than brady leads. Therefore, distal MIO as evident in a very small percent (.030%) of brady 4004/4004M leads is not necessarily indicative of a similar occurrence in the 6966 lead. A videotape illustrating the clinical flex performance differences between brady and tachy leads was presented during the FDA/Medtronic meeting on February 18.

Analysis of the Model 6966 lead, as it relates to the potential for MIO, indicates that it would be more likely to occur on the middle versus the outer or innermost insulations. Lead failure due to MIO typically is found on the inner insulation on returned bipolar brady leads. Therefore, this failure mechanism is not expected to significantly affect the (b)(4) outer insulation of the 6966 lead. Should MIO occur on the outer insulation of the 6966 lead, the net effect would be an increased defibrillation electrode surface area. This would not be expected to significantly affect system performance. Additionally, the more resistant properties of (b)(4) (to MIO), of the 6966 innermost insulation, are expected to further reduce the potential for MIO (99.7% survival Model 4058/M at three years, see Product Performance Report, Appendix C).

For the Model 6966 lead, should the middle, (b)(4) insulation fail, it would likely present initially as an intermittent short (as is more typical with brady leads) and can progress over time if not identified and treated, to a hard (direct) short. These could manifest initially as oversensing, and ultimately as integrated bipolar sensing, respectively (intermittent versus hard short). In the case of a hard short of the middle insulation, specifically, shorting the pacing tip to the common

defibrillation electrode, an integrated bipolar sensing system is created. In this type of system, sensing occurs between the unipolar pacing tip and the common defibrillation electrode (versus standard bipolar sensing between the pace/sense tip and the ring electrodes). This type of sensing system is identical to the (b)(4) (b)(4) currently in clinical trials, and also to Medtronic's historic Transvene RV lead, the Model SP2100 lead. These type of integrated systems have been shown to be clinically acceptable. Note that fifteen Model SP2100 leads were implanted at the start of the Transvene clinical study. There have been no observations or reported problems related to the SP2100 lead performance. (Data from the SP2100 lead have been incorporated in the clinical experience analysis reported in this PMA application.)

Intermittent sensing could result in oversensing, if the detection criteria are also met, and this could result in delivery of inappropriate, i.e., not needed, therapies. This can be considered a "safe failure" given the system would "err" by oversensing (versus undersensing) and the patient could receive an unnecessary therapy. Also, patients are instructed to report therapies to their physicians; this facilitates identification of any inappropriate therapy.

Recently, a Model 6884[1] lead was explanted after 27 months when the patient received a heart transplant. The lead was fully functional at explant, however, returned product analysis has indicated the presence of some MIO in the clavicular region. Transvene leads, like brady leads, are implanted by subclavian insertion and are susceptible to being crushed between the clavicle and first rib. As indicated above, with brady leads this can result in conductor fractures, insulation failures or both. Analysis of the specific Model 6884 lead is ongoing and a more detailed report will be provided in approximately 30 days.

It should be noted that MIO is only one potential failure mechanism of implantable leads. As discussed, others include fracture due to crush in the area of subclavian insertion, environmental stress cracking due to stresses the in-vivo environment may impart to the lead and lead dislodgement.

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[1] The Model 6884 lead is the earlier version of the Model 6966 lead and differs only in the connector pin configuration; the 6884 has a (b)(4) high voltage connector pin and the 6966 has a (b)(4) high voltage connector pin. Otherwise the leads are the same.

Transvene Clinical Assessment Experience

Given over 2000 worldwide Transvene patients implanted to date, ranging from zero to forty months implant duration, there have been no reports of undersensing, insulation failures, or oversensing that could not be managed via reprogramming. Furthermore, the benefits of Transvene implantation are dramatically apparent from the perspective of perioperative mortality, 0.7 percent for Transvene versus 5.3 percent for epicardial implants. Transvene survival from SCD is 99.5 percent and overall survival is 93.3 percent at one year. Additionally, Transvene implants, on average, require 8 days in hospital versus 11 days for an epicardial system; a significant cost savings. In summary, the benefits of the Transvene system performance clearly surpass the potential for MIO, or other potential failure mechanisms, in the 6966 lead.

Conclusions

Although Medtronic cannot assure that MIO or other lead failure mechanisms will not occur in the Model 6966 lead, the actual benefits of the Transvene system, as previously discussed, would appear to exceed the potential risk due to MIO. Analysis shows that the potential for MIO to occur in the 6966 lead would result in a "safe failure." Note that preclinical and animal testing cannot completely simulate the long-term implant environment, thereby eliminating all potential for lead failures in-vivo. This was recognized by Congress in implementing the Postmarket surveillance provision in the Safe Medical Device Act of 1990. It is clear that postmarket surveillance mechanisms, e.g., returned product analysis and chronic lead monitoring, are more appropriate mechanisms for evaluating and managing potential failure mechanisms of implantable cardiac leads.

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FAILURE MECHANISMS

(CLINICAL/ELECTRICAL FAILURES FROM RETURN PRODUCT ANALYSIS)

MECHANISM	MODEL 4004/4004M	MODEL 4058/4058M
(b)(4)	(b)(4)	

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TACHY/BRADY LEAD COMPARISON

Parameter	Model 6966	Model 4016A	Model 4058/M[1]
(b)(4)			

[1] 4004M, 4058M and 4082 are the IS-1 versions of the respective leads.

TACHY/BRADY LEAD COMPARISON (CONTINUED)

Parameter	Model 4024	Model 4004/M[1]	Model 4012/4082[1]
		(b)(4)	

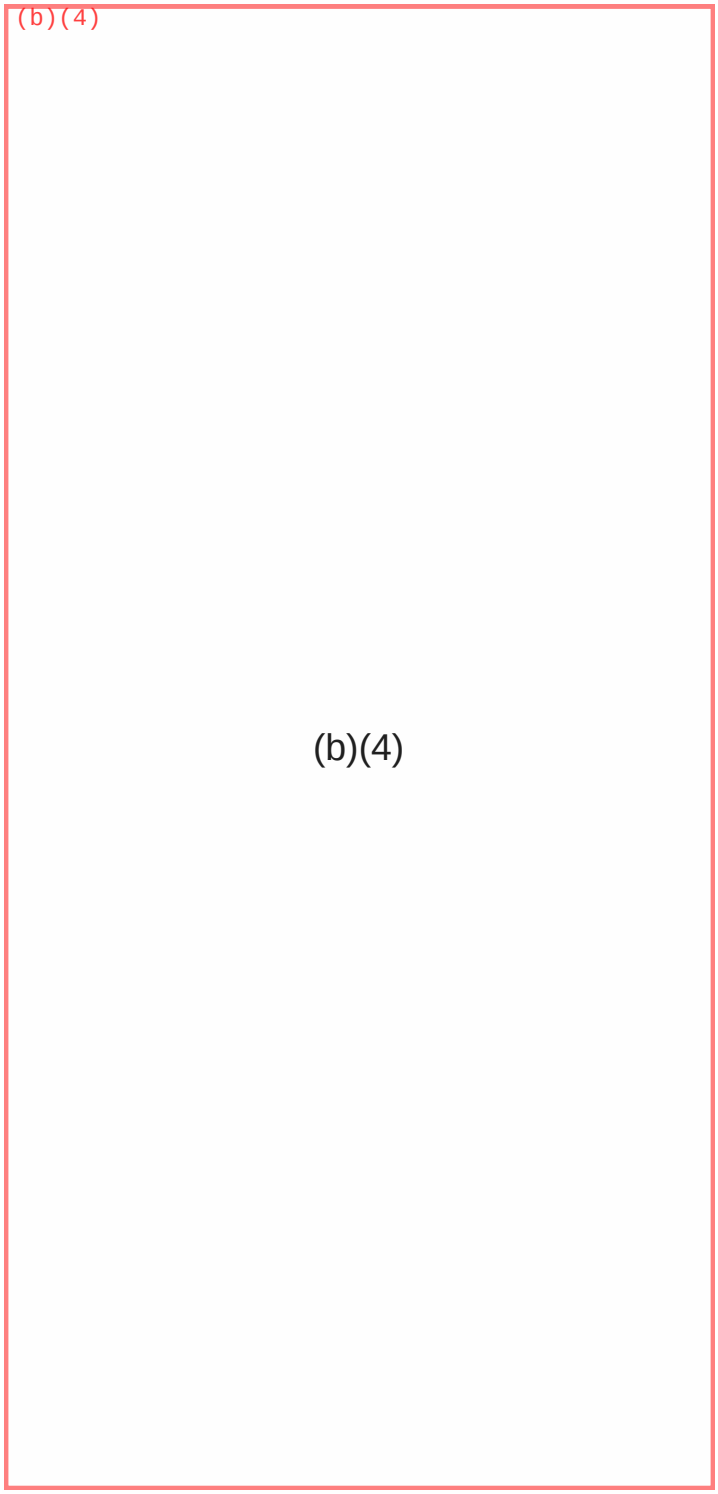
[1] 4004M, 4058M and 4082 are the IS-1 versions of the respective leads.

(b)(4)

(b)(4)

MODEL 4016A

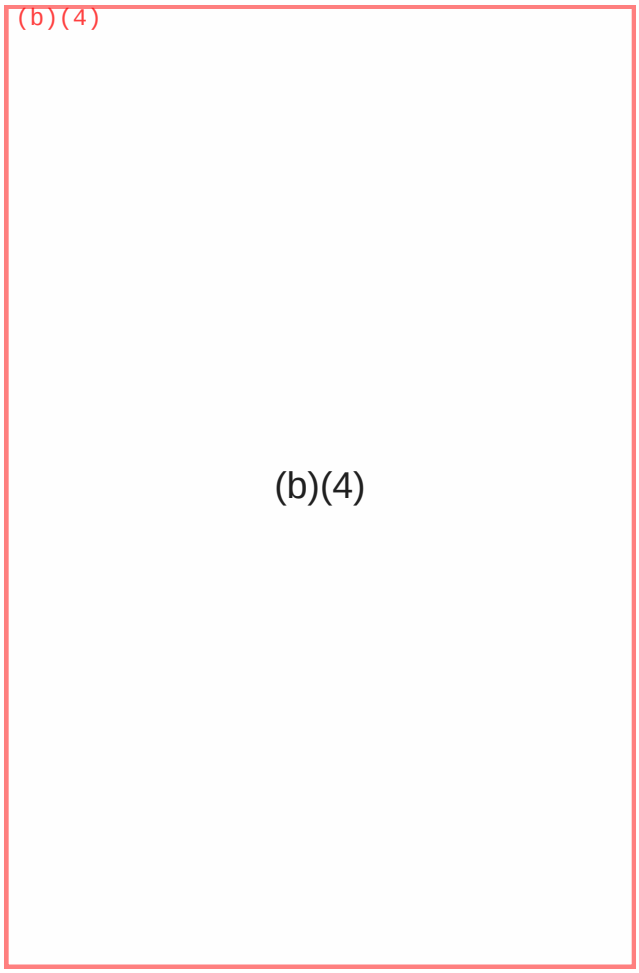
(b)(4)



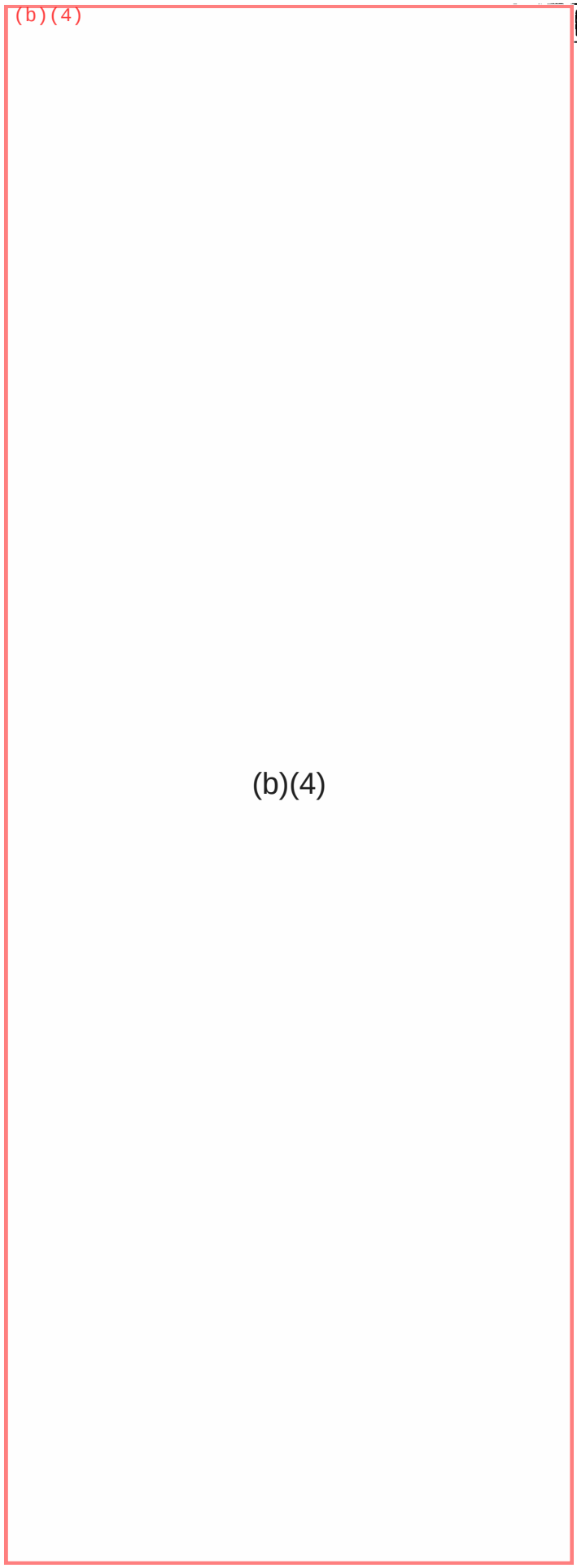
MODEL 4016A

al

(b)(4)



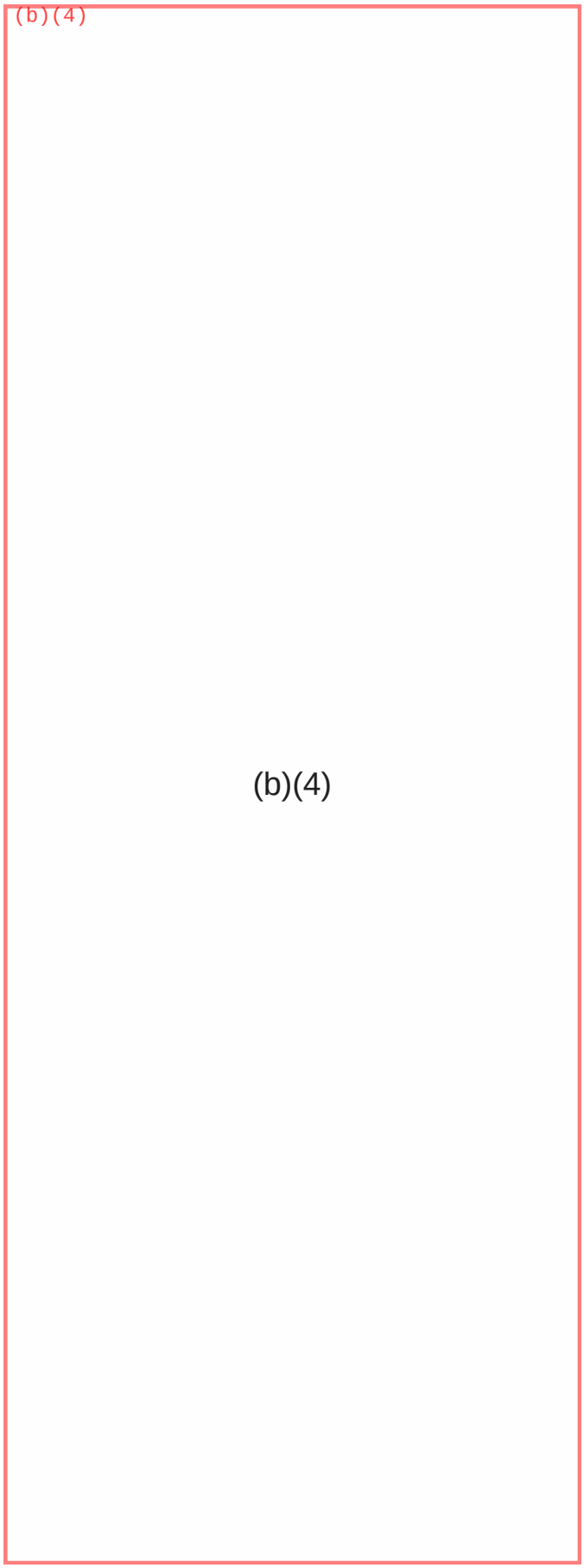
MODEL 4016A



MODEL 4016A

23

(b)(4)



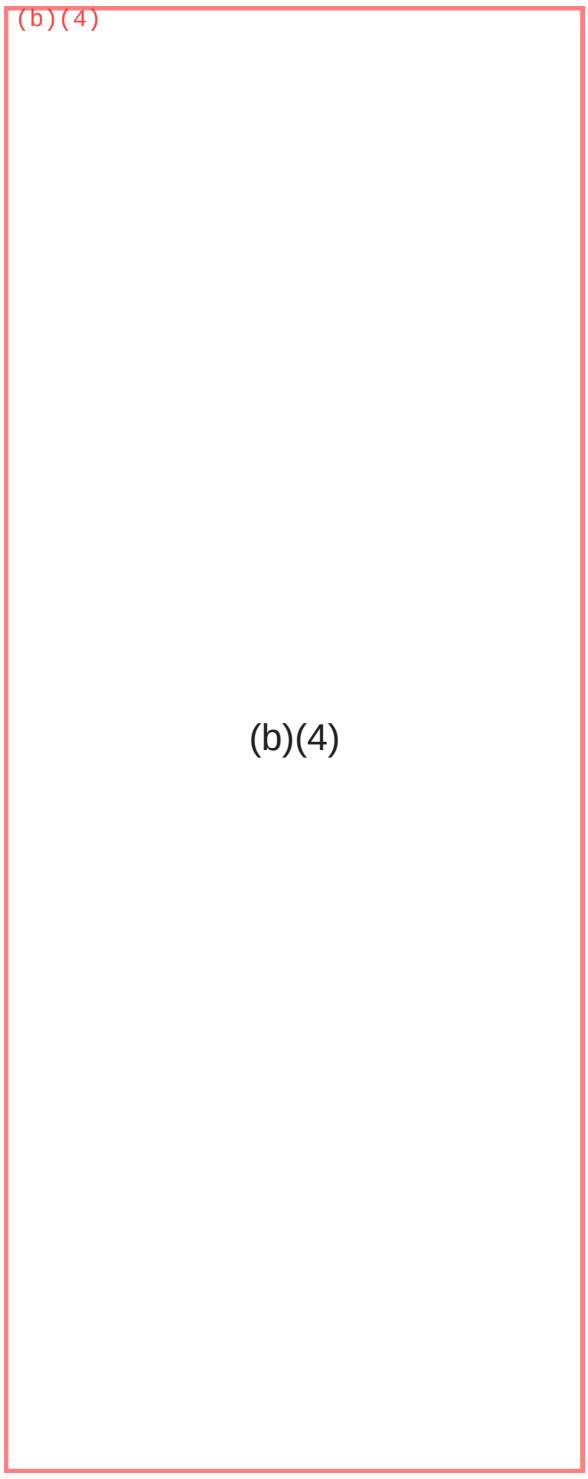
MODEL 4058/M

(b)(4)

(b)(4)

MODEL 4058/M

(b)(4)

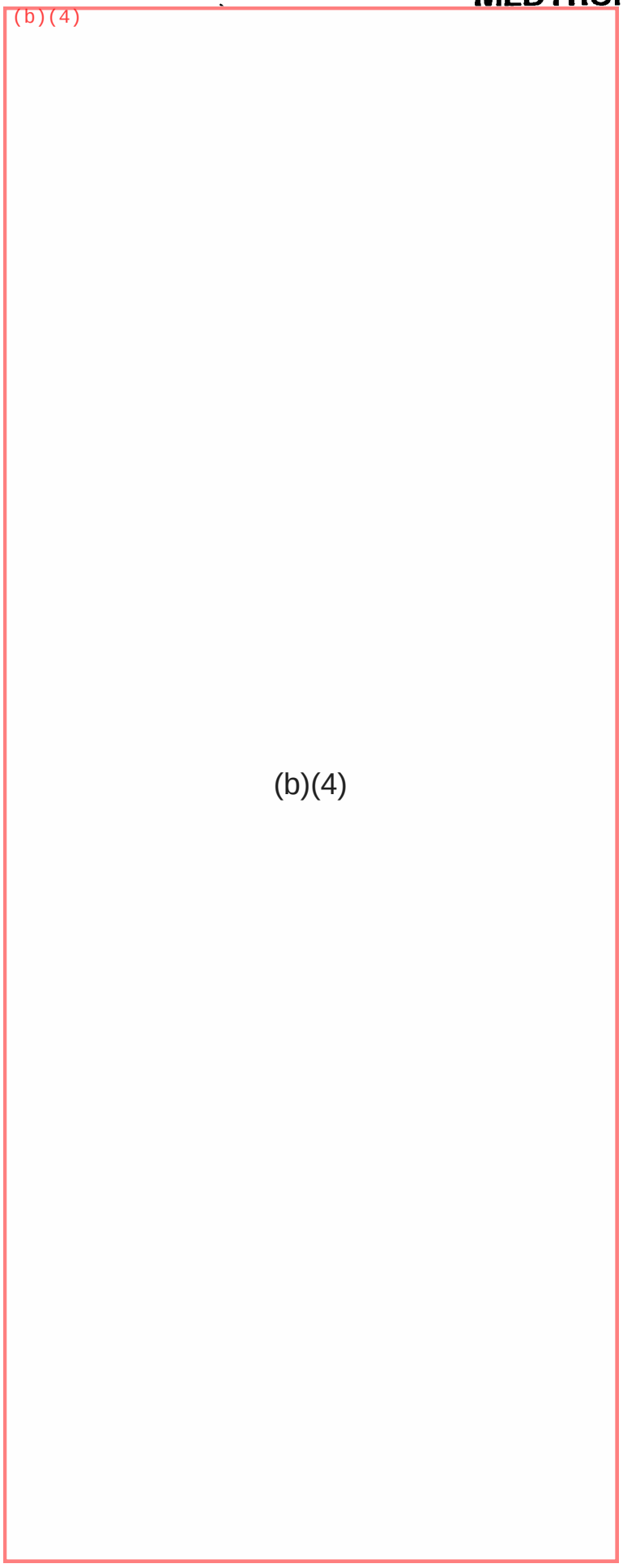


MODEL 4058/M

(b)(4)

MODEL 4058/M

(b)(4)



MODEL 4024

ASSEMBLY

(b)(4)

(b)(4)

MODEL 4024

TIP AND CONNECTOR ASSEMBLIES

(b)(4)

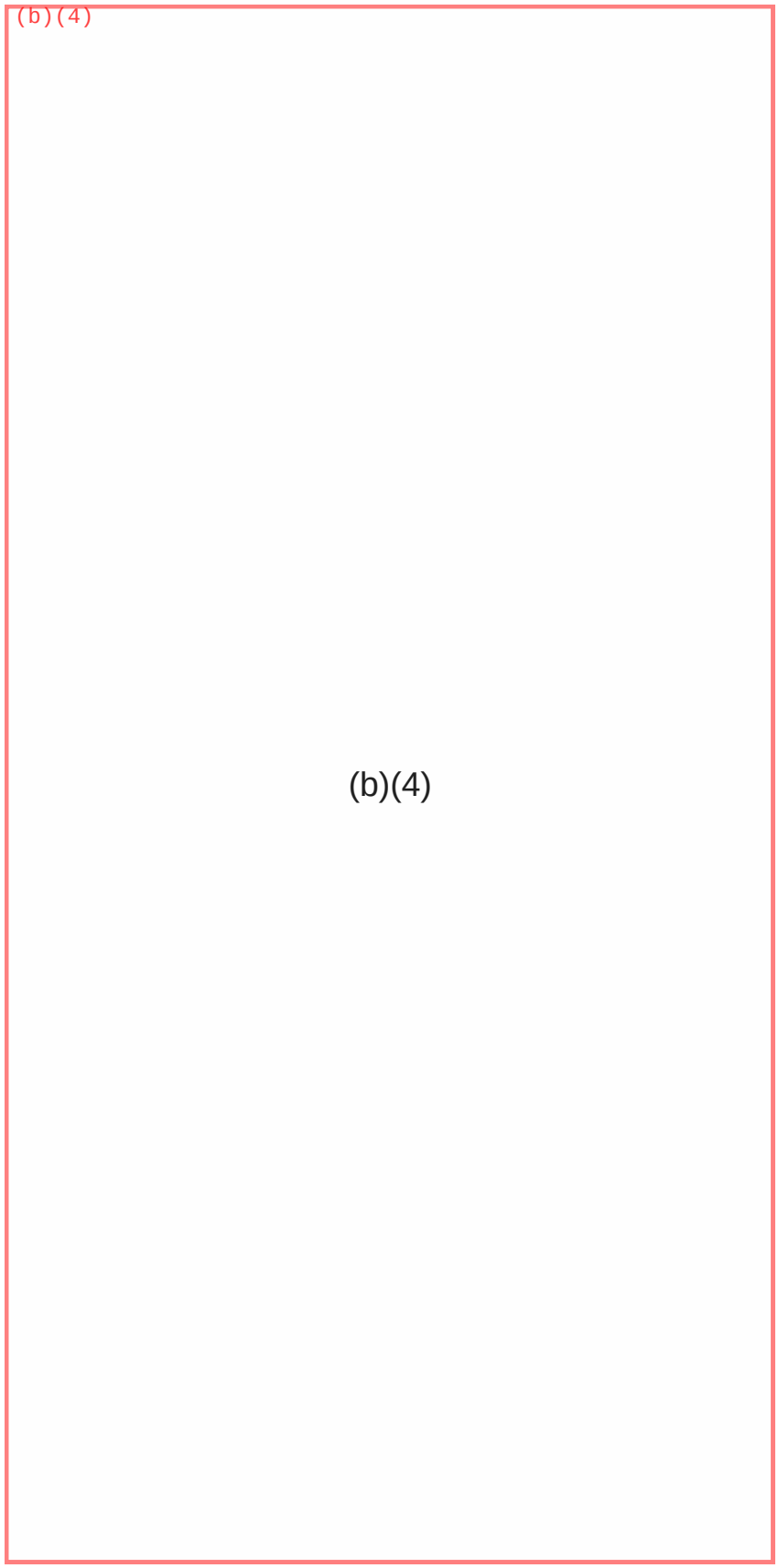
MODEL 4004M

(b)(4)

CONNECTOR ASSEMBLY

30

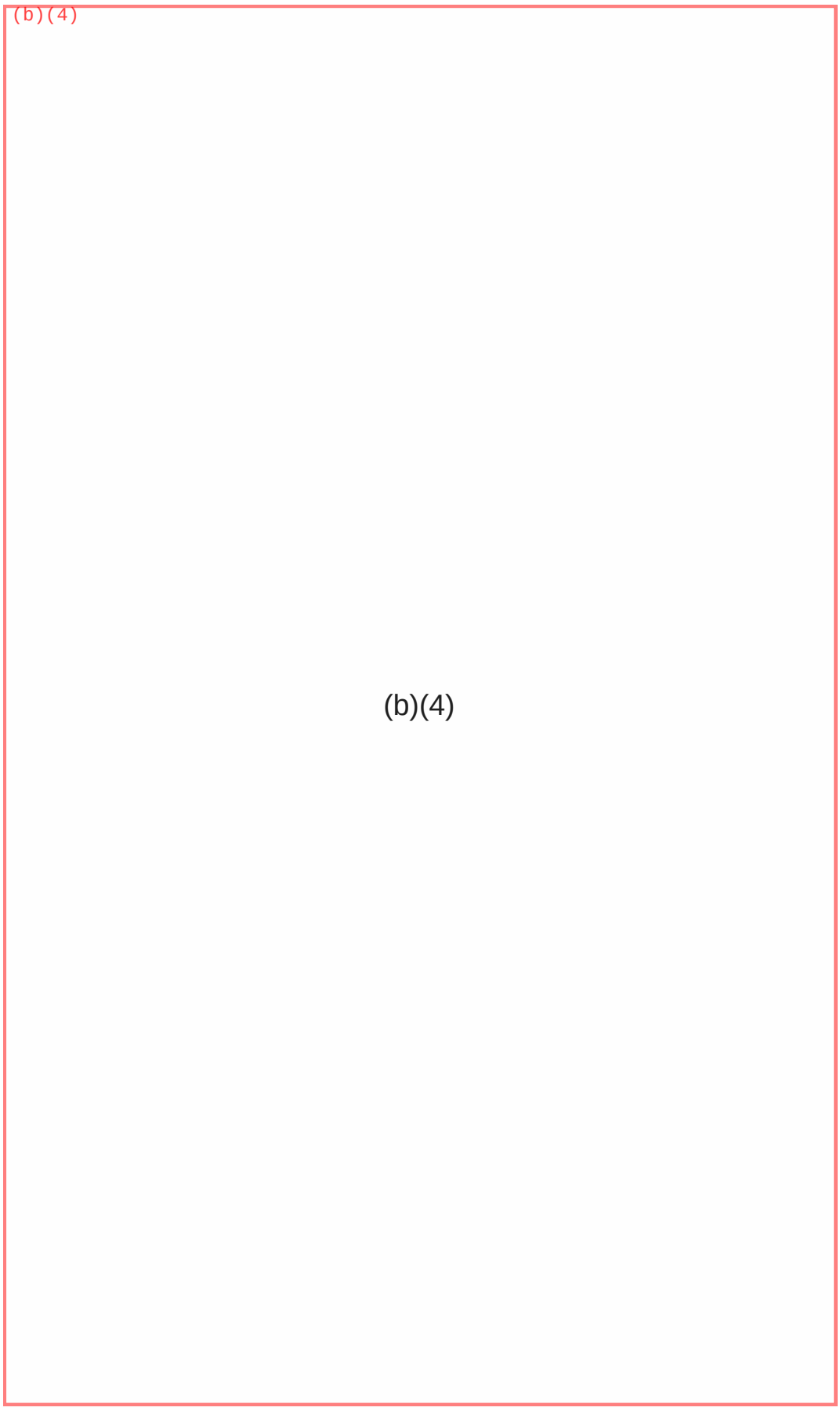
(b)(4)



MODEL 4004M

DISTAL ASSEMBLY

(b)(4)



MODEL 4082

CONNECTOR ASSEMBLY

37

AA
PEDO
pCRNO

P J015/S000

14-Jun-1993

FROM:	LETTER DATE	LOGIN DATE	DUE DATE
MEDTRONIC INC. ATTN: JENNIFER M. MARRONE 7000 CENTRAL AVENUE, N.E. MINNEAPOLIS,, MN 554323576	06/11/93	06/14/93	/ /
	DOCUMENT: PMA	CONTROL # P920015/S000 AMENDMENT	

SUBJECT:
MEDTRONIC(R) TRANSVENE LEAD SYSTEM

	OFFICE	DATE REFERRED
25 COPIES OF VOLUME 1	~~CK~~ A	6/14/93
25 COPIES OF VOLUME 2	DCRND	6/15/93
25 COPIES OF VOLUME 3		
25 COPIES OF VOLUME 4		
____ COPIES OF VOLUME ____		
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date October 29, 1993

From Mathematical Statistician (T. C. Lu) HFZ-162
Statistics Branch, Division of Biometric Sciences, OSB

Subject Statistical Review of PMA P920015 Panel Package, Medtronic Multiprogrammable Tachyarrhythmia Control System with Non-thoracotomy Cardioversion and Defibrillation Electrodes, Medtronic, Inc.

To

Doris Terry - HFZ-450
Division of Cardiovascular, Respiratory, and Neurological Devices, ODE
Through: Director, Division of Biometric Sciences, OSB
Through: Chief, Statistics Branch, DBS, OSB

In my July 9, 1993 memo to you, I asked for the numerators and denominators used for the percent success (Table I-1, page 233, Table 1F-2, page 287 and Table 1F-4, page 290, PMA Amendment, March 26, 1993) for the treatment of spontaneous episodes. After thorough investigation, I have the following results:

Spontaneous VT % success 98.4% of Table I-1, p. 233 can be obtained from Table 8-1, p. 110, June 11, 1993. (9864/10027 = 98.4%)

Spontaneous VF % success 98.4% of Table I-1, p. 233 can be obtained from Table ID2-6, p.98, June 11, 1993. (1951/1982 = 98.4%)

Spontaneous VT % success 99.0% after 12 months of follow-up of Table 1F-2, p. 287 can be obtained from Table ID3-1, p.78, Vol. 2, June 11, 1993. (6273/6338 = 99.0%)

Spontaneous VF % success 98.6% after 12 months of follow-up of Table IF-2, p. 287 can be obtained from ID3-1, p. 78, Vol. 2, June 11, 1993. (1090/1105 = 98.6%)

I couldn't locate the section or table to address 6 months of follow-up for spontaneous VT and VF % success.

Table IF-4, p. 290, March 26, 1993 agrees with the table in the June 11, 1993 panel package.

If you have any questions concerning this memorandum, please contact me at 594-0627.

T. C. Lu

cc: Thomas J. Callahan, Ph.D. HFZ-450 PMS Group HFZ-402
Donald F. Dahms HFZ-450 Medical Device File
Lynne A. Reamer HFZ-450 Board File

MEMORANDUM TO THE RECORD

From: R. Subramanian, M.D., DCRND

Subj: Addendum to review of death summaries, Medtronic Transvene Lead - P920015

Date: October 1, 1993

::

The death summaries were rereviewed to determine if the infections noted:
a) were related to the device, and to
b) obtain further details regarding time and sites of infection.
This rereview does not include "pocket infections" which have been listed separately in the submission and have been addressed previously (see memo from Dr. J. Jones).

1. A total of 68 deaths were reported in the PCD Transvene System population of 1330.

2. Eleven (11) of these patients had clinical evidence of (or were clinically suspected to have had) infections as follows:

#	Patient #	Infection	Autopsy
1.	(b)(6)		
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			
10.			
11.			

(b)(6)

NA = Not available

Conclusion: Although the information provided in the death summaries is limited, there does not appear to be any evidence of device related infection causing death in this group of patients.

CC Ms. Doris Terry, reviewer, DCRND
a:\deathsum.rcs

3

MEMORANDUM

From: Doris Terry (HFZ-450)
To: File # P920015
Subject: Medtronic® Transvene® Lead System
Date: August 16, 1993
Office: DCRND/ODE

On August 2, 1993, the Circulatory System Devices Panel reviewed the PMA application for the Medtronic® Transvene® Lead System. Specific questions and labeling concerns generated from FDA's review of the PMA application are included in my memoranda of July 9, 1993 (FDA review and panel presentation).

The panel addressed all FDA's questions, and concurred with the labeling recommendations.

The panel recommended approval of the Medtronic® Transvene® PMA with modifications to the labeling. A list of FDA's and the panel's recommendations are listed below.

FDA's and the Panel's Recommendations

The labeling should be modified to include the following:

- diagrams which show proper insertion of the endocardial leads and how the patch lead should be applied to the subcutaneous tissue;
- a caution statement that the patch lead is not for use on the pericardium or epicardium;
- efficacy data of the different lead configurations via the different pathways;
- pictures or diagrams of the various electrode configurations which serve as a guide for selection;
- information and/or recommendations about implanting the leads and testing the different configurations. For example, when to use a two-lead versus a three-lead configuration and when to implant in the superior vena cava (SVC) versus the coronary sinus CS);
- information or recommendations regarding implanting in patients who do not have the 10 Joule safety margin;
- information about how the incidence of infection can be reduced;
- a reference about using 5-minute intervals between ventricular fibrillation (VF) inductions during testing;

- stronger language regarding the use of dual anchoring sleeves on the right ventricle (RV), SVC and CS leads;

- information which states that a thoracotomy after extensive testing with a nonthoracotomy lead system should be delayed at least 2 days (the clinical data showed that when a thoracotomy was performed immediately after testing, the perioperative mortality rate was increased from 0.7 to 9.3 percent);

- guidance regarding separating pacemaker leads from the Transvene leads;

- a statement which emphasizes the need for x-rays and pace/sense threshold testing at follow-up to check for lead dislodgement;

- information regarding placing the leads via the cephalic vein when possible; and

- an explanation regarding the necessity for explant and return of the leads upon the patient's death.

In addition the manufacturer should note the following:

- The indications and contraindications for use of the Medtronic® Transvene® Lead System should be the same (with certain modifications) as those for the PCD™ Epicardial System.

- The technical manuals for the Transvene® Leads should state that the leads are for use together as a system. The labeling (where appropriate) should be consistent in all of the Transvene® Lead manuals. The information regarding the Transvene® Leads in the PCD™ Manual should also be included in the Transvene® Lead manuals.

- There should be an identifying mark on the package label which distinguishes nonthoracotomy leads from thoracotomy leads.

- The Warnings and Precautions in the labeling should be identified and reported separately according to FDA's Blue Book Memorandum of March 8, 1991 (a copy of this memorandum was previously sent to you).

- Postmarket surveillance will track the explanted leads for evidence of metal ion oxidation (MIO).

The manufacturer should provide a copy of the Patient's Manual which includes a reference to use of the nonthoracotomy leads with the PCD™ models.

Recommendation

The above information will be included in an approvable letter to the manufacturer.

MEMORANDUM

From: Doris Terry (HFZ-450)
To: File # P920015
Subject: Review - Transvene PMA
Date: July 9, 1993
Office: DCRND/ODE

Description of the System

The PCD Transvene System consists of the Model 7217B PCD pulse generator, programmer, external accessories and leads (Model 6966 RV lead, Model 6966 CS/SVC lead and the Model 6999 patch lead, see description of leads and summary of testing in attached memo and in Volume 3, Section A, Bench Testing). The leads may be implanted in 3 configurations: RV/CS/SQ, RV/SVC/SQ and RV/CS/SVC via a single, simultaneous or sequential pathway.

Study Design and Objectives

The PCD Transvene System was designed to evaluate the safety and effectiveness of the Model 7217B PCD and Transvene leads. The objectives of the study include the following: (1) evaluating and monitoring the system in the detection and treatment of VT and VF; and (2) estimating the survival from sudden cardiac death and overall survival.

The manufacturer used two controls: the Model 7217B PCD Epicardial Lead System as a concurrent control and the Ventak P AICD Epicardial Lead System as a historical control.

The manufacturer believed that a study which employed randomization of a nonthoracotomy lead system and a thoracotomy lead system was not clinically or ethically appropriate.

Patient Population

The total patient population (patients screened and implanted with the Transvene Lead System) includes 897 patients (see patient tree, Vol 2, page 36). The PMA population includes 757 patients (447 U.S. and 315 foreign) implanted at 78 centers (35 U.S. and 43 foreign). The U.S. and foreign data were pooled to evaluate the safety and effectiveness of the Transvene Lead System. Statistically significant variations were found between the U.S. and foreign populations. These variations included a higher mean age, a greater percentage of patients with CAD and cardiomyopathy and a lower mean ejection fraction within the U.S. population versus the foreign population. Also, there were more U.S. patients with VT as a primary indication. Even though the

(b)(5)

(b)(5)

differences between the two populations were statistically significant, the manufacturer does not consider the factors to be clinically significant to require stratification of the data.

The PMA patient population is predominantly male (80.6 percent) with a mean age of 59.4 years. There are 377 (49.8 percent) patients with recurrent sustained VT without an episode of sudden cardiac death (SCD); 281 (37.1 percent) SCD patients; and 99 (13.1 percent) patients with a combination of recurrent sustained VT and SCD.

Of the 757 Transvene patients, 744 (97.6 percent) patients were implanted with the PCD Model 7217B and 18 (2.4 percent) patients were implanted with the PCD Model 7216A. Sixteen patients have brady pulse generators in conjunction with the PCD. Five hundred and seventy-four patients were implanted using the sequential defibrillation pathway, 178 patients were implanted using the simultaneous pathway and 10 patients have the single pathway. Data were collected on each patient during: preimplant assessment; lead system testing at implant; prehospital discharge; and follow-up evaluations at 1 month, 3 months (chronic testing period) and at 3 month intervals thereafter. There are 657 patients followed for 6 months and 393 patients followed for 12 months. The mean follow-up of the patient population is 11.7 months with 8894.8 total device months of experience. Patient compliance to follow-up is within a range of 95.3 to 97.6 percent from 12 to 24 months.

The PMA population was stratified by primary indication, patients who met implant criteria, patients who did not meet the implant criteria, patients followed for one year and greater, patients with non-standard lead configurations and additional patients who were not counted in the PMA cohort.

Clinical Experience

As of February 1, 1993 (the data cutoff), the clinical experience includes data from 762 implants in 757 patients. The data (stratified as described above) were provided in support of the Transvene Lead System. The data included the following: (1) the results of testing at implant and the follow-up intervals; (2) the efficacy of the treatment of VT and VF (spontaneous and induced episodes); (3) complications and observations; (4) patient deaths; and (5) survival. A comparison of the data obtained from the patient population and the different subgroups is also included.

Defibrillation Threshold (DFT) Testing

Three hundred and sixteen patients had DFT testing at implant. The mean DFT was 14.8 Joules (J). The remaining patients had testing which involved the lowest energy to

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defibrillate (LED) and/or DFT testing. The mean LED was 16 J (N= 702).

Twenty patients were implanted with the Transvene System without a 10 J safety margin (see Volume 2, page 42).

Spontaneous and Induced Episode Experience and Treatment Efficacy of VT and VF - Total Patient Population

- 597 (78.9 percent) patients had a spontaneous VT or VF episode or had VT or VF induced post implant.
- 458 (60.5 percent) patients had a spontaneous episode of either VT and/or VF treated by the PCD Transvene System.
- 141 (60.5 percent) patients had VT only.
- 142 (18.8 percent) patients had VF only.
- 175 patients (23.1 percent) had an episode of VT and VF.
- 90.7 percent of VT episodes were successfully treated with VT therapy # 1.
- 89.1 percent of the VF episodes were successfully treated with VF therapy # 1.
- 60 patients experienced 163 (1.6 percent) spontaneous VT episodes which the PCD Transvene System was ineffective in terminating the arrhythmia (see Volume 2, page 19).
- 16 patients experienced 31 (1.3 percent) spontaneous VF episodes which the PCD Transvene System was ineffective in terminating the arrhythmia (see Volume 2, pages 20 - 21).
- 450 (59.5 percent) patients had induced or spontaneous episodes by the 3 month follow-up.
- 532 (70.3 percent) patients had either a spontaneous or induced episode by the 6 month follow-up.
- 597 (78.9 percent) patients had a spontaneous or induced episode by the 12 month follow-up.

Device Experience - Patients Followed for 6 months or More

- Of 657 patients followed for 6 months or more, 544 (82.8 percent) patients had an induced or spontaneous episode at predischarge or later.

- 113 patients did not have a chronic episode, however pace/sense parameters were measured at the chronic follow-up intervals on all patients except one (see Appendix I).

Summary of Complications and Observations

- 176 complications (required invasive intervention) occurred in 147 patients, included pocket infection (24), lead fracture (9), patch crinkling (7), explants (4) and total lead dislodgement (91). (The 91 cases of lead dislodgement occurred in 86 patients, see Appendix I).

- 212 observations (corrected by reprogramming or antiarrhythmic drug therapy) in 178 patients included inappropriate VT delivery (57), oversensing (52), seroma (17), hematoma (17), patch crinkling (5) and total lead dislodgement (12).

The manufacturer provided tables which report the complications and observations over time (see Table IB3-2 and Table IB3-3, Volume 2, pages 24-25).

The manufacturer stratified the complications and observations by U.S. and foreign patients (see Table IB3-6 Vol. 2, page 28). The complication and observation rates were comparable for the two patient groups. However, more total lead dislodgements (complications) were reported for the U.S. patients and more cases (observations) of inappropriate delivery of VT therapy occurred in the foreign population. There was also a higher incidence of oversensing (observations) in the U.S. population. It should be noted that there should be 7 observations related to loss of capture for the foreign patients instead of 9 (Volume 2, Table IB3-6, page 28).

Because of our concerns about the complications involving lead dislodgement and infection the manufacturer responded as follows: In resolving the concern regarding lead dislodgement, the manufacturer received IDE approval (September 1992) to use dual anchoring sleeves on the Models 6963 and 6966 leads. However, it is unclear if all patients, after IDE approval, are implanted with dual sleeves. The manufacturer confirmed that all patients are receiving dual sleeves. In support of the dual anchoring

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sleeves in reducing the rate of lead dislodgement, a report of the clinical experience of additional patients was provided. Data from 439 patients (not a part of the PMA cohort) implanted with dual anchoring sleeves were submitted. Of the 439 patients, 292 were followed for 1 month, 195 were followed for 3 months and 17 were followed for 6 months. Thirteen dislodgements in 10 patients were reported (incidence of dislodgement of 2.3 percent (10/439). Regarding the cases of infection, the manufacturer stated that the incidence of infection in the Transvene study is not significantly different from that reported for the Ventak P Epi study. Therefore, the applicant feels that there is no substantial increase, and that labeling to address this concern is not warranted. (b)(5) (b)(5)

Patient Deaths

There have been 51 deaths (sudden cardiac (5), nonsudden cardiac (31), noncardiac (15). Five perioperative deaths (sudden cardiac (2), nonsudden (2) and noncardiac (1)) are counted within the 51 deaths. None of the deaths were attributed to the PCD Transvene System.

Explants

Sixty-three PCD Transvene Systems were explanted (N=762), patient death (22), infection (22), heart transplant (9), low battery voltage (1), PCD performance issues (4), integrated circuit problem (1) and lead problems (4). The results of analyses on 42 units returned indicated that the devices were performing within specifications.

Of the 42 PCD Transvene Systems returned, (b)(4) lead systems or portions of systems were returned and analyzed. Of these the helix of one Model 6966 lead was damaged. The remaining leads were found to be within specification. The analyses (b)(4) lead systems are still outstanding. (It should be noted that one of the Model 6884 leads (implanted for 27 months) which was explanted due to heart transplant, exhibited metal ion oxidation (MIO) upon analysis. Metal ion oxidation can cause the polyurethane of the leads to degrade (see Volume 2, Section on Explants, page 296 or Appendix I).

Survival Analysis

The survival analyses encompassed all patients (screened and implanted). The projected one year actuarial survival rates for the PMA cohort (N=757) are as follows: sudden cardiac death (99.5 percent); nonsudden cardiac (96.2 percent); all cardiac (95.8 percent); noncardiac (98.1 percent); and overall (93.3 percent). The perioperative mortality is 0.7 percent.

The survival rates for 854 patients are included in Volume 2, Table IB4-2, page 31. The survival data were updated to include the 897 patients screened for the Transvene System. The one year actuarial survival rates for these patients are as follows: sudden cardiac death (99.5 percent); nonsudden cardiac (96.6 percent); all cardiac (96.1 percent); noncardiac (98.4 percent); and overall (92.9 percent). The perioperative mortality rate is 1.6 percent (see Appendix I).

Comparison Between the Patients Who Met the Implant Criteria and Patients Who Did Not Meet the Implant Criteria

A comparison of the clinical outcome between the patients who met the implant criteria and those patients who did not meet the implant criteria was included. The comparison was made to determine if there was a greater risk of morbidity and mortality among the patients who did not meet the implant criteria and received the Transvene System. The data showed the following: The efficacy of the patient groups in the treatment of spontaneous episodes of VT and VF was similar. There was no significant difference in the one year sudden cardiac death survival and the overall survival reported for the two groups. Ninety-one per cent of the patients who did not met the implant criteria had at least one successful termination of an induced ventricular comparison at 24 joules or less. In addition, there were 170 patients who had successful defibrillation of VF at less than or equal to 24 Joules. As a result the manufacturer requested and received IDE approval for a change in the implant criteria. Instead of 3 of 4 successes at 18 Joules or less, the manufacturer can implant with successful defibrillation at 24 Joules (referenced in Volume 2, page 53).

Labeling

The manufacturer has included information about the Transvene leads in the PCD Manual as well as in the technical manual for each Transvene lead model.

The technical manuals of the Transvene Models 6966, 6963 and 6999 leads should be modified to included additional information. The following modifications are included for the Panel's consideration:

- The indications and contraindications for use of the Transvene lead system should be identical to those of the PCD (with certain modifications).

- The technical manuals for the Models 6966, 6963 and 6999 leads should state that the leads are intended for use together as a system. The labeling (where appropriate) should be consistent throughout the manuals. The

information in the PCD Manual regarding the Transvene leads should also be included in the technical manuals for the leads.

- There should be more explicit diagrams in the technical manuals which show the proper insertion of the endocardial leads and the various positions for placement of the patch lead.

- Efficacy data of the different lead configurations via the different pathways should be included.

- The labeling should recommend and/or provide some direction about implanting the leads and testing the different configurations. For example, when to use a two lead versus a three lead configuration and when to implant in the SVC versus the coronary sinus.

- Information or recommendations regarding implanting in patients who do not have the 10 J safety margin should be addressed.

- There should be stronger language regarding the use of 2 anchoring sleeves.

- The labeling should address how the incidence of infection can be reduced.

Questions

(b)(4)

(b)(4)

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MEMO

To: Doris Terry
From: Quynh Hoang
Date: 7/9/93

Regarding: Descriptions of the Transvene leads from Medtronic - P920015

Parameter	Model 6963	Model 6966	Model 6999
(b)(4)			

(b)(4)

15

(b)(4), (b)(5)

(b)(4), (b)(5)

16

(b)(4), (b)(5)

(b)(4), (b)(5)

(b)(4), (b)(5)

(b)(4), (b)(5)

(b)(4), (b)(5)

(b)(4), (b)(5)

19

(b)(4), (b)(5)

(b)(4), (b)(5)

30

(b)(4), (b)(5)

(b)(4), (b)(5)

MEMORANDUM

From: (b)(6) (b)(6)
To: File # P920015
To: (b)(6) (b)(6)
Subject: Transvene Lead System - Consulting Review
Date: July 6, 1993
Office: DCRND/ODE

Please review the death summaries included in the referenced file (Volume 2, Section III, Death Summaries). The review should evaluate the accuracy in classifying the deaths. In addition, please look at the causes of death to determine if any of the deaths could be possibly linked to device performance.

Please note the following: A definition of the different death classifications can be found in Volume 2, page 293. Medtronic, Inc. has reported 51 deaths (sudden cardiac (5), nonsudden cardiac (31), noncardiac (15) in the PCD Transvene population (N=757). The perioperative deaths (5) are counted within the following classifications: sudden cardiac (2) nonsudden (2) and noncardiac (1).

Please let me know if you can review the data. If so, when do you think you will be done? Hopefully, by the first of next week? Your assistance is greatly appreciated.

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MEMORANDUM

To: Doris Terry, DCRND

From: R. Subramanian, DCRND

Subj: Review of death summaries, Medtronic Transvene lead - P920015

Date: August 4, 1993

==========

I have reviewed the death summaries provide with the amendment to the above application. As we have discussed previously:

1. The classification of deaths appears to be reasonable.

2. It is not possible, with the information provided in the death summaries, to state categorically, whether or not any of the deaths could be possibly linked to device performance.

3. As indicated by the sponsor, there appears to be only one death (Patient (b)(6) vol 2, page 134) that is clearly device related.

Recommendation: In future studies, instances where the cause of death is considered unknown, and no autopsy is performed, such death should classified as device related.

a:transvene. rcs

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date .July 9, 1993

From Mathematical Statistician (T. C. Lu) HFZ-162
Statistics Branch, Division of Biometric Sciences, OSB

Subject Statistical Review of PMA P920015 Panel Package, Medtronic Multiprogrammable Tachyarrhythmia Control System with Non-thoracotomy Cardioversion and Defibrillation Electrodes, Medtronic, Inc.

To Doris Terry - HFZ-450
Division of Cardiovascular, Respiratory, and Neurological Devices, ODE
Through: Director, Division of Biometric Sciences, OSB
Through: Chief, Statistical Branch, DBS, OSB

1. Background

The original PMA was submitted in April 1992. Amendment two was submitted for review in March 1993. The purpose of this memo is to review the response from the sponsor to the deficiencies stated in the FDA letter and in the telephone conference call held on July 7, 1993. Information provided in this panel package includes clinical experience of 757 patients through February 1, 1993.

2. Reviewer's Comments

2.1. Cox Regression

This reviewer wants the sponsor to provide a description of the computer program, including data input and output, and the decision criteria used to support the sponsor's claim that primary indication and gender do not impact survival. Sponsor stated that "Appropriate data will be submitted in the panel volumes to address this issue" in response to statistician's review. In the telephone conversation, the sponsor stated that (b)(4) was used for survival curve comparison, but the (b)(4) test was used for testing the equality of survival curves. (Table 1D2-10, page 76).

2.2. Actuarial Survival

In my March 10, 1993 memo to you, I asked for the number of deaths, number at risk for transvene and epicardial by month intervals (0-3, 3-6, 6-9 and 9-12). Sponsor claims that Table 1B1-5, page 17 "Patient Compliance" will serve this purpose. The compliance rate is very high, according to this table. However, to use this patient compliance table for survival analysis would be misleading, because it does not give survival probability. Sponsor said they will fax a copy of their survival curve graphical comparison.

2.3. Percentage Success

This reviewer needs to review the numerators and the denominators used for the percent success (Table I-1, page 233, Table 1F-2, page 287 and Table IF-4, page 290) for the treatment of spontaneous episodes. Sponsor pointed out that those numbers are located in other sections of the panel package.

2.4. P-values

The sponsor was asked to address the calculation of the p-values reported in Table 2.165, page 24. I calculated the p-values and obtained different values than those reported by the sponsor. Sponsor claimed that (b)(4) was used for the calculation. Subsequently, a computer output was faxed to me by the sponsor for review.

3. Conclusion

In my previous memos to you, I raised questions about the safety and effectiveness of the device. My telephone conversation with the sponsor certainly helped to answer some of these questions. The safety and effectiveness of the device should be evaluated from a clinical perspective.

T. C. Lu

cc: Thomas J. Callahan, Ph.D. HFZ-450
Donald F. Dahms HFZ-450
Lynne A. Reamer HFZ-450
Medical Device File
Board File

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Medtronic

Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576
Telephone: (612) 574-4000
Cable: Medtronic Telex: 29-0598
FAX: (612) 574-4879

June 11, 1993

Office of Device Evaluation
Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

RECEIVED
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FOOD ADMIN/ODE/DMC

Re: Transvene® Lead System, PMA Amendment
(Document Control Number P920015)
Panel Package

AC2V1

The purpose of this submission is to provide information for FDA Panel review of the Transvene System Premarket Approval Application.

Information in this submission is consistent with that provided to the FDA in the March 26, 1993 PMA amendment. However, the information has been rearranged and/or represented to facilitate review, and in some cases, updated to incorporate the most recent data, e.g., complications, patient deaths, device explants.

Clinical experience information is provided on 757 patients implanted with a Transvene System between October 16, 1990 to February 1, 1993. Mean implant duration for these patients is 11.7 months. Information is provided on 573 additional patients implanted in the U.S. from June 25, 1992 to February 1, 1993.

Clinical data presented in this Amendment demonstrates the PCD Transvene System performs as specified and is, therefore, safe and effective for its intended use. Results indicate 99.3 percent survival from sudden cardiac death at one year (N = 1330).

Following this cover letter is a telephone conversation record that documents several discussions between FDA and Medtronic regarding the Transvene file. FDA's questions and/or requests for clarification of clinical information are presented as discussed in these conversations, along with the applicable sections of the Clinical Experience Report and Appendices where the topics are addressed.

Volume 1 contains an abbreviated Summary of Safety and Effectiveness for the Transvene System. A detailed Table of Contents is provided in the front of Volume 2, detailing the contents of Volumes 2, 3 and 4.

The existence of this PMA Amendment and the data and other information it contains are confidential, and the protection afforded to such confidential information by 18 USC 1905 and other applicable laws is hereby claimed.

Twenty-five copies of this PMA Amendment are provided. Should additional information be required by the Agency, please contact the undersigned.

Sincerely yours,

MEDTRONIC, INC.

Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
(612) 574-4688
(612) 574-6424 FAX

Attachment

Telephone Conversation Records -- Transvene PMA Application, P920015; April 29, May 3, 12, 13, 17, 27, June 2; 1993

The following is a summary of telephone conversations that occurred with Medtronic and FDA regarding Medtronic's Transvene PMA application. Medtronic participants included: Jennifer Marrone, Sue Norenberg, Diana Roberts and Dan Schaber.

A primary objective of these discussions was to emphasize that the deficiency responses provided in the March 1993 amendment (and in some cases, September 1992 amendment) be incorporated into the text of the clinical report for the Panel package, in the appropriate sections. Further format detail addressed organization of sections, specifically, tabbing key sections in the Clinical Report such that Panel members will be able to identify them with relative ease.

Several topics were discussed as they related to the information provided in the March 26 PMA amendment (response to FDA deficiency letter). In some cases, data are represented or rearranged, and/or clarified. These topics are presented below, along with the applicable section(s) of the Clinical Experience Report and Appendices, where they can be found in this submission.

Lead-related complications/observations, e.g., pace/sense complications and dislodgements (use of dual anchoring sleeves), and their recurrence. Relative to dislodgements, occurrence pre and post 30 days are presented, as well as more chronically, e.g., at three and six months post implant. Section I.B.3.

Patients not meeting implant criteria and those that later received epicardial systems, non-standard lead configurations, e.g., combination epicardial/ Transvene system, implanted at the time of Transvene implant screening or sometime later, post implant. Note that some non-standard (those patients implanted with a three-lead system) were included in the 757 PMA population and some were not. This is delineated. Section I.C.2.d.

Study design, objectives and use of concurrent epicardial system as control, and identification of the pros and cons of an epicardial vs. a Transvene system. Section I.A.2.

Specific patient groups are stratified relative to survival, e.g., by indication. Specific patient populations are discussed, e.g., non-standard system (I.D.4.), not meeting implant criteria (I.C.2.), implants greater than one year (I.D.3.).

Episode experience, both spontaneous and induced, via follow-up. Appendix D.

Some data presented only in text form is represented in tables and/or graphs, e.g., survival of non-standard implant patients.

Further clarification (via presentation of data in table format) of the subgroups from the population that did not meet implant criteria (n = 214) is provided, i.e., patients with LEDs less than 24 joules are stratified as those in which it was difficult to induce VF and received a 10 joule safety margin (and later were induced) vs. those patients in which their condition precluded VF induction. Section I.C.2.b.

A cross reference of explants vs. device (lead) analyses is provided to clarify those explanted devices and their subsequent analysis, if indeed the device(s) was returned. Section I.E.1. Include returned product analysis procedure (Appendix F).

As provided in the March amendment, complications/observations are updated relative to pace/sense and dislodgements. The resulting population was N = 1330, (757 + 573 = 1330). The additional 573 are represented separately. Section IV.

The tree diagram (flow chart) on page 236 of the March amendment was modified to include the number of patients (in addition to the percentages), and also to include the total number of non-standard systems implanted (currently only some of the non-standard are presented on this page, although all non-standard are clearly discussed in the text). Sections I.B.1., I.C.

The protocol compliance table, as presented in the September 1992 amendment, is included. Section I.B.1.

Foreign data demographic information (justification for pooling) is delineated. Section I.A.3.

Survival curves are provided along with the tables of survival statistics that are provided. Section I.B.4.

Comparison table of PCD epicardial to PCD Transvene. Include number of patients along with percentage. Section I.D.2. Also, Ventak-P comparison data is provided in table form. Section I.D.1.

Death information includes devices programmed off, both the N and percent, incorporated by type of death (e.g., SCD, non SCD, etc.). Section I.D.2.

Literature update, e.g., anything relevant to lead dislodgement and subcutaneous patch locations. Appendix C.

Foreign versus U.S. complications/observations are discussed with any differences noted in reporting methods between international and U.S. Section I.B.3.

All statistical tests are identified, e.g., Chi-square, t-test, Hochberg, Wilcoxin, etc. Appendix E.

The recurrence of ineffective therapies is addressed in complications/ observation section. Of 60 ineffective, there were 39 ineffective VT therapies due to AF and 21 inappropriate therapies. None of these 21 were related to patient deaths. Section I.B.2.

Any reprogramming due to observations is noted and put in table format in observation section. Section II.

Incidence of infection rate, Transvene versus epicardial. Section I.D.2.

Clarify the null hypothesis of a three-lead configuration based on patient demographics. Section I.A.3.

Choice of lead configuration made by the physician. Section I.B.1.

Measurements made for those patients followed for a year or greater. Assessment of pace/sense parameters, dislodgements, etc. Section I.D.3.

Patients followed for one year or longer. Take the 393 patients followed for one year or longer and look at their spontaneous and induced VT and VF episodes. Provide evidence of system performance, spontaneous and induced. Section I.D.3.

Analysis showed the epicardial and Transvene patient groups were comparable; provide the statistics that support this. Appendix E.

Describe the computer program used to show comparable groups. Include the data inputs and outputs, and description of the decision used to support the claim of comparable groups. Provide the data set used for survival calculations, e.g., the denominator and numerator. (Because of the immense amount of raw data, we are providing a description of how we did this.) Appendix E.

Provide the confidence intervals for one year and overall survival. Section I.D.1.

Provide justification for denoting 30 days as the acute cutoff point with respect to dislodgements. Section II.D.7.

Address patients lost to follow up or withdrawn from the study and how they were addressed in calculations. Appendix E.

Use page 93, table 4.6 of "Statistical Methods Used For Survival Data Analysis," by Elisa Lee, for our survival analysis. Appendix E.

Provide numerator and denominator for spontaneous VT and VF episodes. Section I.B.2.

What lead configurations are recommended in the labeling? Was a two-lead configuration used? If so, how many and what are they? Does the labeling also address these? Data for the two-lead non-standard configurations are reported consistent with the rest of the lead configurations. Section I.D.4. and Appendix G.

How many patients of the 757 were implanted via a subclavian stick procedure? Were the cases of lead fracture related to the use of subclavian insertion? How many fractures were there? Were the physicians following instructions? At what point in time did the fractures occur? Compare the N = 757 to the N = 573 population relative to fractures (N = 1330 total). Section II.D.

Where/how is the subcutaneous patch implanted? Section I.B.1.

Regarding complications, specifically, increased defibrillation requirements, were there any recurrences of the N = 14 of these reported? Section II.

PMA Amendment to Transvene®
(Document Control Number P920015)
Panel Package
June 11, 1993

Volume 1

Transvene Summary of Safety and Effectiveness

Volume 2

Clinical Experience Report

Volume 3

Nonclinical Testing
- Bench Testing
- Animal Testing

Volume 4

Appendices

(Technical Manuals are in Appendix G)

Safety
Effectiveness

Transvene Summary of Safety and Effectiveness (June 11, 1993)

A. Indications For Use

The Medtronic PCD Model 7217B Multiprogrammable Tachyarrhythmia Control System with Nonthoracotomy Cardioversion and Defibrillation Electrodes (hereafter referred to as the PCD Transvene System) is intended to treat patients at risk of sudden cardiac death due to ventricular tachyarrhythmias. Indications for use include:

- Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or
- Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.
- Patients undergoing replacement of a previously implanted implantable cardioverter defibrillator.

The patients who meet the above patient selection criteria should have also undergone a complete cardiological evaluation that includes electrophysiological testing. Electrophysiologic evaluation and testing of the safety and efficacy of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the PCD Transvene System.

The PCD Transvene System components, except for the defibrillation lead system, are identical to the PCD Epicardial System which was unanimously recommended for approval by the FDA Advisory Panel on February 3, 1992 and granted FDA premarket approval on February 11, 1993.

Market approval is not being sought for use of the PCD Device with other manufacturers transvenous defibrillation lead systems. In addition, market approval is not being sought for the use of the PCD Transvene lead system with other manufacturers implantable cardioverter defibrillators.

One Place Your Text Could Go (see Documentation Section 6)

B. Description of the Transvene Lead/PCD System

The Medtronic Tachyarrhythmia Control System consists of two fundamental configurations: (1) the implantable configuration and (2) the external configuration. Both configurations use the Transvene lead system. See Figure III B-1

The implantable configuration is composed of a Pacer-Cardioverter-Defibrillator (PCD) device, implantable leads, and a programmer. The PCD device is an implantable, multiprogrammable, automatic tachyarrhythmia control device.

The external configuration is composed of an External Tachyarrhythmia Control Device (ETCD), a patient cable, implantable leads, and a programmer. The ETCD is an externally-operated, multiprogrammable, tachyarrhythmia control device.

Intended Uses - Transvene Leads

Model 6963 Lead

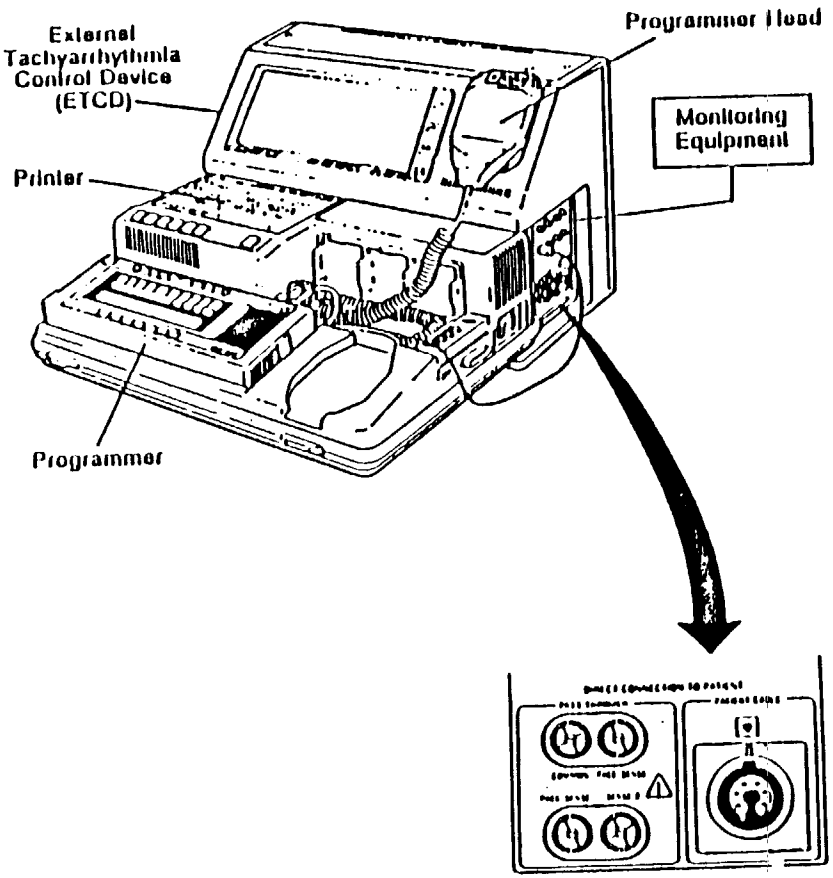
The Medtronic Transvene Model 6963 Unipolar, Coronary Sinus or Superior Vena Cava, Transvenous Lead features an electrode for the delivery of cardioversion and defibrillation therapies. It is intended for long-term use in the coronary sinus or superior vena cava and is designed to be used with an implantable tachyarrhythmia control device along with at least one other lead, such as the Model 6966 Tripolar, Right Ventricular, Transvenous Lead.

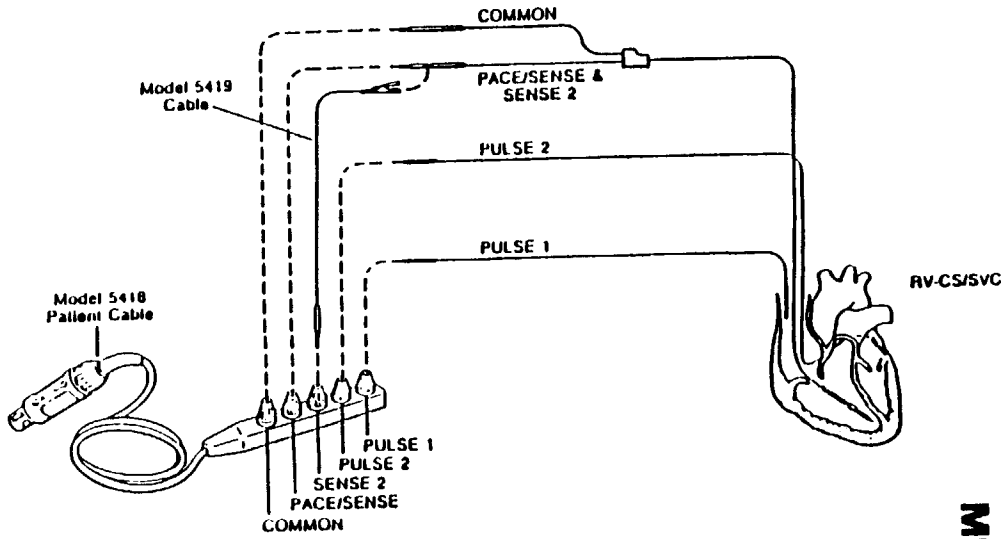
The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

Model 6966 Lead

The Medtronic Transvene Model 6966 Tripolar, Endocardial, Screw-In Lead is designed for pacing, sensing, and delivering cardioversion and defibrillation pulses in the ventricle. The lead has application where implantable tachyarrhythmia control systems are indicated.

The Model 6966 lead has a helical electrode made of platinum alloy that can be actively fixed in the endocardium. The helix can be extended or retracted by rotating the lead connector pin with a special fixation tool.





Connections to Model 5418 Patient Cable for
Typical Simultaneous or Sequential Pathway (RV-CS/SVC).

FIGURE III B-1

MEDTRONIC CONFIDENTIAL

Active fixation leads are particularly beneficial for patients who have smooth or hypertrophic hearts where lead dislodgement may be potential a problem.

The three electrodes of this lead are the coil, ring, and helix:

The defibrillating coil electrode is most proximal to the pulse generator and connects electrically to the connector pin of the unipolar leg of the bifurcation. This unipolar leg will not accept a stylet.

The ring electrode is proximal to the helix and connects electrically to the connector ring of the bipolar leg of the bifurcation.

The helix tip electrode is most distal to the pulse generator and provides active fixation in the endocardium. It can be extended or retracted by rotating the lead connector pin with a special fixation tool. The helix electrode connects electrically to the connector PIN of the bipolar leg of the bifurcation. This bipolar leg is the only one that will accept a stylet.

The helix tip electrode and the ring electrode may be used for bipolar pacing and sensing; the coil electrode is intended to be used for delivery of cardioversion and defibrillation pulses.

The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

Model 6999 Lead

The Medtronic Model 6999 Unipolar, Subcutaneous, Oval, Patch Lead features an electrode for the delivery of cardioversion and defibrillation therapies. It is intended for long-term use and is designed to be used with an implantable tachyarrhythmia control device along with at least one complementary defibrillating electrode and a pacing/sensing lead; a third defibrillating electrode may also be used.

The lead has application for patients in whom implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

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Intended Uses - PCD Device

The Model 7217B PCD device is intended for use in patients who are at high risk of sudden death due to ventricular tachyarrhythmia.

Current medical research indicates that such patients should:

- have survived at least one episode of a cardiac arrest, presumably due to a ventricular tachyarrhythmia as evidenced by resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; or

- in the absence of a prior cardiac arrest, have recurrent, sustained ventricular tachycardia that occur spontaneously or can be induced, despite the most efficacious antiarrhythmic drug therapy that can be tolerated chronically.

Extensive electrophysiologic evaluation and testing of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the Model 7217B PCD device. Before permanently programming the PCD device to the automatic detection and delivery of the VT and/or VF therapies, the patient should have demonstrated a satisfactory response to the proposed therapy.

Intended Uses - ETCD

The Model 5355 External Tachyarrhythmia Control Device is intended for use in conjunction with an antitachycardia/defibrillation lead system during diagnostic studies for implanting the Model 7217B PCD device.

Indications for use of the ETCD include:

- Patients experiencing recurrent episodes of ventricular tachyarrhythmia,

- Patients who survived a cardiac arrest due to a ventricular tachyarrhythmia and are at risk for repeated episodes,

- Patients who are undergoing an assessment of the efficacy of antitachycardia pacing, cardioversion, or defibrillation therapies in anticipation of an implantable cardioverter-defibrillator.

Components of the System

A list of components used in the system is given below. It is separated into a listing of those components for which market approval is sought and those components that are now commercially available. Market approval is not being sought for use of the PCD Device with other manufacturers transvenous defibrillation lead systems or for the use of the PCD Transvene lead system with other manufacturers implantable cardioverter defibrillators.

Seeking Approval:

Transvene Leads
- Model 6963
- Model 6966
- Model 6999

Pacer-Cardioverter-Defibrillator (PCD) Device
- Model 7217B

External Tachyarrhythmia Control Device (ETCD)
- Model 5355 ETCD
- Model 5418 Patient Cable
- Model 5419 Patient Cable
- Model 5414 Test Load
- Model 5417 EGM Cable

Programmer Software Cartridge
- Model 9788 - Memory Module for 7217B PCD Device and 5355 ETCD Devices

Lead Accessories
- Model 6701 Lead End Cap

Commercially Available:

Programmers Model 9710 and accessories

Printers Model 9751/9712

Components Used in the Implantable Configuration

The implantable configuration is composed of a PCD Device, lead system, and a 9710 Programmer with applicable software cartridge. The implantable device is a Model 7217B PCD Device. The PCD device requires an appropriate lead system consisting of up to three cardioversion/defibrillation electrodes. See Figure III B-2. The Transvene leads used with the Model 7217B PCD Device are the Models 6963, 6966, and 6999.

The Model 9710 Programmer is commercially available. Two printers are also commercially available. When higher printing speeds are desired, it is recommended that the programmer be used with the faster printer, the Model 9751. If slower printing speeds are acceptable, as may be the case in some follow-up situations, the Model 9710 Programmer can be used with the battery-powered Model 9712 Printer.

Components used in the External Configuration

The external tachyarrhythmia control system is composed of the Model 5355 ETCD, a Model 5418 Patient Cable, a Model 5419 cable, lead system, and a Model 9710 Programmer with applicable software cartridge, see Figures IV-A-3, 4. The ETCD uses replaceable batteries as its power source. The Model 5418 Patient Cable and Model 5419 Cable are designed to connect the Transvene leads to the ETCD. Like the implantable system, the ETCD uses the same Transvene leads (Models 6963, 6966, and 6999).

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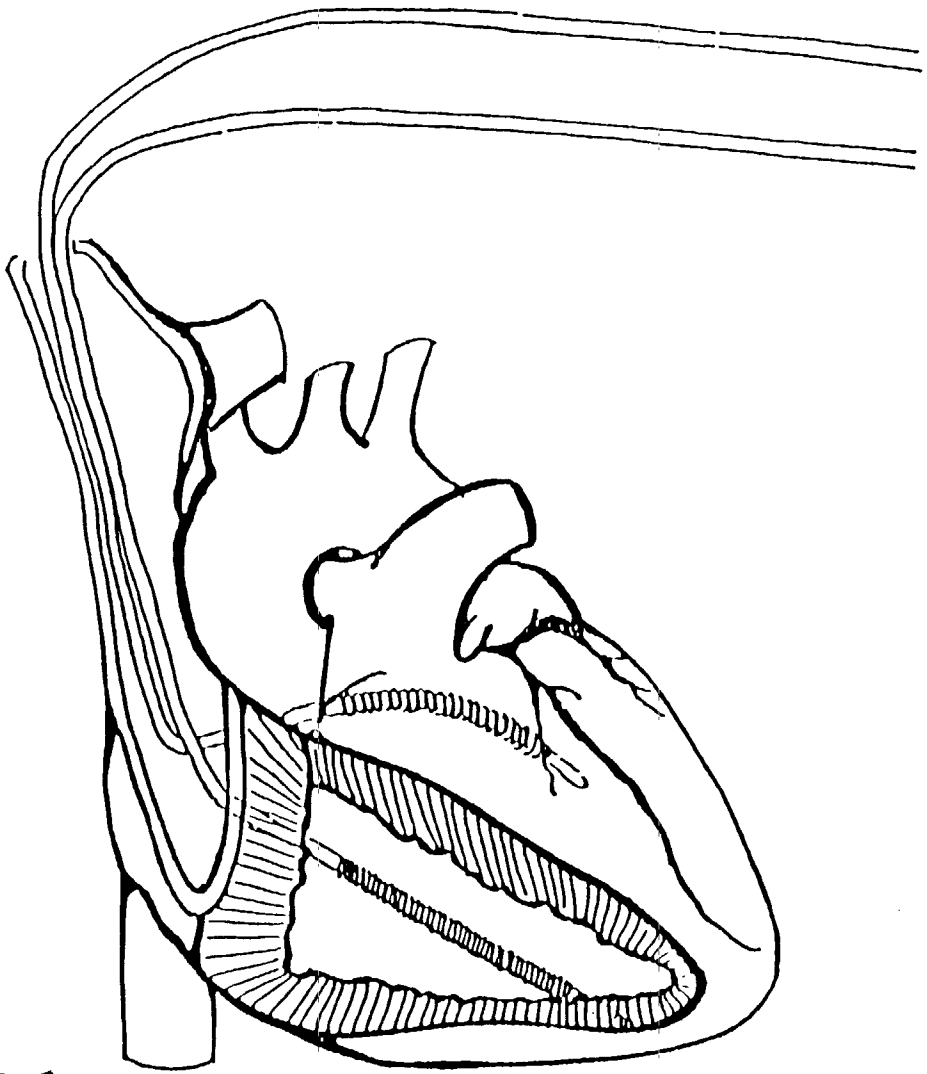
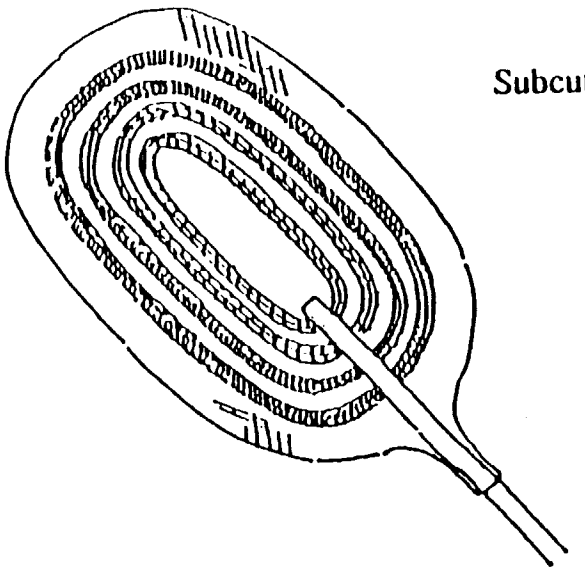
Non-Thoracotomy Lead System for PCD



Model 6963 Coronary Sinus or Superior Vena Cava

Model 6966 Right Ventricle

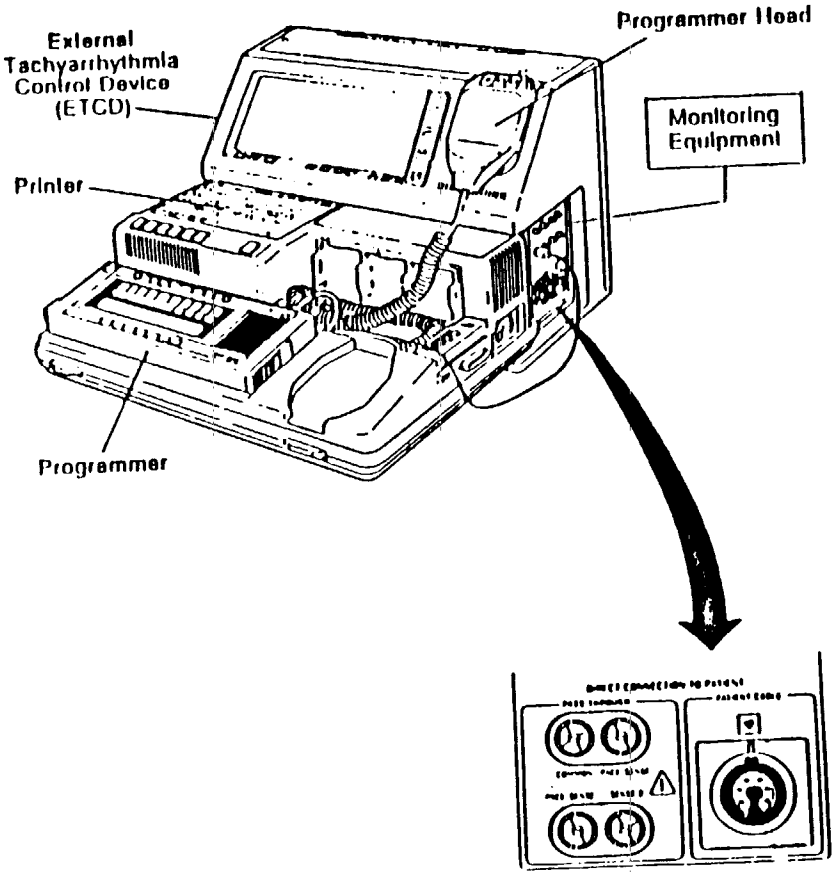


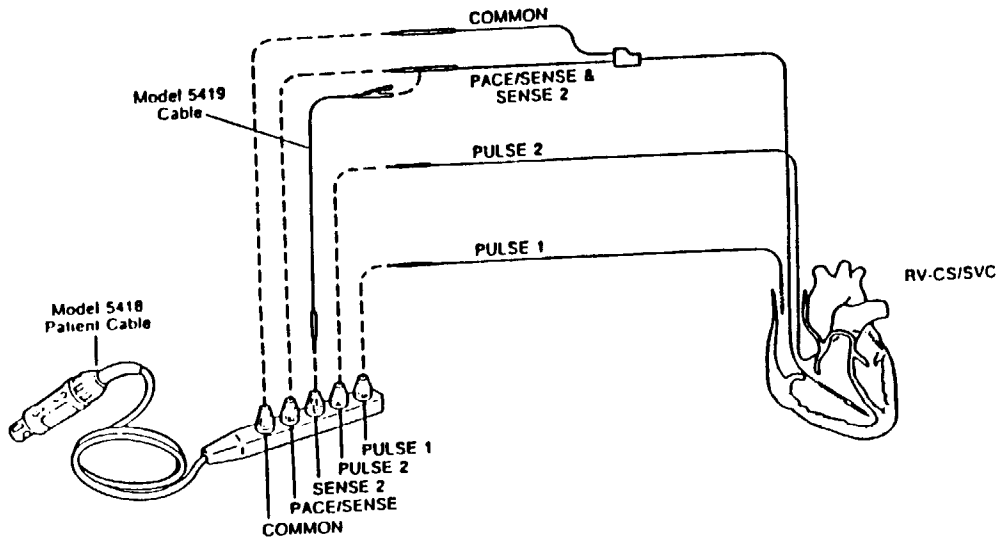
Subcutaneous Patch

Model 6999

Figure III-B-2

IH





Connections to Model 5418 Patient Cable for
Typical Simultaneous or Sequential Pathway (RV-CS/SVC).

Figure IV-A-3

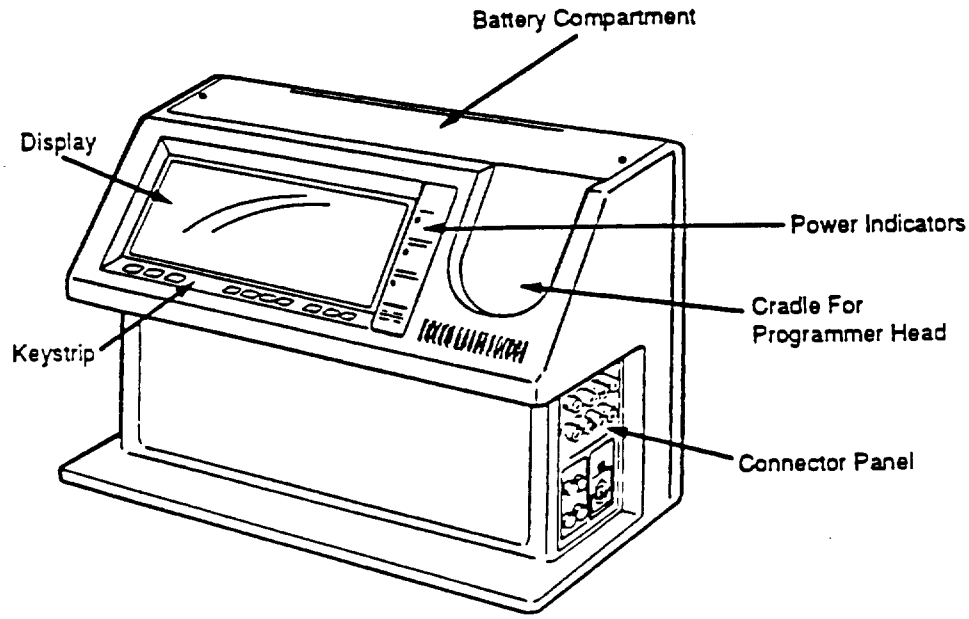


Figure IV-A-4. Model 5355 External Tachyarrhythmia Control Device

Purpose of the System

PCD System Configuration

The PCD Device is an implantable device designed to detect episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF), and upon detection, automatically deliver the appropriate therapy or a progression of therapies programmed by the physician for each patient. The available therapy types that can be programmed are overdrive pacing, cardioversion, and defibrillation. The PCD Device also has bradycardia pacing capability. The Transvene leads allow the PCD device to deliver these therapies to the heart.

ETCD System Configuration

The ETCD is an external tachyarrhythmia control device designed to deliver overdrive pacing, cardioversion, defibrillation, and bradycardia therapies in the same fashion as the PCD device. The ETCD can be programmed to automatically deliver overdrive pacing therapy upon detection of VT. When used as a component of a system that includes the appropriate Medtronic programmer and applicable software cartridge, the ETCD can deliver manually-initiated VT pacing, cardioversion, and defibrillation therapies. The ETCD allows the assessment of the Transvene lead system characteristics and aids in the assessment of lead system pacing and sensing characteristics.

Overview of System Features

General

The PCD device is designed to automatically detect episodes of VT or VF and, upon detection, deliver the appropriate programmed pacing, cardioversion, or defibrillation therapies. The device has two independently programmable detection and therapy procedures, one for VT and a second for VF.

When used as a component of a system that includes the appropriate Medtronic programmer and dedicated software, the ETCD is designed to deliver manually initiated cardioversion and defibrillation therapies. The ETCD is also designed to detect episodes of VT and VF. It can automatically deliver VT overdrive therapies (burst and ramp) upon detection of a VT.

VT Detection and Therapy

Both the PCD device and ETCD use a VT detection algorithm which can use up to three separately programmable criteria as it monitors the cardiac cycle length to identify the presence of a tachycardia. Upon detection, the devices deliver their first programmed VT therapy. If the VT episode persists and is again detected, up to three additional independently programmable VT therapies may be delivered to restore the patient's normal cardiac rhythm. This progression of four VT therapies can be tailored to each patient's need. For the PCD device the therapies may be selected from two methods of overdrive pacing (burst and ramp) and synchronized cardioversion.

For the ETCD the same overdrive pacing therapies can be automatically delivered, with cardioversion therapy being available as a manual therapy.

VF Detection and Therapy

The VF Detection algorithm monitors the cardiac cycle length to identify a VF episode. Upon detection, the PCD device provides a programmable high energy defibrillation pulse for VF therapy. Up to a maximum of four VF therapies may be delivered for ongoing detected VF episodes. Each defibrillation therapy consists of one (single pulse) or two (simultaneous or sequential) high voltage pulses designed to restore the normal cardiac rhythm.

For the ETCD, each cardioversion or defibrillation therapy, which must be initiated manually via the programmer, also consists of one high-voltage pulse or two (simultaneous or sequential) high-voltage pulses in the same fashion as the PCD devices.

Bradycardia Therapy

For both the ETCD and PCD devices, bradycardia pacing is delivered in the VVI mode. Asynchronous, (VOO), pacing is not available, and is avoided even with magnet application since this type of pacing has increased potential to initiate ventricular arrhythmias in patients receiving this system.

Lead Systems

The PCD Device and the ETCD perform pacing, sensing, cardioversion, and defibrillation through multiple electrodes in the lead system. Listed below are the electrodes and their function:

- The PACE/SENSE electrodes are incorporated in the right ventricular defibrillation lead. These electrodes function as the sensing circuit and deliver pacing pulses. The PACE/SENSE electrodes are used for sensing in conjunction with the SENSE2 electrode.
- The COMMON electrode is an electrode coil that serves as the cathode for cardioversion, defibrillation, and pacing.
- The PULSE2 electrode is an electrode coil that serves as the anode for cardioversion and defibrillation.
- The PULSE1 electrode is an optional electrode coil that serves as an additional anode for sequential and simultaneous cardioversion and defibrillation.

Cardioversion and defibrillation current pathways are between the PULSE2 and COMMON electrode coils and, if the additional lead is implanted, between the PULSE1 and COMMON electrode coils.

Other Capabilities

The physician may use the ETCD or the PCD devices to conduct noninvasive electrophysiologic studies (EPS) via the programmer with the appropriate software cartridge. The physician can also manually deliver various therapies via the programmer to manage an induced or spontaneous tachyarrhythmia.

The PCD device will provide the physician with information, via the Programmer, about its present programmed status and data on its operation accumulated between office visits. This information may be printed and retained in the patient's file.

The PCD Device and ETCD can also transmit an electrogram to the programmer. The electrogram is the electrical signal sensed on the leads.

A programmer-generated set of symbols, termed Marker Channel™, allows real-time visualization of sensing, pacing, detection, and therapy events occurring within the device.

In addition, the ETCD provides a display of measurements and other information related to delivered cardioversion and defibrillation pulses.

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With this information and other features, the ETCD can be used to assess the suitability of the lead system and its placement for individual patients.

PCD Battery Longevity Expectations

The longevity of the Model 7217B PCD Device depends upon several factors, including programmed bradycardia pacing parameters, the percentage of paced to sensed events, the pacing load, and on the frequency of high voltage capacitor charging. The longevity projections found in Table IV-A-1 apply under the following conditions:

- 65 ppm pacing rate,
- 5.4 V pacing pulse amplitude,
- 0.49 ms pacing pulse width, and
- 500 ohm pacing lead.

Projected Longevity[1]
Table IV-A-1

Pacing/Sensing	34 Joule Charging Frequency	Average Longevity Model 7217B
100% Sensing	Quarterly	5.0 years
15% Pacing	Monthly	4.2 years
100% Pacing	Monthly	3.4 years

The longevity of the device decreases with the following:

- An increase in pacing rate,
- An increase in pacing amplitude,
- A decrease in pacing impedance,
- An increase in pacing pulse width,
- An increase in the percentage of bradycardia paced to sensed events, or
- An increase in the charging frequency.

Each 34 Joule charging cycle will typically decrease the longevity of the device by approximately six days.

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[1] These preliminary longevity projections are based upon accelerated battery data and device modeling. They include an estimate of five months between time of manufacture of a PCD device and its implant. If a device was stored for the full twelve-month shelf life, the average longevity would be reduced an estimated 4.3 to 5.9 months, depending on device use. With the stated condition, 100% pacing and monthly 34 Joule charging cycles, the minimum longevity of the device will be 2.5 years (7217B). Average refers to the projected mean longevity of the modeled run of PCD devices at the stated conditions. Minimum longevity means that virtually all (i.e., 99.9%) of all modeled production run of PCD devices will attain the value given.

C. Alternative Practices and Procedures

The use of implantable defibrillators in patients with drug refractory ventricular tachycardia/ fibrillation (VT/VF) and in survivors of sudden cardiac death has reduced the arrhythmic mortality in these patients. Other treatments available to treat ventricular tachyarrhythmias include antiarrhythmic drug therapy, ventricular tachycardia surgery, transthoracic defibrillation and other market released implantable defibrillators with epicardial defibrillation lead systems.

D. Marketing History

All of the Medtronic Transvene Tachyarrhythmia Control System device components which have been implanted in the U.S. to date have been part of the IDE clinical study and have followed the FDA approved investigational protocol. In November 1991, the Medtronic PCD Transvene System, and respective components described in this submission, were market released in Europe. In March 1991, the Medtronic PCD Epicardial System, and respective components, were market released in Europe. And in February 1993, the FDA approved the Medtronic PCD Epicardial System.

E. Adverse Effects

Potential adverse effects which may be associated with the use of the PCD Device include but are not limited to: failure to detect ventricular tachycardia or ventricular fibrillation; failure to terminate ventricular tachycardia or ventricular fibrillation; delivery of pacing or shock therapy when no ventricular tachyarrhythmia is present, which would precipitate an episode of ventricular tachycardia or ventricular fibrillation; acceleration of a ventricular arrhythmia; failure to capture after a shock delivery; discomfort or pain during or following the delivery of electrical shock; or infection.

The following additional, potential adverse effects associated with all pacemaker systems include loss of normal pacemaker function due to battery failure or other component failure, inability to program a pacemaker pulse generator because of programmer failure, infection, erosion, undesired muscle or nerve stimulation, and inadequate sensing or pacing. Any demand pulse generator can be affected by magnetic, electrical and electromagnetic signals of sufficient strength or with characteristics which mimic cardiac function. Possible effects of electrical interference on pulse generator operation include reversion to asynchronous pacing, inhibition of output pulses and rapid synchronous pacing. Certain environmental sources can couple sufficient energy into a cardiac pacing system to damage the pulse generator or cardiac tissue adjacent to the electrodes.

Failure of the pulse generator system to function properly may result in the patient experiencing the symptoms for which the pulse generator was originally indicated.

The potential complications related to the use of the PCD Transvene Lead System include, but are not limited to, the following patient-related conditions: fibrillation, air embolism, cardiac perforation, heart wall rupture, cardiac tamponade, pericardial rub, infection, myocarditis, constrictive pericarditis, pneumothorax and hemothorax. Other potential complications related to the lead system include, but are not limited to, the following: lead dislodgement, lead conductor fracture, and insulation failure.

The above referenced information is provided in the labelling of the PCD Transvene System.

F. Summary of Studies

To validate the performance of the Medtronic Tachyarrhythmia Control System nonclinical laboratory (bench) testing, animal studies and human clinical trials were performed. All of the nonclinical bench and animal testing demonstrated that the devices are safe and performed according to design intent.

The nonclinical laboratory (bench) testing provides information relative to the Model 6966, Model 6963 and Model 6999 Transvene Leads, Model 7217B PCD, Model 5355 ETCD, and Model 9788 Memory Module.

The animal studies were performed to evaluate acute and chronic performance PCD Transvene System and to validate that the PCD and ETCD System are safe for human use.

Finally, human clinical trials were performed to evaluate the safety and effectiveness of the PCD Transvene System in treating patients with life-threatening ventricular arrhythmias.

All of the studies have demonstrated that the PCD Transvene System functions safely and is appropriate for human use.

The following summaries are provided in this section.

1. Model 6966, Model 6963 and Model 6999 Nonclinical Testing

2. Non-clinical Testing of the Related Components of the Transvene Lead system: Models 7217B PCD, Model 5355 ETCD and Model 9788 MemoryMod Model 7217B PCD Nonclinical Testing

3. Animal Testing

4. Clinical Study of the PCD Transvene System

1. Model 6966, Model 6963 and Model 6999 Defibrillation Leads: Summary of Nonclinical Testing

To validate the performance of the Medtronic Tachyarrhythmia Control System nonclinical laboratory (bench) testing, animal studies and human clinical trials were performed. All of the nonclinical bench and animal testing demonstrated that the devices are safe and performed according to design intent.

The nonclinical laboratory (bench) testing provides information relative to the Model 6963 CS/SVC lead, Model 6966 RV lead, Model 6999 SQ patch lead, and related system components.

a. Electrical Testing

Electrical D.C. resistance testing was performed to ensure proper functioning of the Model 6963, 6966 and 6999 leads.

Seventeen Model 6963, thirty-five Model 6966 and eighteen Model 6999 leads were submitted for testing. Electrical resistance was measured utilizing a milliammeter under ambient room conditions. All samples measured were within the individual design specifications.

b. Environmental Analysis Testing

The purpose of the testing was to subject the lead to temperature extremes to determine the lead's resistance to the thermal stresses when transported from extremes of climate.

Thermal Shock

Fifteen Model 6963 and thirty-five Model 6966 leads were subjected to five cycles from -45°C to 70°C with a soak time of thirty minutes at each temperature extreme with a transfer time of one minute. Thirty-five Model 6999 leads were subjected to five cycles from -40°C to 66°C with a soak time of thirty minutes at each temperature extreme with a transfer time of one minute.

After the thermal shock testing was completed visual inspection and electrical resistance measurements were performed. There were no visual defects and the electrical D.C. resistance of all the samples met the design specification.

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c. Mechanical Testing

The purpose of the mechanical testing was to determine the mechanical integrity of the leads to ensure that the devices are safe, reliable, and suitable for their intended use and conform to design specifications. The leads and/or assemblies were subjected to the following:

- flex testing
- composite pull strength testing
- crimp/weld pull strength testing
- insertion/withdrawal force testing
- A.C. impedance/leakage testing

Flex Testing

The flex testing consisted of mounting the insulated conductor coils and uninsulated electrode coils of the Models 6963, 6966 and 6999 in a lead flex test fixture. The insulated conductor coils and uninsulated electrode coils were flexed under ambient room conditions at a specified radius. Eleven samples were used in each test. Samples exceeded specifications and therefore are considered to be satisfactory for their intended use.

Lead Joint Tensile Strengths

Pull testing of the various lead joints is conducted to ensure that the integrity of the joint meets the design specification and is, therefore, adequate for its intended application. The testing conducted consists of a composite pull test which evaluates the overall pull strength of the lead and crimp pull testing that evaluates the crimped connections of the leads to assure specification conformance.

Composite Pull Strength

Leads were boiled in Ringer's solution or soaked in normal saline and pull tested, while wet (the lead is usually cut in half to facilitate fixturing limitations) utilizing a tensile testing machine. The samples were pulled until failure at a rate of five inches per minute. The initial failures were then

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analyzed statistically for the confidence level in meeting the specification for the composite lead which is 1.0 lb. minimum.

Model 6963 data demonstrates that with a 95% confidence at least 97% (distal) and 99.9% (proximal) of the leads will meet or exceed the specification.

Model 6966 data demonstrate that with a 99% confidence at least 99.9% of the leads will meet or exceed the specification.

Model 6999 data demonstrate that with a 99% confidence at least 99.9% of the leads will meet or exceed the specification.

Therefore, Models 6963, 6966 and 6999 leads, with respect to composite pull strength, are adequate for their intended use.

Crimp/Weld Pull Strengths

Crimp and weld pull strength tests were conducted to evaluate the strength of the connections to ensure that they meet the design specification and are, therefore, adequate for their intended application. The connections tested are:

- Distal crimp sleeve to conductor coil crimp (6963)
- Double crimp core to conductor coil crimp (6963)
- Electrode coil to double crimp core weld (6963)
- Electrode coil to distal crimp sleeve weld (6963)
- Tip crimp sleeve to conductor coil crimp (6963)
- Connector pin to conductor coil crimp (6963 and 6999)
- Helix electrode to inner conductor coil crimp (6966)
- Electrode ring to middle conductor coil crimp (6966)
- Transition sleeve to electrode coil weld (6966)
- Transition sleeve to outer conductor coil crimp (6966)
- Fixed connector pin to outer conductor coil crimp (6966)
- Connector ring to middle conductor coil crimp (6966)
- Rotating connector pin to inner conductor coil crimp (6966)
- Manifold crimp sleeve to conductor coil crimp (6999)
- Manifold crimp sleeve to electrode coil (b)(4)(b)(4) crimp (6999)
- Manifold crimp sleeve to electrode coil (b)(4)(b)(4) crimp (6999)

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Subassemblies were submitted for testing and pull tested by using a tensile testing machine. The samples were pulled until failure at a rate of four inches per minute.

Pull strength testing consisted of a minimum of 15 subassemblies of each crimp connection and a minimum of 7 subassemblies of each weld connection All samples tested exceeded the individual specification. The test results indicated that with a 95% confidence, at least 95% of the leads will have crimp and weld strengths that exceed the specification.

Therefore, the Model 6963, 6966 and 6999 leads, with respect to crimp and weld connection pull strengths, are adequate for their intended use.

Insertion/Withdrawal Forces

Insertion/withdrawal forces are measured to ensure compatibility with the implantable device without causing damage to the lead. Twenty five each of the lead Models 6963, 6966 and 6999 were tested with the Model 7217B PCD Device connector modules. There were no physical changes and all measurements met the design specification.

A.C Impedance/Leakage Testing

Fluid leakage tests are conducted on the lead assemblies/implantable device connector to determine leakage. Ten of each lead model Models 6963, 6966 and 6999 were tested with the Model 7217B connector modules. A.C. impedance was measured from the PCD device case to the lead connections while immersed in fluid. All samples met the design specification.

d. Biocompatibility Testing

The materials used in the Models 6963, 6966 and 6999 that are directly exposed to body tissue are:

- Polyurethane
- Silicone rubber (methylvinylpolysiloxane)
- Silicone rubber/titanium dioxide
- Platinum/Iridium

These materials have been shown to be biocompatible through many years of use in Medtronic permanent implantable endocardial/myocardial permanent pacing leads. In addition to extensive implant experience with these materials, standard biocompatibility tests have been performed to verify the biocompatibility of the above-listed materials. Testing has demonstrated that all materials are nonhemolytic, nonpyrogenic, nontoxic, nonmutagenic and biocompatible. Therefore, the materials passed the tests and are considered suitable for human implant. The materials used in the Models 6963, 6966 and 6999 are identical to those used in other commercially available Medtronic pacing leads.

e. Lead System (Life) Testing

In addition to the aforementioned tests, the Transvene leads were subjected to system, or life, testing. Further testing also evaluated the leads with respect to crush resistance. Testing included subjecting the leads to soaking, flexing and high-voltage pulsing. A separate test evaluated crush performance. The purpose of these tests was to subject the leads to severe conditions and assess the overall integrity of the system.

D.C. resistance values and intermittance data measured before and after being subjected to soaking, multiple flexing and high voltage pulsing, as well as crushing, demonstrated the non-thoracotomy leads satisfied requirements and are therefore acceptable for their intended use.

2. Non-clinical Testing of the Related Components of the Transvene Lead system: Models 7217B PCD, Model 5355 ETCD and Model 9788 MemoryMod

Non-clinical testing of these components was provided Volume 4 of the original PMA application (P900061) dated September 27, 1990, Volume 3 of the amendment dated March 8, 1991, and Volume 2 of the amendment dated August 30, 1991. A summary of the test results for each of the components is provided.

Model 7217B PCD: Summary of Nonclinical Testing

Testing of the Model 7217B pulse generators and the peripheral devices that comprise the system, i.e., the Pacing System Analyzers, the Model 9710 Programmer utilizing the Model 9788 MemoryMod and the Model 9751 Printer have been tested and found to be acceptable. All aspects of system interaction and operation are in accordance with the Model 7217B PCD Device and Model 9788 technical manuals and system specifications. Therefore, the Medtronic Tachyarrhythmia Control System, in its entirety, is acceptable for its intended use.

Model 9788 Memory Module: Summary of Nonclinical Testing

The Medtronic Model 9788 MemoryMod Cartridge was designed for insertion into the commercially available Model 9710 Programmer. When inserted, it becomes an integral part of the non-invasive programming system for the implantable PCD devices to establish pacing, ventricular tachycardia (VT) detection and therapy, ventricular fibrillation (VF) detection and therapy, and electrophysiological study (EPS) capabilities of an implanted pacemaker/ cardioverter/defibrillator (PCD). Both the Model 7217B PCD device and the Model 5355 ETCD are programmed with the Model 9788 MemoryMod cartridge when used with the Model 9710 Programmer.

Testing of the Model 9788 MemoryMod cartridge has demonstrated conformance to specification requirements. Therefore, the Model 9788 MemoryMod is acceptable for its intended use with the Model 7217B PCD Devices and the Model 5355 ETCD Device.

Model 5355 ETCD: Summary of Nonclinical Testing

Testing of the Model 5355 ETCD and respective accessories has shown conformance to specification requirements. Therefore, the Model 5355 ETCD Device/accessories are acceptable for their intended use.

3. Animal Testing

The information presented in this section is an accumulation of several studies, some of which FDA has previously reviewed in IDE submissions (G870102). These studies demonstrate the safety of the Transvene lead Models 6963, 6966 and 6999.

A variety of non-thoracotomy leads were evaluated in a series of four canine studies. Descriptions of the leads, as well as the study number(s) (1, 2, 3 or 4) in which they were evaluated, are presented below.

Description: Non-thoracotomy Leads

CORONARY SINUS/SUPERIOR VENA CAVA LEADS

Model 6963, evaluated in Study No. 4, is a silicone, unipolar, coronary sinus or superior vena cava lead with a 6.5 mm connector and platinum alloy electrode for delivery of cardioversion and defibrillation therapies.

Model 6881, evaluated in Study Nos. 2, 3 and 4 is functionally equivalent to the Model 6963 except the 6881 has a 3.2 mm connector.

Model 10285, evaluated in Study No. 1, is the temporary version of the Model 6963/6881.

RIGHT VENTRICULAR LEADS

Model 6966, evaluated in Study No. 4, is a polyurethane, tripolar, extendable/retractable, screw-in lead with a 6.5 mm connector and platinum alloy electrode for delivery of cardioversion and defibrillation therapies. Additionally, the 6966 has a 3.2 mm connector for pacing and sensing.

Model 6884, evaluated in Study Nos. 2 and 3, is functionally equivalent to the Model 6966 except the 6884 has a 3.2 mm connector in place of the 6.5 mm connector for the cardioversion-defibrillation electrode.

Model 10284, evaluated in Study No. 1, is the temporary version of the Model 6966/6884.

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SUBCUTANEOUS PATCH LEADS

Model 6999, evaluated in Study No. 4, is a silicone, unipolar, oval, subcutaneous patch with a 6.5 mm connector and platinum alloy electrode coils that are partially embedded in the silicone patch for delivery of cardioversion and defibrillation therapies. Additionally, the patch is embedded with (b)(4) (b)(4)

Model 6895, evaluated in Study Nos. 2 and 3, is functionally equivalent to the Model 6999 except the 6895 has a 3.2 mm connector and is covered with (b)(4) (b)(4)

Model 10317, evaluated in Study No. 3, is functionally equivalent to the 6895 except it is embedded on the outer edge with (b)(4) (b)(4)

Although model numbers differ, all leads in each of the three groups are functionally equivalent. The various model numbers reflect an evolution of temporary to transvenous lead development, as well as minor changes, such as the connector pin modification from 3.2 mm to 6.5 mm.

Additional devices were used to evaluate the non-thoracotomy lead studies in canines. These are described below.

External Devices for Implant Support

Model 5355 External Tachyarrhythmia Control Device (ETCD)

The Model 5355 ETCD provides the same detection capabilities as the implantable Model 7217B PCD Device. Therapies are identical except that the maximum output energy is 40 joules (J) and automatic defibrillation and cardioversion are not available in the Model 5355. The Model 5355 ETCD provides measurement and display of output waveform parameters and ETCD status, an isolated electrogram signal, and passthrough connections of pacing and sensing electrodes to external instrumentation.

Model 2394 External Cardioverter/Defibrillator (ECVD)

The Model 2394 ECVD instrument can deliver: (1) a single stimulation pulse on one output channel, or (2) a pair of pulses, delivered individually on the two different output channels. Monophasic and biphasic pulses are provided, output capacitance

can be varied between 10 and 150 microFarads (mf) depending on which external capacitor modules are used, and pulse width can be specified as a fixed duration (0.1-19.9 ms) or "tilt" (10-90%). Pulse output voltages can range between 50 and 1090 volts and may be delivered asynchronously (upon manual command) or synchronized with an intrinsic sensed event.

Model 2376 External Cardioverter/Defibrillator (ECVD)

The output stimulation parameters of the Model 2376 are very similar to those of the Model 2394 except for the following modifications:

- All pulses are monophasic, truncated, exponential waveforms.
- Output capacitance is fixed at 50 microFarads and pulse width is determined by a fixed pulse duration only.
- Pulse output voltages can range between 50 and 1090 volts and may be delivered asynchronously (upon manual command) or synchronized with an intrinsic sensed event.

Study Methods

All canine studies were conducted according to the 1966 and 1970 Animal Welfare Acts, 1985 NIH Laboratory Animal Use and Care Guidelines and GLP regulations. Adult mongrel canines were used for all studies. The dogs weighed 20 kg or more.

Specific details of each study are presented in the following "Animal Studies/Results" section.

Each study is briefly described below. Both acute and chronic studies were performed to assess the toxicity of the non-thoracotomy lead system as well as its stability over time.

Study #1: Acute Toxicity Testing of Non-thoracotomy Leads

The objective of this study was to quantify the amount and nature of shock-induced damage to the myocardial tissue resulting from multiple, high energy defibrillation shocks delivered through transvenous defibrillation leads and a subcutaneous patch. This information has previously been submitted to the agency in the Non-Thoracotomy IDE, reference Document Control Number G870102/S23; FDA Approved October 4, 1990. Lead models evaluated in this study are functionally equivalent to the Models 6963, 6966 and 6999. Results of these studies revealed only

minimal shock-induced necros (b)(4) (b)(4)
which did not result in functional impairment of the cardiac tissue. Therefore, the use of the Model 6963, 6966 and 6999 leads did not result in significant myocardial damage in canines and could be safely implanted in humans.

Study #2: Model 6881, 6884 and 6895 Chronic Lead Evaluation

The objective of this study was to evaluate the suitability of the lead system for human clinical use. Lead models evaluated in this study are functionally equivalent to the Models 6963, 6966 and 6999. Study results demonstrate that the performance of the non-thoracotomy lead system when used with the PCD and ETCD devices is in conformance with system design and expected operation.

One canine in this study has presented with two mastocytomas; a common type of skin tumor in middle-aged canines. This observation is not related to the PCD system, nor is it relevant to the clinical application of the PCD system. The tumors were excised and the animal remains in good health.

Study #3: Model 6881, 6884 and 6895 Chronic Lead Defibrillation Study

This study is an evaluation of the chronic stability of the non-thoracotomy lead system via the monitoring of defibrillation and pacing thresholds. In addition, histopathological examinations have been performed to assess the amount and nature of shock-induced damage to the myocardial tissue resulting from defibrillation shocks. Lead models evaluated in this study are functionally equivalent to the Models 6963, 6966 and 6999. Results demonstrate stable pacing, sensing and defibrillation thresholds over time. Additionally, histopathology analysis shows no cardiac tissue damage due to delivery of defibrillation shocks.

Study #4: Model 6963, 6966 and 6999 Chronic Lead Defibrillation Study

This study is an ongoing evaluation of the non-thoracotomy lead system to assess chronic defibrillation threshold stability, pacing thresholds, intracardiac sensing capabilities and tissue damage. Results indicate the lead system performs as intended; DFTs and

pacing thresholds have remained stable throughout the study (60 weeks) and intracardiac sensing is appropriate. Additionally, pathology data, to date, indicates minimal localized trauma to the cardiac tissue (<0.05 percent by weight).

Conclusion

All of these canine studies have demonstrated that the non-thoracotomy lead system, which includes the Model 6963 CS/SVC lead, 6966 RV lead and 6999 SQ patch lead, functions safely and is therefore appropriate for human use.

4. Clinical Experience Report

A. System and Study Description

The efficacy and safety of implantable cardioverter defibrillator (ICD) therapy for recurrent ventricular tachycardia (VT) and ventricular fibrillation (VF) has been well established. The current market released device provides defibrillation therapy for VF or hemodynamically unstable VT, however, this type of therapy may not be optimal for patients with stable, well tolerated VT that is amenable to antitachycardia pacing. It is necessary to perform a significantly more invasive procedure, a thoracotomy, in order to implant the epicardial leads. Thus, the need to incorporate programmability, multiple detection and therapeutic options, and a less invasive lead system has lead to the development of a tiered therapy device, the PCD™ Transvene™ System.

This report represents a full report of Medtronic's clinical experience with the Medtronic PCD Model 7217B Multiprogrammable Tachyarrhythmia Control System with Transvene Cardioversion and Defibrillation Electrodes (Reference IDE G870102). The data included in this analysis is all data that was received by Medtronic and entered onto the clinical database as of **February 1, 1993.**

The PCD Model 7217B Multiprogrammable Tachyarrhythmia Control System described in this submission is identical to the system which was recommended for approval by the FDA advisory panel on February 3, 1992, and approved by the FDA February 11, 1993, with the addition of Transvene leads.

This summary provides an overview of the clinical experience which verifies that the PCD Transvene System is safe and effective in the indicated patient population.

1. Implanted Devices, Leads, and Pulse Generator

The Pacer-Cardioverter-Defibrillator (PCD) device is an implantable, multiprogrammable, automatic tachyarrhythmia control device. The PCD Device is used in conjunction with appropriate lead systems for the treatment of patients with ventricular tachycardia (VT) and/or ventricular fibrillation

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(VF). The PCD Device also provides backup pacing in the VVI mode and noninvasive electrophysiologic (EP) study capabilities.

The PCD Device is programmed with the market released Medtronic programmer and a Model 9788 or equivalent MemoryMod™ Cartridge. The PCD Device incorporates a two-way telemetry system which receives operational instructions from the programmer and transmits status, electrogram and event information back to the programmer for display and/or printout.

The External Tachyarrhythmia Control Device (ETCD) is an external, multiprogrammable, tachyarrhythmia control device. Its operation is similar to the PCD Device except that cardioversion and defibrillation therapies are delivered manually. In addition, it displays measurements of cardioversion and defibrillation therapy parameters. The ETCD is used for making defibrillation threshold measurements during the PCD Device implantation procedure.

Components

The Medtronic PCD Transvene System, which is represented in Figures 1A and 1B, for which market release approval is being requested, consists of the following components:

Implanted Device and Related Programming System
Pacer-Cardioverter-Defibrillator (PCD) Device
Model 7217B

Programmer
Model 9710 programmer and related accessories (currently market released), plus
Model 9788 MemoryMod™ Software Cartridge

Lead System
Electrode Leads:
Model 6966
Model 6963
Model 6999
Market Released Medtronic Epicardial Leads

Implant Measurements System
Model 5355 ETCD™ External Tachyarrhythmia Control Device
Model 5418 Patient Cable
Model 5414 Test Load
Model 5417 EGM Cable
Model 5419 Jumper Cable

The physical characteristics of the Model 7217B are summarized in Table IA1-1:

PCD Model 7217B Physical Characteristics	
Feature	**Model 7217B**
Volume	113 cc
Weight	198 grams
Connector Module	Four connector ports
Power Source	Wilson Greatbatch Model 8830 Lithium Silver Vanadium Oxide
Sensing Configuration	Standard Bipolar
Pacing Configuration	Integrated Bipolar

Table IA1-1: Features: Model 7217B - 2/1/93

The Model 7217B PCD Device uses the pace/sense leads for sensing, thus providing **standard bipolar** sensing. Pacing is delivered in the integrated bipolar configuration.

2. Study Design and Objectives

The clinical study was designed to evaluate the operation, safety and effectiveness of the PCD System components in detecting and treating episodes of ventricular tachycardia and ventricular fibrillation.

The analysis focuses on data supporting the safety and effectiveness of the PCD system, including the implantable pulse generator and associated transvenous lead system and its therapy in this patient population. The analysis includes the clinical experience with the PCD system, pace/sense, detection and therapy functions in both the

acute and chronic implant settings. In addition, data is provided on clinical observations, clinical complications and deaths in this patient population.

The objectives of the clinical study were:

* to evaluate the sensitivity and specificity of the PCD Device with Transvene lead systems to detect episodes of VT and VF, and to evaluate the ability of the system to appropriately discriminate between VT/VF and other potentially nonmalignant rhythms;

* to monitor the efficacy of the PCD Device with Transvene lead systems in treating VT and VF episodes. VT/VF therapy efficacy is determined as the ratio of successful termination of episodes detected to the total number of episodes detected in which one or more therapies were delivered (Successful Termination/Number of Detected Episodes with Therapy Delivered). Investigators were free to choose from any of the available leads and VT/VF therapies that the efficacy was first evaluated acutely;

* to evaluate the performance of the Model 6966, 6963 and 6999 Transvene leads;

* to monitor the patient selection criteria and patient management methods required by the PCD Device and Transvene leads.

Clinical data was collected at the following study points to support the safety and efficacy of the PCD System:

Pre-implant Patient Assessment
Lead System Testing at Implant
Implantable Pulse Generator Testing at Implant
Pre-hospital Discharge Testing
Follow-up Evaluation 1 and 3 months post implant then at 3 month intervals

Specific data was collected at each of these points to meet the objectives of the clinical study. This included:

Pre-implant Patient Assessment - extensive pre-implant testing was performed to ensure that the general patient selection criteria were met. This testing included at least an electrophysiologic evaluation, measurement of ejection fraction, and assessment of the patient's New York Heart Association

(NYHA) classification of their cardiovascular status. Depending on the patient history, cardiac catheterization and exercise testing were also conducted.

Lead System Testing - implant evaluation was performed to verify that one of the specified lead systems was capable of properly detecting and treating episodes of ventricular fibrillation and, when appropriate, ventricular tachycardia. The Market Released Model 5355 ETCD™ or the 2394 External Cardioverter Defibrillator (ECVD) was used for testing.

This testing included pacing and sensing thresholds during sinus rhythm, evaluation of VF electrogram amplitudes and defibrillation efficacy evaluation. The PCD Device implant criteria were:

1) successful VF termination at least 3 times in 4 attempts with an output energy of 18 Joules or less and

2) a 2:1 VF sensing safety margin.

Implanted Pulse Generator Testing - this implant evaluation was performed to demonstrate proper detection and termination of ventricular fibrillation by the implanted PCD System with VF Therapy #1 programmed to 34 Joules in addition to pacing and sensing thresholds.

Pre-hospital Discharge Testing - testing performed at the pre-hospital discharge included proper detection and termination of induced ventricular tachycardia. Final sensing and therapy parameters are programmed at the PHD.

Follow-up Evaluation - regular testing was performed to evaluate the chronic stability of detection and therapy parameters of the PCD System. This testing included an assessment of the relative stability of the energy required to defibrillate a patient and efficacy and acceleration rate assessment of the VT therapies. The number of spontaneous VT/VF episodes treated by the PCD Device were evaluated. Complication rates and patient mortality data were also evaluated.

Patients were evaluated prior to hospital discharge and/or one (1) month post implant, three months post-implant and then at intervals of every three months. In some cases additional testing was performed at physician discretion to evaluate spontaneous events and/or potential clinical complications.

Medtronic collected all clinical data on the PCD System and its components under the clinical protocol outlined in the Investigational Plan. A common protocol was used on all study patients on a worldwide basis.

Clinical data presented in this summary includes experience with the Model 7216A and 7217B PCD Devices with the Model 6966, 6884, 6963, 6881, 6999, and 6895 Transvene Leads (the only difference between the Models 6884/6881/6895 and Models 6966/6963/6999 are the size of the connector pins). This report presents the clinical evaluation of the safety and efficacy of the PCD Device with Transvene Leads implanted in 757 patients of which 657 have implant durations equal to or greater than six months.

International centers were subject to the appropriate requirements (e.g., the Declaration of Helsinki) in order that the data met the statutory requirements of the FDA. All clinical data, U.S. and International, obtained with the PCD System with Transvene Leads is included in this report.

Patient data from U.S. and International patients, Model 7216A and 7217B, and the three implanted lead configurations (RV/CS/SQ, RV/SVC/SQ, and RV/CS/SVC) analyzed in this report were compared with the appropriate statistical tests to justify data pooling. Data analyzed included: age, sex, ejection fraction, primary indication, NYHA classification, and underlying heart disease. No clinically significant differences were found among the patient groups.

Indicated Patient Population

The PCD System is intended to treat patients at risk of sudden cardiac death due to ventricular tachyarrhythmias which have been shown to be reliably terminated, and in the case of VF, terminated at an energy level below the maximum output of the PCD Device.

Results provided in this application will support Medtronic's request for market release of the PCD Transvene System for use in the following patient population:

* Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or

* Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

These are the same indications that were approved for the PCD Epicardial System.

For this patient population the primary benefits from the use of the PCD System center on the detection and termination of life-threatening ventricular arrhythmias. The use of pacing therapies for the treatment of ventricular tachycardia reduces patient trauma associated with higher energy cardioversion pulses and extends the longevity of the PCD pulse generator.

The PCD System allows the titration of therapies for patients with ventricular tachycardia while providing the critical defibrillation backup. Defibrillation backup is important in the event that an episode of VT accelerates to VF whether spontaneously or as a result of a delivered therapy. The capacity to provide programmable extrastimuli pacing allows noninvasive electrophysiologic studies to be performed. The potential benefits from permanent cardiac pacing provide support for chronic and transient episodes of bradycardia. Finally, the benefits of programmability of tachyarrhythmia detection and therapy parameters, VVI parameters and stored telemetry data on the delivery of therapy may avert the need for reoperation in the event of changing patient conditions or complications.

Study Controls

The clinical experience obtained in the PCD Epicardial System clinical study provides a concurrent control for comparing the clinical performance of the PCD Transvene

System. Using the PCD Epicardial System clinical data as a control is appropriate because the patients were being enrolled in the two studies concurrently by the same investigators, and the patient indications, implant criteria, and clinical data requirements were identical for the two patient groups.

The Ventak-P Epicardial System is used as a historical control, since it was the most similar implantable defibrillation system that was market released and had published performance data.

The PCD investigators believe that there is a class of patients who cannot tolerate the thoracotomy required for the utilization of the epicardial patch lead defibrillation lead system and who are at high risk of sudden cardiac death. For these patients, the PCD Transvene System is the only therapy available. Therefore, randomization between the Epicardial and the Transvene lead systems would not be feasible or clinically or ethically appropriate in these patient groups. There was no market released transvenous system available which would make a randomized study design possible.

3. Justification for Data Pooling

This section will describe the results of the analysis to demonstrate that the data from the U.S. and International investigative centers and the two device model numbers may be pooled. This section will also compare the three lead systems which will be presented throughout the report.

a. Comparison of U.S. and International Patients

Statistical comparisons were made between the two populations age, sex, ejection fraction, primary indication, NYHA, and previous cardiovascular history. Table E1 in Appendix E summarizes the results of statistical analysis.

All study investigators used the same:

a. patient selection criteria,
b. investigational protocol procedures, and
c. indications for implant of PCD™ Transvene™ System.

Of the variables analyzed patient age, ejection fraction, primary indication, NYHA classification, coronary artery disease and cardiomyopathy showed a statistically significant difference between the U.S. and the International patient populations at a 0.05 significance level. The difference in NYHA classification becomes insignificant when adjusting for multiple inference using the Hochberg procedure (Dunnett and Tamhane, "A Step-Up Multiple Test Procedure," Journal of the American Statistical Association, March 1992, 87:162-170). See Appendix E for multiple inference adjustments. Coronary artery disease, ejection fraction, cardiomyopathy, primary indication and age remain statistically significant after adjusting for multiple inference. The U.S. patient population has a higher percentage of patients with coronary artery disease and cardiomyopathy, lower mean ejection fraction, more patients with VT as their primary indication and a higher mean age. The difference in age may explain the differences in underlying disease and cardiac ejection fraction. These factors that are statistically significant but are not considered to be clinically significant enough to require stratification of the U.S. and International patient populations. The differences may have to do with regional attitudes toward access to health care for the aged.

b. Comparison of Model 7216A and Model 7217B

Table E2 in Appendix E summarizes the results of statistical analysis comparing the Model 7216A to Model 7217B. No parameters were found to be statistically significant between the two PCD models at a 0.05 significance level.

c. **Lead Configurations**

Table E3 in Appendix E shows comparisons of patient variables for the three lead systems. This was done to document that there were no significant differences in patient characteristics between the implanted lead configurations.

Of the variables analyzed in Table E3 sex and cardiomyopathy showed a statistically significant difference between the three lead configurations at a 0.05 significance level. The difference in sex and percentage of patients with cardiomyopathy becomes insignificant when adjusting for multiple inference using the Hochberg procedure (Dunnett and Tamhane, "A Step-Up Multiple Test Procedure," Journal of the American Statistical Association, March 1992, 87:162-170). See Appendix E for multiple inference adjustments.

d. **Statistical Analysis Conclusions**

The statistical comparisons between the U.S. and International populations indicated no clinically significant differences therefore the data may be pooled. Analysis of the patients receiving the two PCD models indicates no statistically significant differences therefore the data from the two devices may be pooled.

The results from the comparison of lead systems indicated no statistically significant differences in patient demographics, primary indication, or heart disease.Data Pooling/U.S. Demographics

B. **Overview of Clinical Experience**

This report covers a total of 762 implants of the PCD Device with the Transvene Defibrillation Lead System in 757 patients who received a 3 lead system. There was a total of 97 patients that were screened for Transvene system that did not meet the implant criteria and received a Medtronic Epicardial system and a total of 43 patients that received a non-standard lead system. These

n3

patients are described in Section C2, Patients not Meeting Implant Criteria and Section D4, Non-standard Lead Configurations, respectively.

A total of 78 investigative centers participated in the clinical trial with 35 centers in the U.S. and 43 Internationally. The first implant occurred internationally on October 20, 1989, and the first implant in the U.S. occurred on October 16, 1990. Table IB-1 shows the distribution of Model 7216A and Model 7217B patients between U.S. and International investigators.

PCD Transvene System Implant Distribution			
	Total	U.S.	Int'l
7216A	18 (2.4%)	3 (0.7%)	15 (4.8%)
7217B	744 (97.6%)	444 (99.3%)	300 (95.2%)

Table IB-1: PCD Transvene System - Implant Distributions - 2/1/93

The mean documented implant duration for this patient population is 11.7 months and ranged from implant to 37.4 months. The cumulative implant duration is 8894.8 months. There are 657 patients with implant durations equal to or greater than 6 months and 393 patients with implant durations equal to or greater than 1 year.

The patient population enrolled in the clinical trial was predominately male (80.6%) with a mean age of 59.4 years. In half of the patients (49.8%), the primary indication for implant was recurrent, sustained ventricular tachycardia without an episode of sudden cardiac death. Sudden Cardiac Death was the primary indication for 37.1% of the patients and SCD in combination with recurrent, sustained VT was the primary indication in 13.1%. Coronary artery disease was the primary heart disease in 74.1% of the patient population with a mean reported ejection fraction of 35.6% Table IB-2 provides a data summary on these patients. Also included is the data summary of the patients with 6 months and 12 months of follow-up.

PCD Transvene System Data Summary			
	All Patients (3 Electrode Systems)	Patients with 6 months of Follow-up	Patients with 12 months of Follow-up
Number of Patients	757	657	393
Device Months Follow-up	8894.8	8602.6	6454.6
Mean Follow-up Time	11.7 mo	13.0 mo	16.3 mo
Maximum Follow-up Time	37.4 mo	37.4 mo	37.4 mo
Number, % Male Number, % Female	610 80.6% 147 19.4%	527 80.2% 130 19.8%	310 78.9% 83 21.1%
Mean Age	59.4 yrs	59.1 yrs	58.8 yrs
Primary Indication: SCD VT SCD/VT	 281 37.1% 377 49.8% 99 13.1%	 249 37.9% 326 49.6% 82 12.5%	 150 38.2% 191 48.6% 52 13.2%
Coronary Artery Disease	561 74.1%	483 73.5%	272 69.2%
Mean Ejection Fraction	688 35.6%	595 36.6%	357 38.0%
Defibrillation Pathway: Sequential Simultaneous Single	 574 75.3% 178 23.4% 10 1.3%	 496 74.9% 156 23.6% 10 1.5%	 296 74.9% 93 23.6% 6 1.5%
Mean LED	16.0J (N=702)	16.0J (N=609)	15.6J (N=365)
Mean DFT	14.8J (N=316)	14.8J (N=277)	14.3J (N=184)
Spontaneous VT: Number of Patients Number of Episodes % Success	 316 10027 98.4%	 288 8820 98.3%	 186 6338 99.0%
Spontaneous VF: Number of Patients Number of Episodes % Success	 317 1982 98.4%	 292 1742 98.3%	 176 1105 98.6%
One Year SCD Survival	99.5%	99.7%	100.0%

Table IB-2: PCD System Data Summary - All Transvene Patients versus Transvene Patients with 6 mo Follow-up - 2/1/93

1. Implant Information

Implants of the PCD Device may use two or three Transvene leads. The physician has the flexibility to use whichever lead system best meets the patient's needs.

The venous entry site used for placement of the Transvene leads is determined by the implanting physician. Table IB1-1 shows that the Left Subclavian vein is the most popular venous entry site regardless of type of lead or intended lead location. The total number of RV lead entry sites is greater than the total number of patients included in this report because of patients with multiple lead evaluation sessions (e.g. patients that received a second PCD Transvene system if the initial system was removed due to infection).

PCD Transvene System Venous Entry Site			
	RV Lead Models 6884/6966/SP2100	CS/SVC Lead Models 6881/6963	All Transvene Leads
Left Subclavian	483	583	1066
Right Subclavian	40	47	87
Left Cephalic	213	180	393
Right Cephalic	8	7	15
Left Internal Jugular	7	9	16
Right Internal Jugular	11	9	20
Other	5	4	9
Total	767	839	2097

Table IB1-1: Venous Entry Site - 2/1/93

The location of the subcutaneous patch is presented in Table IB1-2. Location is defined by both anatomical line and intercostal space. The study protocol does not restrict investigators in subcutaneous patch placement. Investigators are free to place it in the most appropriate location for each individual patient.

The most common subcutaneous patch location laterally is the mid axillary line (55.7%). the next most common location is the anterior axillary line (34.3%). The majority of subcutaneous patches are placed between the third and sixth intercostal (53.4%).

The majority of the investigators (92.8%) placed the patch electrode subcutaneously. Fifty-two (52) or 7.2% if investigators placed the patch electrode in a submuscular location.

PCD Transvene System
Location of the Subcutaneous Patch Electrode

Intercostal Space	Mid Clavicular Line	Anterior Axillary Line	Mid Axillary Line	Posterior Axillary Line	Subscapular	Total
1-2	11	1	3	0	0	15 2.1%
3-6	21	127	237	1	0	386 53.4%
7-11	1	17	18	0	0	36 5.0%
Not Specified	17	103	145	6	15	286 39.5%
Total	50 6.9%	248 34.3%	403 55.7%	7 1.0%	15 2.1%	723 100.0%

Table IB1-2: Location of the Subcutaneous Patch Electrode - 2/1/93

Table IB1-3 illustrates the lowest energy of defibrillation (LED) and defibrillation threshold (DFT) for the implanted lead systems. The implant criteria for the PCD Device was 3 of 4 episodes of VF successfully terminated at 18 Joules or less with a given lead configuration. Some patients did not have a LED at implant. The LED is only identified if the investigator reported the induced rhythm as VF. Conversion of VT or V Flutter (as defined by the physician) to sinus rhythm was not included in the determination of the LED. In addition, it is not a protocol requirement to obtain a DFT at implant. However, recommendations have been provided to those institutions that prefer to obtain DFT's during the implant procedure.

PCD Transvene System Mean LED and DFT Values				
Lead System	Implant Frequency	Mean LED	Implant Frequency	Mean DFT
Total Systems	702	16.0J	316	14.8J
RV-SVC-SQ	455	16.7J	187	15.8J
RV-CS-SQ	210	14.6J	110	12.8J
RV-CS-SVC	37	15.2J	19	16.0J

Table IB1-3: PCD Transvene System - LED and DFT Values - 2/1/93

The mean implant Lowest Energy of Defibrillation (LED) for all lead systems was 16.0J and mean implant Defibrillation threshold (DFT) for all lead systems was 14.8J. As the mean DFT's and LED's indicate, VF was reliably terminated at an energy value below the maximum output (34 Joules) of the PCD Device.

There was a statistically significant difference between the mean DFT obtained with the RV-CS-SQ lead configuration and the mean DFT obtained with the other lead configurations. Since there were no differences in the patient populations implanted with any of the 3 lead configurations, this may be a configuration that results in lower DFTs than the other configurations. In theory, this may be due to better defibrillation current distribution throughout the myocardium. There is no intent to show that a lower DFT results in a better patient outcome. The premise of the PCD Epicardial and Transvene studies was to demonstrate that if a patient was evaluated at implant and shown to meet the implant criteria, that they would be reliably defibrillated over time, and therefore, have a high probability of survival from SCD regardless of which lead system or defibrillation pathway was chosen or the absolute value of the DFT.

Follow-up Data - Quantity

The combined experience from the Model 7216A and the Model 7217B with Transvene lead systems discussed in this analysis is 762 implants in 757 patients followed for a mean of 11.7 months. Maximum follow-up is 37.4 months

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with 8894.8 total device months of experience. Six-hundred-fifty-seven (657) patients have been followed for at least 6 months and 393 patients have a minimum of one year of follow-up.

2. Spontaneous VT and VF Episode Experience

Of the 757 patients who received a PCD Transvene System, 597 patients (78.9% - 597/757) have either experienced a spontaneous VT/VF episode or had VT/VF induced during a post implant electrophysiology study. A total of 458 patients (60.5%) have experienced a spontaneous episode of either VT and/or VF that has been detected and treated by the PCD Device. A total of 141 (18.6%) experienced VT only, 142 patients (18.8%) experienced VF only and 175 patients (23.1%) experienced both an episode of VT and VF.

There have been a total of 12,009 episodes of spontaneous VT or VF as detected by the PCD. The overall PCD Device success rate in terminating spontaneous VT/VF episodes as detected by the PCD is presented in Table IB2-1.

For those episodes where all four programmed VT/VF therapies failed to terminate the episode, the clinical follow-up data form was reviewed for investigator's comments on the episode. The investigator reviewed the patient's symptoms at the time of the episode as well as the stored episode information provided by the PCD Device and indicates on the clinical dataform whether the ineffective therapy was due to a nonventricular tachyarrhythmia such as sinus tachycardia or atrial fibrillation. If there is no such indication on the clinical dataform, it is assumed that the ineffective therapy was for a spontaneous VT or VF episode. It should be noted that for all current ICD Systems, the delivery of inappropriate therapy for atrial fibrillation or sinus tachycardia is a known risk of the therapy.

PCD Transvene System Success Rate for Spontaneous VT/VF Episodes		
	Spontaneous VT Episodes	**Spontaneous VF Episodes**
Mean Follow-Up	11.7 months	11.7 months
Number of Episodes	10,027	1982
Number of Patients with Episodes	316	317
% Overall Efficacy	9,864/10,027 98.4%	1951/1982 98.4%
% Unsuccessful Termination (VT or VF)	68/10,027 0.7%	5/1982 0.3%
% Unsuccessful Termination (AF,ST, other)	95/10,027 0.9%	26/1982 1.3%

Table IB2-1: PCD Transvene System: Success Rate for Termination of Spontaneous VT/VF Episodes (n = 757) - 2/1/93

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a. **Spontaneous VT**

For the purposes of this clinical trial, spontaneous VT was defined as those episodes that satisfied the programmed VT detection criteria. Specifically, all programmed VT detection criteria must be fulfilled to detect a VT episode. Successful termination of the episode was defined as satisfying the VT episode termination criteria.

To date, 10,027 spontaneous episodes of VT have been detected by the PCD Device in 316 patients. The mean number of episodes per patient with VT was 31.7 (316/10,027) and ranged from 1 - 531 episodes.

Most spontaneous VT episodes (90.7%) were successfully treated with VT Therapy #1 and 98.4% were successfully treated with one of the four programmable VT therapies.

Of the 9864 successfully terminated spontaneous VT episodes, 91.4% were treated with one of the programmed antitachycardia pacing therapies incorporated in the PCD Transvene System. The clinical benefit of tiered therapy is the reduction of delivery of high energy shocks for the treatment of stable recurrent ventricular tachycardia. This greatly enhances the patient acceptance of ICD therapy since antitachycardia pacing is usually not perceived by the patient.

Sixty patients experienced 163 (1.6%) episodes in which the PCD Device was ineffective in terminating a spontaneous episode of VT despite delivery of all four programmed VT therapies. Thirty-nine patients experienced 95 ineffective episodes that were due to sinus tachycardia or atrial fibrillation/flutter (SVT) with a rapid ventricular response that had been detected as VT. These episodes were resolved with either modification of programmed parameters or of antiarrhythmic drug therapy. It should be noted that the PCD Device responded appropriately based on the programmed detection parameters.

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The remaining 68 episodes occurred in 21 patients in which the programmed VT therapies were ineffective in terminating a spontaneous VT episode. **No patient deaths occurred as a result of ineffective VT therapy**. Reprogramming and pharmacologic intervention resolved these events.

b. Spontaneous VF

For purposes of this clinical trial, VF is defined as those episodes that satisfy the programmed VF detection criteria. Specifically, all programmed VF detection criteria must be fulfilled to detect a VF episode. Successful termination of the episode is defined as satisfying the VF detection criterion for episode termination.

To date, 1982 spontaneous episodes of VF have been detected by the PCD Device in 317 patients. The mean number of episodes per patient was 6.3 and ranged from 1 - 77 episodes. A review of the chart by the investigator for this patient that experienced the 77 episodes of VF revealed that 75 were most likely due to atrial fibrillation. VF detection parameters were modified in this patient.

Most (89.1%) spontaneous VF episodes were successfully treated with VF Therapy #1 and 98.4% were successfully treated with one of the four programmable VF therapies.

Sixteen patients experienced 31 episodes (1.3%) in which the PCD Device was ineffective in terminating a spontaneous episode of VF despite delivery of all four programmed VF therapies. Nine patients had 22 reported ineffective VF spontaneous episodes that were due to sinus tachycardia or atrial fibrillation with rapid ventricular response rather than VF. Reprogramming and pharmacologic intervention resolved these problems.

Four patients experienced 5 ineffective episodes that were detected as VF by the PCD® System. One of these patients (b)(6) required external defibrillation

to convert the VF episode. This patient's antiarrhythmic drug regimen was modified to improve defibrillation efficacy. Another patient (b)(6) had an episode recorded as ineffective on the event counters but presented in sinus rhythm. Subsequent evaluation demonstrated appropriate PCD function. Another of these patients (b)(6) had two spontaneous episodes of VT that were detected as VF by the PCD while in the hospital for progressive CHF. These episodes required external cardioversion. The patient requested the PCD be turned OFF. The patient was alive at the last known follow-up. The last of these four patients (b)(6) experienced cardiac arrest at home and was found by the paramedics to be in sinus rhythm. While on a monitor the patient developed VF. The PCD delivered the programmed therapy which terminated the episode but the patient developed EMD, arrived at the ER comatose and died.

Four patients (one patient (b)(6) experienced 2 episodes due to AF but is described below again) experienced 4 episodes in which the PCD detected the episodes as VF but were actually episodes due to extraordinary circumstances. One patient (b)(6) experienced an episode where all four therapies failed secondary to RV lead fracture. The patient had Twiddlers Syndrome. Reoperation was required. It appears that the inappropriate therapy was not due to VT/VF but due to noise. Another patient (b)(6) had a surgical procedure (CABG) where the CS lead dislodged post surgery. The episode that was detected was due to the lead dislodgement. The third patient (b)(6) had incessant episodes of fast VT (cycle length 280 ms) that were eventually resolved by drugs. The fourth patient (b)(6) was in the hospital and there was an episode of VF detected by the PCD and therapy was delivered. However, the device was interrogated before termination of the episode was detected by the PCD. There was external intervention (transthoracic defibrillation) associated with the terminal event. However, the patient ultimately expired. The device was not interrogated again.

The evaluation of spontaneous episode experience indicates that the PCD Transvene System's VT and VF detection and therapy functions have performed safely and effectively in the indicated patient population.

3. Summary of Complications and Observations

The use of a multiprogrammable implantable cardioverter defibrillator (ICD) device allows the physician to resolve most relevant medical events by noninvasively changing programmed parameters thus, avoiding invasive procedures. However, there will continue to be certain relevant medical events which will require invasive procedures for resolution.

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following definitions:

COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

As of February 1, 1993, there have been a total of 176 complications identified in 147 patients and 212 observations identified in 178 patients in the PCD Transvene System patient population. Thus, 19.4% (147/757) of the patients have experienced a clinical event which was defined as a complication and 23.5% (178/757) of the patients have experienced a clinical event which was defined as an observation.

Table IB3-1 summarizes the reported PCD Transvene System complications and observations by category. The reported complications and observations are recognized clinical events that may occur with **any** of the current ICD devices. These complications and observations are discussed in the PCD device and Transvene manual. **None of the reported complications or observations have resulted in a patient death.**

PCD Transvene System Reported Complications/Observations By Category		
Category	**Complications**	**Observations**
	Num (% of Pts)	Num (% of Pts)
Increased Defibrillation Requirements	9 (1.2%)	8 (1.1%)
Inappropriate VF Therapy Delivery	-	14 (1.9%)
Inappropriate VT Therapy Delivery	-	57 (2)* (7.5%)
Loss of Capture	6 (0.8%)	11 (1)* (1.7%)
Oversensing	-	52 (2)* (6.9%)
Undersensing	-	-
Skin Erosion	5 (0.7%)	1 (0.1%)
Pocket Infection	24 (3.2%)	10 (1.3%)
Seroma	6 (0.8%)	14 (1.8%)
Hematoma	6 (0.8%)	17 (2.2%)
Pneumothorax	2 (0.3%)	1 (0.1%)
Pacemaker Syndrome	-	2 (0.3%)
Perforation	6 (0.8%)	-
Subclavian Vein Thrombosis	1 (0.1%)	3 (0.4%)
Lead Fracture	9 (1.2%)	-
Subcutaneous Patch Crinkling	7 (0.9%)	5 (0.7%)
Early Device Explant	4 (0.5%)	-
Total Lead Dislodgement	86 (5)* (11.4%)	12 (1.6%)
Total	**171 (176)**	**207 (212)***

Table IB3-1: PCD Transvene System: Reported Complications and Observations - 2/1/93

* This number indicates the number of patients with 2 events

Table IB3-4 contains a description of the lead dislodgements that have occurred in less than 30 days and in greater than 30 days. The $\leq$30 day period is defined as the acute period. This definition is consistent when compared to endocardial bradycardia lead terminology.

PCD Transvene System
Reported Complications/Observations
Lead Dislodgements <30 days and >30 days

Category	Complications		Observations	
	Num (% of Pts)		Num (% of Pts)	
	<30 days	>30 days	<30 days	>30 days
RV Lead Dislodgement n=741	14 (1.9%)	10 (1.3%)	0 (0)	1 (0.1%)
CS Lead Dislodgement n= 261	12 (4.6%)	10 (3.8%)	2 (0.8%)	2 (0.8%)
SVC Lead Dislodgement n=535	16 (3.0%)	29 (5.4%)	1 (0.2%)	6 (1.1%)
Total Lead Dislodgement n=757	42 (5.6%)	49 (6.5%)	3 (0.4%)	9 (1.2%)

Table IB3-4: PCD Transvene System: Lead Dislodgements <30/>30 days - 2/1/93

There have been a total of 58 lead dislodgements reported in patients at greater than 30 days. None of the lead dislodgements resulted in an ineffective therapy for a spontaneous VT of VF episode or patient death. Lead dislodgements were documented by fluoroscopic examination during electrophysiologic evaluation, chest x-ray obtained during routine follow-up, or during pacing/sensing threshold evaluation during routine follow-up. In 49 cases, reoperation was required to reposition the lead and reestablish an effective defibrillation lead system and in 9 cases repositioning of the lead was not required..

Lead dislodgements are not specific to the PCD Transvene System and have been reported with dual chamber pacemakers and the current market released implantable cardioverter defibrillator (ICD) system. The early history of dual chamber pacemakers witnessed a high lead dislodgement rate of at least 20% (Smyth, PND, et al. Permanent perivenous atrial sensing and pacing with a new J-shaped lead. J Thoracic Cardiovascular Surgery. 1976;72:565-570). Winkle, et al reported that the incidence of dislodgement of the superior vena cava spring

leads with the current market release ICD system to be 6.3%. (Winkle, et al. Automatic Implantable Cardioverter-Defibrillator: Efficacy, Complications, and Survival in Patients with Malignant Ventricular Arrhythmias. JACC. June 1988; Vol.11, No.6:1278-86).

In an attempt to reduce the rate of lead dislodgement, modifications were made to the lead anchoring sleeve and a second sleeve was added to the lead. The sleeve was modified to increase the grip pressure on the lead body and two sleeves were provided on each lead at the time of manufacture. Analysis has been completed on 439 patients implanted with the Transvene system using leads that are packaged with two anchoring sleeves. **(NOTE: These 439 patients were enrolled in the Clinical Trial after 6-24-92 and are not included in the 757 patient population).** Table IB3-5 contains a data summary for the 439 patients. This group of patients has similar characteristics to the 757 patient population in most areas with a slightly higher percentage of patients with VT reported as the primary indication for implant than the 757 group of patients (61.1% vs 49.8%).

PCD Transvene System **Data Summary of Patients with Two Anchoring Sleeves**	
Number of Patients	439
Number, % Male **Number, % Female**	354 80.6% 85 19.4%
Mean Age	61.2 yrs
Primary Indication: **SCD** **VT** **SCD/VT**	 137 31.2% 268 61.1% 34 7.7%
Coronary Artery Disease	324 73.8%
Mean Ejection Fraction	32.5% (N=390)

Table IB3-5: PCD System Data Summary for Patients with Two Anchoring Sleeves -2/1/93

Of these 439 patients, 292 have completed their 1 month follow-up and 195 have completed their 3 month follow-up and 17 have completed a 6 month follow-up. Since the introduction of the dual anchoring sleeve the incidence of

lead dislodgement has been dramatically reduced. There has been 13 dislodgements in 10 patients for a per patient incidence of dislodgement of 2.3% (10/439).

U.S. versus International

Table IB3-6 contains a summary of the complications and observations for the U.S. patients versus the Internal patients.

PCD Transvene System
Reported Complications/Observations
By Category - U.S. and International

Category	Complications		Observations	
	Num (% of Pts)		Num (% of Pts)	
	U.S.	Int'l	U.S.	Int'l
Increased Defibrillation Requirements	6 (1.4%)	3 (1.0%)	4 (0.9%)	4 (1.3%)
Inappropriate VF Therapy Delivery	-	-	3 (0.7%)	11 (3.5%)
Inappropriate VT Therapy Delivery	-	-	19 (4.3%)	38 (12.1%)
Loss of Capture	4 (0.9%)	2 (0.6%)	4 (0.9%)	9 (2.9%)
Oversensing	-	-	31 (7.0%)	21 (6.7%)
Undersensing	-	-	-	-
Skin Erosion	1 (0.2%)	4 (1.3%)	1 (0.2%)	-
Pocket Infection	12 (2.7%)	12 (3.8%)	7 (1.6%)	3 (1.0%)
Seroma	4 (0.9%)	2 (0.6%)	1 (0.2%)	13 (4.1%)
Hematoma	4 (0.9%)	2 (0.6%)	6 (1.4%0	11 (3.5%)
Pneumothorax	1 (0.2%)	1 (0.3%)	1 (0.2%)	-
Pacemaker Syndrome	-	-	2 (0.5%)	-
Perforation	4 (0.9%)	2 (0.6%)	-	-
Subclavian Vein Thrombosis	1 (0.2%)	-	2 (0.5%)	1 (0.3%)
Lead Fracture	5 (1.1%)	4 (1.3%)	-	-
Subcutaneous Patch Crinkling	-	7 (2.2%)	3 (0.7%)	2 (0.6%)
Early Device Explant	4 (0.9%)	-	-	-
Total Lead Dislodgement	53 (12.0%)	33 (10.5%)	6 (1.4%)	6 (1.9%)
Total	99	72	90	119

Table IB3-6: PCD Transvene System: Reported Complications and Observations - 2/1/93

4. Summary of Patient Deaths

The positive impact of implantable cardioverter defibrillator (ICD) therapy on sudden cardiac death mortality has been well documented in the medical literature. The use of device therapy for the treatment of recurrent ventricular arrhythmias has become an accepted and important clinical tool. An analysis of the sudden cardiac death and overall survival in the PCD Transvene System patient population was performed based on the categorization by the investigators and subsequently reviewed by the Clinical Event Review Committee (CERC).

For purposes of the clinical study, each of the patient deaths was categorized using the following definitions:

Non-Cardiac:	Deaths that occurred where the primary cause of death was determined to be non cardiac in nature, e.g. stroke, cancer, etc.
Cardiac:	Deaths that occurred where the primary cause of death was determined to be cardiac in nature.
Non-Sudden:	Deaths that occur greater than one hour after the onset of symptoms.
Sudden:	Deaths that occur within one hour of the onset of symptoms or where the death is unwitnessed. Sudden cardiac deaths were also categorized as being **Witnessed** or **Unwitnessed**.
Perioperative:	Deaths that occur within thirty days of implant.
System Related:	A death which results from a malfunction (operation not according to design specification) of a PCD System component, or as a result of a device induced arrhythmia, or an interaction between a PCD System component and the patient.
Procedure Related:	A death which occurs as a result of a procedure required to implant, follow or test a PCD System.

All deaths and significant complications have been and will continue to be reviewed by a committee comprised of PCD Transvene System investigators and other physicians. Two committees (Clinical Event Review Committees) have been formed, one to review North American deaths and complications, and the other to review European clinical events. The primary purpose of these reviews was to determine whether the PCD System was related to the deaths or significant complications that have occurred and, if so, what changes may be required to prevent such events in the future.

There have been a total of 51 patient deaths reported in the PCD Transvene System patient population. Table IB4-1 summarizes how these patient deaths have been classified.

PCD Transvene System
Summary of Death Classifications
(n = 757)

Classifications	Number of Deaths
Sudden Cardiac	5
Non-Sudden Cardiac	31
Noncardiac	15
TOTAL	51

Table IB4-1: PCD Transvene System - Summary of Death Classifications - 2/1/93

None of the patient deaths were attributed to a malfunction of the PCD Transvene System.

Actuarial survival analysis on the PCD Transvene System was done on all patients who were either evaluated for implantation or in whom the device was implanted. Thus, the analysis is done from the perspective of **intention to treat**. Those patients in whom the PCD Device was OFF at the time of death or in whom no device was implanted **are** included in the survival analysis. Those patients that were screened for a PCD Transvene System but failed to receive a Transvene system and received a Medtronic Epicardial system are also included in this analysis.

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Projected one year survival calculations for the various death classifications are provided in Table IB4-2. **The actuarial projections include perioperative deaths only in the calculation of one year survival from death due to all causes (shown in the row labelled Overall).** The perioperative death rate defined as deaths which occurred within thirty days of implant was 0.7% (5/757) which is considerably less than the perioperative mortality for the PCD System with Epicardial leads (5.3% - 39/742). Included in this table are the projected one year survival calculations for patients who ultimately received a PCD Transvene System (n = 757) and all patients that were screened for a PCD Transvene System (n = 854) regardless of implant outcome. The outcome of the 854 patients screened for a PCD Transvene System are described more fully in section IC2.

PCD Transvene System One Year Actuarial Survival		
	Received a Transvene System (N = 757)	**Screened for a Transvene System (n = 854)**
Sudden Cardiac Death	99.5%	99.4%
Non-Sudden Cardiac	96.2%	96.6%
All Cardiac	95.8%	96.1%
Noncardiac	98.1%	98.3%
Perioperative	0.7%	1.6%
Overall	93.3%	92.9%

Table IB4-2: PCD Transvene System - One Year Actuarial Survival - 2/1/93

The positive impact of the PCD Transvene System on patient mortality is clearly obvious from this analysis. The sudden cardiac death survival rate in this patient group is 99.5% for those in the patient group that received a Transvene System and 99.4% for those who were screened for a Transvene System. This is marked improvement when compared with the reported survival of similar patient groups treated with drug therapy alone of between 34% and 73% at one year.

C. Specific Patient Populations

1. Clinical Experience By Primary Indication

Medtronic is requesting approval for use of the PCD Transvene System in the following patient population:

* Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or

* Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

Note: These patient indications are identical to those approved for the Medtronic PCD Epicardial System.

Sudden cardiac death without recurrent VT (**SCD**) was the indication for implant in 37.1% of the patients, recurrent ventricular tachycardia without an episode of sudden cardiac death (**VT**) was the indication for implant in 49.8% of the patients, and sudden cardiac death and recurrent VT (**SCD/VT**) was the indication for implant in 13.1% of the patients.

The performance of the PCD Transvene System in these three groups are summarized in Table IC1-1.

In all three patient groups, coronary artery disease was the predominant heart disease and the patients exhibited moderate left ventricular dysfunction as demonstrated by mean ejection fractions of less than 40%. The mean LED at the time of implant was similar among the patient groups as was the mean DFT.

The overall efficacy in terminating spontaneous VT/VF episodes in the SCD patient group was 98.4%, in the VT patient group 98.3%, and in the SCD/VT group 99.1%. Thus, independent of the indication for implant, the PCD Transvene System was highly effective in terminating spontaneous episodes of VT/VF.

The one year sudden cardiac death survival rates for all groups was greater than 98.6%

This analysis indicates that the PCD Transvene System has performed safely and effectively in the indicated patient groups and should be approved for use in the indicated patient population.

PCD Transvene System
Data Summary by Primary Indication

	SCD	VT	SCD/VT	All Patients
# of Patients	281 (37.1%)	377 (49.8%)	99 (13.1%)	757
Number, % Male Number, % Female	212 75.4% 69 24.6%	309 82.0% 68 18.0%	89 89.9% 10 10.1%	610 80.6% 147 19.4%
Mean Age	56.8 yrs	61.2 yrs	60.0 yrs	59.4 yrs
Coronary Artery Disease	191 68.0%	292 77.5%	78 78.8%	229 72.2%
Mean Ejection Fraction	39.1% (N=259)	33.7% (N=339)	32.5% (N=90)	35.6% (N=688)
Defibrillation Pathway: Sequential Simultaneous Single	 201 71.5% 74 26.3% 6 2.2%	 295 77.6% 82 21.6% 3 0.8%	 76 76.8% 22 22.2% 1 1.0%	 574 75.3% 178 23.4% 10 1.3%
Mean LED	15.3J (N=264)	16.2J (N=351)	17.3J (N=87)	16.0J (N=702)
Mean DFT	14.0J (N=117)	15.5J (N=155)	13.9J (N=44)	14.8J (N=316)
Spontaneous VT: # of Patients # of Episodes % Success	 58 1157 99.2%	 206 7591 98.1%	 52 1279 99.0%	 316 10027 98.4%
Spontaneous VF: # of Patients # of Episodes % Success	 107 686 96.9%	 162 916 99.1%	 48 380 99.5%	 317 1982 98.4%
1 Year SCD Survival	100.0%	99.4%	98.6%	99.5%

Table IC1-1: PCD Transvene System Data Summary by Primary Indication - 2/1/93

2. Patients Not Meeting Implant Criteria

a. Overview

For purposes of the PCD Transvene System, the implant criteria was defined as successful VF termination at least 3 times in 4 attempts with the final lead configuration with an output energy of 18 Joules or less.

A total of 897 patients had an evaluation of a PCD Transvene System and are divided into the following groups: (1) patients who received a PCD Transvene System, (2) patients screened for a PCD Transvene System and received a PCD Epicardial System, and (3) patients who received a non-standard lead system. Figure 1 provides an overview of the outcome of these patients.

As can be seen, 88.6% (757/854) of the patients who were screened for a PCD Transvene System ultimately received a 3 lead system. Of these 757 patients, 71.7% (543 patients) met the recommended defibrillation implant criteria, which compares favorably with the predicted success rates published in the literature (Wilber et al). However, 28.3% (214/757) of the patients did not meet the recommended defibrillation efficacy implant criteria and still received the PCD Transvene System.

Ninety-seven (97) patients (10.8%) were screened for a Transvene lead system but received an epicardial system. Forty-three (43) patients (4.8%) were screened for a Transvene lead system but received an non-standard system.

PCD TRANSVENE SYSTEM IMPLANT EVALUATION

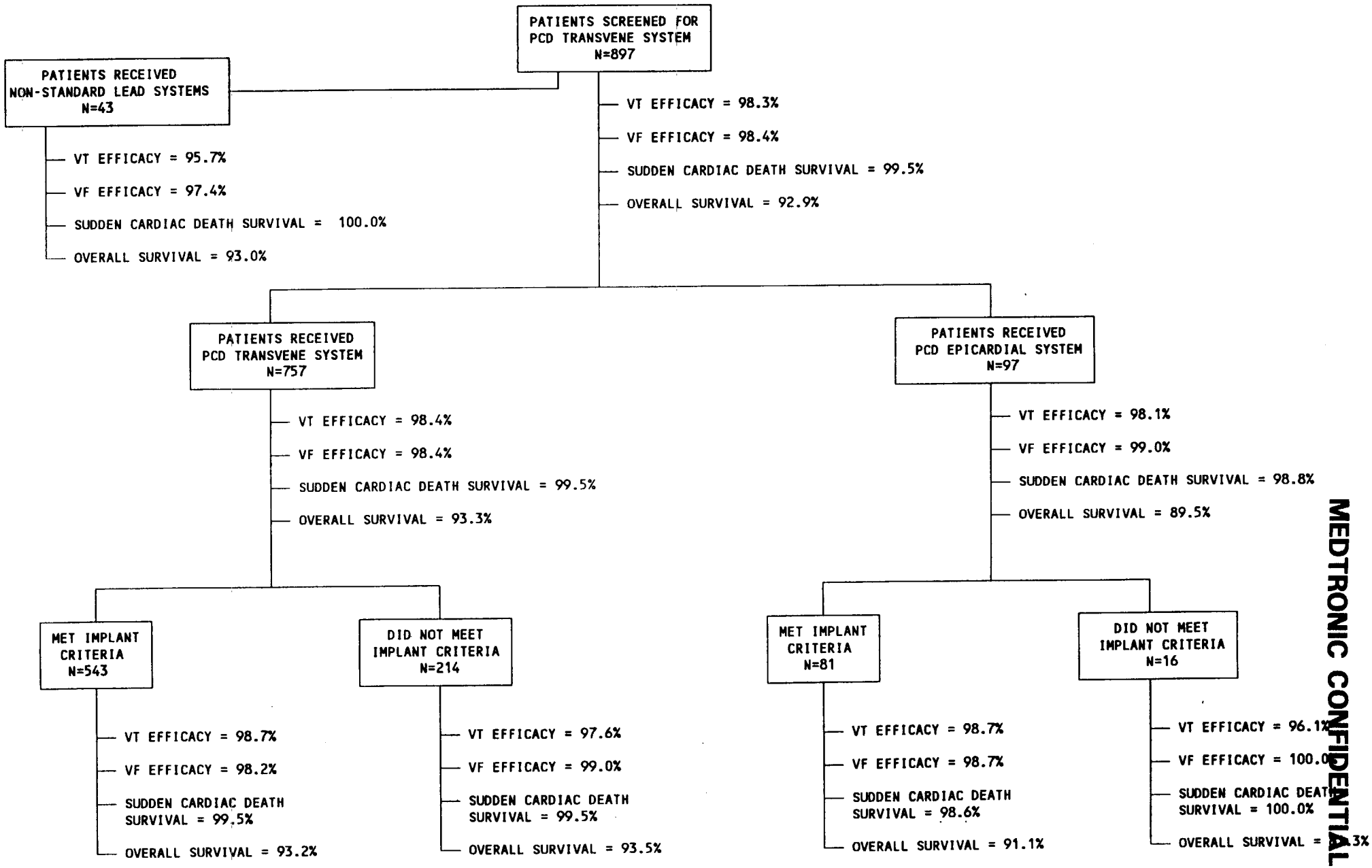

Figure 1: Patients Screened for a Transvene System

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a. **Overview**

The physician's justification for implanting the PCD Transvene System despite not meeting the recommended defibrillation implant criteria are presented in Table IC2-1. As noted previously, the patients not meeting implant criteria (N = 214) were divided into three groups (1) Successful defibrillation at an energy level of equal to or less than 24 Joules (79.4% of the patients); (2) Difficult to induce VF (11.2% of the patients); and (3) Implant procedure terminated due to poor patient condition (9.4% of the patients).

PCD Transvene System
Reasons for Not Meeting Implant Criteria
Physician Justification

Reason	Number of Patients (% of Total)
Success at $\leq$ 24 Joules	170 (79.4%)
Difficult/Unable to Induce VF	24 (11.2%)
Patient Condition	20 (9.4%)
Total	214

Table IC2-1: PCD Transvene System: Physician Justification for Not Meeting Implant Criteria - 2/1/93

Table IC2-2 contains the patient characteristics of the patients not meeting implant criteria presented by physician justification.

PCD Transvene System Patients Not Meeting Implant Criteria by Justification			
	Success at ≤ 24 Joules	Difficult/Unable to Induce VF	Patient Condition
Number of Patients	170	24	20
Mean Follow-Up	9.6 months	9.8 months	14.4 months
Male Female	151 (88.8%) 19 (11.2%)	19 (79.2%) 5 (20.8%)	18 (90.0%) 2 (10.0%)
Mean Age	59.8 yrs	57.5 yrs	60.0 yrs
Indication SCD VT SCD/VT	 63 (37.1%) 77 (45.3%) 30 (17.6%)	 6 (25.0%) 13 (54.2%) 5 (20.8%)	 3 (15.0%) 9 (45.0%) 8 (40.0%)
Cardiovascular History CAD Cardiomyopathy	 132 (77.7%) 58 (34.1%)	 19 (79.2%) 2 (8.3%)	 14 (70.0%) 5 (25.0%)
Mean EF	32.7%	37.7%	36.8%
NYHA Class I II III IV	 45 (27.6%) 90 (55.2%) 24 (14.7%) 4 (2.5%)	 5 (22.7%) 14 (45.5%) 7 (31.8%) 0	 2 (10.0%) 10 (70.0%) 4 (20.0%) 0

Table IC2-2: PCD Transvene System: Patient Characteristics by Justification - 2/1/93

Table IC2-3 contains the clinical outcomes the patients not meeting implant presented by physician justification.

PCD Transvene System Patients Not Meeting Implant Criteria 170 Patients with Successful Defibrillation at 24J			
	Success at ≤ 24 Joules	Difficult/Unable to Induce VF	Patient Condition
Number of Patients	170	24	20
Spontaneous VT Episode Efficacy	2206/2240 98.5%	129/159 81.1%	372/376 98.9%
Spontaneous VF Episode Efficacy	522/525 99.4%	100/102 98.0%	48/50 96.0%
Number of Patient Deaths	10/170 5.9%	1/24 4.2%	2/10 10%
Perioperative Mortality	1/170 0.6%	0	0
One Year Survival			
Sudden Cardiac	99.4%	100.0%	100.0%
Non-Sudden Cardiac	98.7%	100.0%	85.5%
All Cardiac	98.1%	100.0%	85.5%
Noncardiac	96.3%	100.0%	100.0%
Overall	94.0%	100.0%	85.5%

Table IC2-3: PCD Transvene System: Patients Not Meeting Implant by Justification - Clinical Outcome - 2/1/93

In summary, the physician made an appropriate judgement to implant the PCD Transvene system based on the clinical outcome of the patient especially those patients with a 10 Joule safety margin. Their outcome is clinically equivalent to that of the entire 757 patient population.

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1) **Lowest Energy of Defibrillation < 24 Joules**

There were 170 patients in whom the PCD Transvene System was implanted with a defibrillation safety margin of at least 10 Joules. Table IC2-4 provides an overview of these patients clinical experience.

These data indicate that the final implanted PCD Transvene System was evaluated and significant attempts were made to meet the recommended implant criteria. In most of these patients (79.4%), a safety margin of 10 Joules was obtained between the successful defibrillation energy (24 J or less) for ventricular fibrillation and the maximum output of the PCD Device (34 J). The investigators decided in certain circumstances that this was appropriate demonstration of device effectiveness and that the PCD Transvene System could be implanted.

Of these patients, 159 (93.5%) have had VT or VF induced at a chronic follow-up visit and in each case, VT or VF was successfully terminated by the PCD Transvene System. In addition, 65 patients (38.2%) have experienced a spontaneous VF episode with an overall efficacy of 99.4%.

Thus, the clinical outcome in these patients was not adversely affected by not meeting implant criteria since their spontaneous VF episode efficacy was 99.4% and the one year sudden cardiac death actuarial survival was also 99.4%. The duration of follow up, an average of 9.7 months, is similar to that of the entire patient group (11.7 months).

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PCD Transvene System Patients Not Meeting Implant Criteria 10J Safety Margin Provided	
Number of Patients	170
Lowest Energy of Defibrillation	
1 Success with 10J Safety Margin	87
2 Success with 10J Safety Margin	58
3 Success with 10J Safety Margin	18
> 3 Success with 10J Safety Margin	7

Table IC2-4: PCD Transvene System: Patients Not Meeting Implant Criteria with 3/4 Successes at ≤ 24 Joules Clinical Experience - 2/1/93

2) Difficult or Unable to Induce VF

There were 24 patients who did not meet the recommended PCD Transvene System implant criteria because at least three episodes of VF were not induced at the time of implant. Of these, 15 patients had ventricular tachycardia induced and successfully reverted. The remaining 9 patients had ventricular flutter induced and successfully reverted. In all 24 patients, the lowest successful energy was equal to or less than 18 Joules.

The indication for implant was sudden cardiac death (SCD) in 6 patients (25%), recurrent ventricular tachycardia (VT) in 13 patients (54.2%) and sudden cardiac death associated with recurrent ventricular tachycardia (SCD/VT) in 5 (20.8%) patients. Thus the majority of the patients, 75%, had documented recurrent ventricular tachycardia as part of their ventricular tachyarrhythmia history. Eight of these patients (33.0%) were on Amiodarone therapy which may have contributed to the inability to induce VF.

Of the 24 patients who did not meet the recommended PCD Transvene System implant criteria because at least three episodes of VF were not induced at the time of implant, 13 patients (54.2%) have experienced a spontaneous VF episode

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and 21 patients (87.5%) have had VT or VF induced during a chronic follow-up. In all cases, VF was successfully reverted by the PCD Transvene System.

There has been one reported patient death (b)(6) in this patient group (at xx months) with a resultant one year sudden cardiac death and overall actuarial survival of 100%.

3) Patient Condition

There were 20 patients in whom the implant procedure was terminated due to poor patient condition. These patients received a PCD Transvene System without at least a 10 Joule defibrillation safety margin. The implant circumstances of these patients are summarized as follows:

- At least one successful defibrillation was obtained at an energy level greater than 24 Joules but less than 34 Joules (N = 11 patients);
- Multiple inductions of VT were performed and successfully reverted with an energy level of 18 Joules or less. However, induced VF was not successfully reverted by an energy level of less than or equal to 34 Joules (N = 6 patients); and
- Physician elected to terminate the procedure due to the patient's condition before inductions with the final implanted lead configuration were performed (N = 3 patients).

The mean ejection fraction of this group was 26.9%, indicating more severe underlying cardiovascular disease, and may have contributed to the physicians decision to terminate the implant procedure prior to meeting implant criteria. This group had a mean of 6.8 VF inductions, 2.2 lead configurations evaluated and a mean duration of VT/VF for the implant procedure of 220 total seconds. The circumstances of the implant procedures, mainly the duration of induced ventricular tachyarrhythmia and associated hemodynamic compromise, limited the number of inductions that could be performed and whether the recommended implant criteria could be met.

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Of these 20 patients, VT or VF has been induced at a chronic follow-up visit in 16 patients (80%) and in all cases successful defibrillation with the implanted PCD Transvene System was documented.

The overall spontaneous VF episode efficacy for this patient group was 96.0%. However, examination of events indicated that one patient experienced multiple episodes of atrial fibrillation that was detected as VF and in whom all four programmed VF therapies were ineffective. This patient's antiarrhythmic drug therapy was modified and there were no further reports of ineffective therapies.

Thus there have been no patients who have experienced an actual spontaneous VF episode where all four programmed VF therapies failed to terminate the episode.

There have been two reported patient deaths, Patient ID (b)(6) which was classified as non-sudden cardiac secondary to end stage heart failure and Patient ID (b)(6) which was also classified as non-sudden cardiac. The one year sudden cardiac death survival in this patient population is 100% while the overall one year survival was 85.5%. This lower overall one year survival may be due to the lower mean ejection fraction of this patient group.

The VF Therapy efficacy and SCD survival in these twenty patients was not adversely affected by not meeting implant criteria since there was no reports of failure to terminate a spontaneous VF episode and the overall one year sudden cardiac death survival was 100%.

c. **Complications and Observations: Patients Not Meeting Implant Criteria**

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following previously described definitions:

COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

Of the 170 patients with successful defibrillation at 24 Joules, as of February 1, 1993, there have been a total of 41 complications reported in 33 patients and 34 observations reported in 31 patients in the PCD Transvene System patient population. Thus, 19.4% (33/170) of the patients had a clinical event reported which was categorized as a complication and 18.2% (31/170) of the patients had a clinical event reported which was categorized as an observation. The percent of patients with complications reported in the overall population of 757 patients was 19.4% (147/757), the same percentage as in this subgroup of 170. There were 23.8% (180/757) of the patients in the overall population with reported observations, a slightly higher percentage than in this subgroup of 170 patients.

Of the 24 patients that did not meet the implant criteria due to difficulty or inability to induce sustained VF, as of February 1, 1993, there have been a total of 4 complications reported in 4 patients and 10 observations reported in 8 patients in the PCD Transvene System patient population. Thus, 16.7% (4/24) of the patients had a clinical event reported which was categorized as a complication and 30.0% (8/24) of the patients had a clinical event reported which was categorized as an observation.

Of the 20 patients that did not meet the implant criteria due to patient condition, as of February 1, 1993, there have been a total of 6 complications reported in 4 patients and 7 observations reported in 5 patients in the PCD Transvene System patient population. Thus, 20.0% (4/20) of the patients had a clinical event reported which was categorized as a complication and 25.0% (5/20) of the patients had a clinical event reported which was categorized as an observation.

Table IC2-5 and IC2-6 summarizes the reported PCD Transvene System complications and observations by category in these 3 patient groups, respectively. The reported complications and observations are recognized clinical events that may occur with **any** of the current ICD devices. These complications and observations are discussed in the PCD device and Transvene manual. **None of the reported complications or observations have resulted in a patient death.**

PCD Transvene System Reported Complications Patients Not Meeting Implant Criteria by Justification			
Justification	**Success at ≤ 24 Joules n=170**	**Difficult/Unable to Induce VF n=24**	**Patient Condition n=20**
	Num (% of Pts)	Num (% of Pts)	Num (% of Pts)
Increased Defibrillation Requirements	5 (2.9%)	-	-
Inappropriate VF Therapy Delivery	-	-	-
Inappropriate VT Therapy Delivery	-	-	-
Loss of Capture	-	-	-
Oversensing	-	-	-
Undersensing	-	-	-
Skin Erosion	-	1 (4.2%)	1 (5.0%)
Pocket Infection	3 (1.8%)	-	3 (15.0%)
Seroma	2 (1.2%)	-	-
Hematoma	1 (0.6%)	-	-
Pneumothorax	-	-	-
Pacemaker Syndrome	-	-	-
Perforation	1 (0.6%)	-	-
Subclavian Vein Thrombosis	1 (0.6%)	-	-
Lead Fracture	2 (1.2%)	-	1 (5.0%)
Subcutaneous Patch Crinkling	2 (1.2%)	-	-
Early Device Explant	1 (0.6%)	-	-
Total Lead Dislodgement	23 (13.5%)	3 (12.5%)	1 (5.0%)
Total	**41**	**4**	**6**

Table IC2-5: PCD Transvene System: Reported Complications - By Justification - 2/1/93

PCD Transvene System Reported Observations Patients Not Meeting Implant Criteria by Justification			
Justification	**Success at ≤ 24 Joules n=170**	**Difficult/Unable to Induce VF n=24**	**Patient Condition n=20**
	Num (% of Pts)	Num (% of Pts)	Num (% of Pts)
Increased Defibrillation Requirements	-	1 (4.2%)	-
Inappropriate VF Therapy Delivery	-	-	1 (5.0%)
Inappropriate VT Therapy Delivery	10 (5.9%)	3 (12.5%)	2 (10.0%)
Loss of Capture	5 (2.9%)	1 (4.2%)	-
Oversensing	7 (4.1%)	4 (16.7%)	-
Undersensing	-	-	2 (10.0%)
Skin Erosion	-	-	-
Pocket Infection	2 (1.2%)	-	-
Seroma	3 (1.8%)	-	-
Hematoma	2 (1.2%)	1 (4.2%)	1 (5.0%)
Pneumothorax	-	-	-
Pacemaker Syndrome	-	-	-
Perforation	-	-	-
Subclavian Vein Thrombosis	1 (0.6%)	-	1 (5.0%)
Lead Fracture	-	-	-
Subcutaneous Patch Crinkling	1 (0.6%)	-	-
Early Device Explant	-	-	-
Total Lead Dislodgement	3 (1.8%)	-	-
Total	**34**	**10**	**7**

Table IC2-6: PCD Transvene System: Reported Observations - By Justification - 2/1/93

d) Comparison of Patients Not Meeting Implant Criteria Versus those Patients who Met the Implant Criteria

Table IC2-7 provides a comparison of patient characteristics between patients who met the PCD Transvene System implant criteria and those patients who did not meet the implant criteria but still received the PCD Transvene System. The characteristics of the 97 patients that were screened for a PCD Transvene system and received an Epicardial system if also provided.

PCD Transvene System
Patients Meeting Implant Criteria
versus
Patients Not Meeting Implant Criteria

Patient Characteristics

Data	Met Criteria	Did Not Meet Criteria	Received EPI
Number of Patients	543	214	97
Mean Follow-Up	12.3 months	10.1 months	12.3 months
Male* Female	422 (77.7%) 121 (22.35)	188 (87.9%) 26 (12.1%)	88 (90.7%) 9 (9.3%)
Mean Age	59.4 yrs	59.6 yrs	58.0 yrs
Indication SCD VT SCD/VT	 209 (38.5%) 278 (51.2%) 56 (10.3%)	 72 (33.6%) 99 (46.3%) 43 (20.1%)	 33 (34.0%) 52 (53.6%) 12 (12.4%)
Cardiovascular History CAD Cardiomyopathy	 396 (72.9%) 173 (31.9%)	 165 (77.1%) 65 (30.4%)	 74 (76.3%) 28 (28.9%)
Mean EF	36.3%	33.7%	32.6%
NYHA Class I II III IV	 164 (30.9%) 278 (52.4%) 82 (15.4%) 7 (1.3%)	 53 (25.8%) 114 (56.6%) 34 (16.6%) 4 (2.0%)	 28 (29.5%) 52 (54.7%) 13 (13.7%) 2 (2.1%)
Number ON Drugs at Implant Number ON Amiodarone	223 (41.1%) 78 (14.4%)	97 (45.3%) 38 (17.8%)	40 (41.2%) 19 (19.6)

Table IC2-7: PCD Transvene System: Patients Meeting Implant Criteria vs Not Meeting Implant Criteria - Comparison of Pt Characteristics - 2/1/93

Statistical analysis was completed on the 543 patients that net implant criteria versus the 214 patients that did not meet criteria. Statistical analysis indicated three significant differences between these two patient groups - patient sex, indication for implant and mean ejection fraction.

Patients not meeting implant criteria had a statistically higher percentage of patients who were male ($p = 0.002$). This difference reflects that the majority of patients with coronary disease with concomitant life threatening ventricular arrhythmias are males.

Analysis indicated the patients not meeting the implant criteria had a statistically higher percentage of patients whose primary indication for implant was sudden cardiac death associated with recurrent ventricular tachycardia ($p = 0.002$). This difference reflects the physicians use of the PCD Transvene System.

Finally, patients who did meet the implant criteria had a statistically lower mean ejection fraction ($p = 0.0342$) which reflects a higher degree of underlying cardiovascular disease in these patients.

It should be noted, that none of these differences should be used as predictors for patients who should be screened for a PCD Transvene System.

Implant data obtained in these two patient groups is presented in Table IC2-8. As would be expected the patients not meeting the implant criteria had higher mean DFT and LED values when compared to the patients who did meet the implant criteria. However, the mean DFT (18.8J) and LED (19.5J) values obtained in patients not meeting implant criteria provided at least a 10 Joule defibrillation safety margin between the successful energy and the maximum output of the PCD Device (34J) in nearly all (97.4%) of the patients.

PCD Transvene System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Implant Data		
Data	**Meeting Criteria**	**Not Meeting Criteria**
Number of Patients	543	214
Mean Number of Inductions	7.0	8.2
Number of Configurations	2.0	2.7
Mean DFT	13.4J	18.8J
Mean LED	14.8J	19.5J
Implanted Lead System		
RV-SVC-SQ	351 (64.6%)	145 (67.8%)
RV-CS-SQ	159 (29.3%)	63 (29.4%)
RV-CS-SVC	33 (6.1%)	6 (2.8%)
Defibrillation Pathway		
Sequential	414 (75.7%)	160 (74.4%)
Simultaneous	127 (23.2%)	51 (23.7%)
Single	6 (1.1%)	4 (1.9%)

Table IC2-8: PCD Transvene System: Patients Not Meeting Implant Criteria versus Patients Meeting Implant Criteria - Comparison of Implant Data - 2/1/93

When the mean number of inductions and the mean number of configurations tested of 8.2 and 2.7, respectively, for those patients that did not meet the implant criteria is compared to those that did meet the implant criteria, 7.0 and 2.0, it is apparent the implanting physicians did induce more VF and were more likely to try more than 1 lead configuration in an attempt to meet the implant criteria.

In order to determine if the patient's not meeting implant criteria had higher risk for morbidity and mortality, a comparison of their clinical outcome was made with those patients who did meet the implant criteria. This comparison is provided in Table IC2-9.

PCD Transvene System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Implant Data		
Data	**Meeting Criteria**	**Not Meeting Criteria**
Number of Patients	543	214
Spontaneous VT Episode Efficacy	98.7%	97.6%
Spontaneous VF Episode Efficacy	98.2%	99.0%
Number of Patient Deaths	37	14
Perioperative Mortality	0.7%	0.5%
One Year Survival		
Sudden Cardiac	99.5%	99.5%
Non-Sudden Cardiac	95.8%	97.2%
All Cardiac	95.4%	96.7%
Noncardiac	98.5%	97.1%
Overall	93.2%	93.5%

Table IC2-9: PCD Transvene System: Patients Not Meeting Implant Criteria versus Patients Meeting Implant Criteria - Comparison of Clinical Outcome - 2/1/93

The two patient groups had similar efficacy in the treatment of spontaneous VT/VF episodes. Importantly, in the patient population who did not meet the implant criteria there were no patients who experienced actual spontaneous VF episodes where all programmed PCD Device therapies failed to terminate the episode.

Five patients experienced 7 episodes in which the PCD® Device was ineffective in terminating a spontaneous episode of VF despite delivery of all four programmed VF therapies. Three patients had 5 reported ineffective VF spontaneous episodes that were due to sinus tachycardia or atrial fibrillation with rapid ventricular response rather than VF. Reprogramming and pharmacologic intervention resolved these problems.

Two patients experienced 2 episodes in which the PCD detected the episodes as VF but were actually episodes due to extraordinary circumstances. The first patient (b)(6)

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had incessant episodes of fast VT (cycle length 280 ms) that were eventually resolved by drugs. The second patient (b)(6) was in the hospital and there was an episode of VF detected by the PCD and therapy was delivered. However, the device was interrogated before termination of the episode was detected by the PCD. There was external intervention (transthoracic defibrillation) associated with the terminal event. However, the patient ultimately expired. The device was not interrogated again.

Eighteen patients experienced 68 episodes in which the PCD Device was ineffective in terminating a spontaneous episode of VT despite delivery of all four programmed VT therapies. Nine patients experienced 44 ineffective episodes that were due to sinus tachycardia or atrial fibrillation/flutter (SVT) with a rapid ventricular response that had been detected as VT. These episodes were resolved with either modification of programmed parameters or of antiarrhythmic drug therapy. It should be noted that the PCD Device responded appropriately based on the programmed detection parameters.

The remaining 24 episodes occurred in 8 patients in which the programmed VT therapies were ineffective in terminating a spontaneous VT episode. **No patient deaths occurred as a result of ineffective VT therapy.** Reprogramming and pharmacologic intervention resolved these events.

There was no difference in the one year sudden cardiac survival or the overall survival in the two groups although follow-up was shorter for patients not meeting implant criteria (10.1 vs 12.3 months). This indicates, that despite not meeting the implant criteria these patients were not at higher risk of sudden cardiac death.

Conclusion

In conclusion, 214 patients received the PCD Transvene System despite not meeting the recommended implant criteria. These 214 patients are divided into the following groups:

- successful defibrillation of VF at 24 Joules or less (170/214),
- difficult to induce at least three episodes of VF at implant (24/214), and
- worsening patient condition which prevented further inductions (20/214).

It should be noted that 91% (194/214) of the patients not meeting the recommended implant criteria had at least one successful termination of induced ventricular tachyarrhythmia (VT, VFlutter or VF) at 24 Joules or less. Additionally, their clinical outcome, especially in the 170 patients with successful defibrillation of VF at $\leq$24 Joules is similar and is part of the support to request changing the implant criteria to the following:

* Two consecutive successful defibrillations with the final lead configuration with a stored output of 24 Joules or less; or
* Three successful defibrillations in four attempts with the final lead configuration at a stored output energy of 24 J or less.

D. System Comparison

The efficacy and safety of implantable cardioverter defibrillator (ICD) therapy for recurrent ventricular tachycardia (VT) and ventricular fibrillation (VF) has been well established. The Ventak-P Epicardial System provides cardioversion and defibrillation therapy for VT and hemodynamically unstable VT. However, this type of therapy may not be optimal for patients with stable, well tolerated VT that is amenable to antitachycardia pacing due to the pain associated with cardioversion shock therapy. The need to incorporate programmability, multiple detection and therapeutic options has lead to the development of the PCD Device.

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However, the Ventak-P Epicardial System and PCD Epicardial System are implanted only with a defibrillation lead system requiring a thoracotomy. The PCD Transvene System allows the implantation of an ICD System without the potential increased perioperative morbidity and mortality associated with a thoracotomy. This allows the application of ICD therapy in patients who may not otherwise be candidates for this type of therapy.

In the PCD Transvene System PMA Application a comparison of the PCD Transvene System clinical experience was made to both the Ventak-P Epicardial System and the PCD Epicardial System. (Reference: Clinical Experience Report Section X, Comparison to AICD Clinical Results and Section XI, Comparison to PCD Epicardial System Clinical Results). A comparison to the Ventak-P Epicardial System was done because this was the most similar FDA approved ICD System available at the time of the original submission. A comparison to the PCD Epicardial System was done since this system incorporated the same tiered therapy ICD Device as well as being a concurrent clinical study using the same protocol and clinical investigators.

The comparison between the Ventak-P Epicardial System and the PCD Transvene System was limited in scope due to the limited availability of clinical data from the Ventak-P Epicardial System Summary of Safety and Effectiveness, but included patient characteristics, implant defibrillation thresholds, incidence of spontaneous VT/VF episodes, incidence of complications and one year actuarial survival.

The comparison between the PCD Transvene System and the PCD Epicardial System included patient characteristics, implant data, implant defibrillation thresholds, programmed parameter status, spontaneous VT/VF episode efficacy, incidence of complications and observations and one year actuarial survival.

1. **Comparison to AICD (Ventak-P) Epicardial System**

   The current AICD (Ventak-P) Epicardial System is implanted only with a defibrillation lead system requiring a thoracotomy. The PCD Transvene System allows the implantation of an implantable cardioverter defibrillator (ICD) system without the potential increased perioperative morbidity and mortality associated with a thoracotomy.

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This allows the application of ICD therapy in patients who may not otherwise be candidates for this type of therapy. Though the PCD Transvene System will have complications and observations that are specific to the lead system, the overall performance should be at least equivalent to that reported with the current AICD Epicardial System.

This section provides a comparison of the PCD Transvene System clinical experience to that of the reported AICD Epicardial System clinical experience. The following areas will be discussed:

- Patient characteristics
- Clinical performance
- Survival analysis

For purposes of comparison, the Ventak-P Epicardial System patient population described in the Summary of Safety and Effectiveness Data (PMA Application Number P890061) dated May 2, 1991 will be used. A copy of this summary was obtained through the Freedom of Information Act.

a. Patient Characteristics

In comparing the clinical experience with the PCD Transvene System to the reported Ventak-P Epicardial System clinical experience, it is important to determine that the patients who received the device are comparable.

The characteristics of the patients receiving the PCD Transvene System were compared to the characteristics of patients discussed in the Ventak-P Summary of Safety and Effectiveness Data and are presented in Table ID1-1.

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PCD Transvene System Comparison of Patient Characteristics PCD versus AICD		
	PCD	**Ventak-P**
Number of Patients	757	292
Mean Follow-Up Time	11.7 months	6.8 months
% Males **% Females**	610 (81%) 147 (19%)	231 (79%) 61 (21%)
Mean Age	59.4 years	61.5 years
Primary Indication: **SCD** **VT** **SCD/VT**	 281 (37%) 377 (50%) 99 (13%)	 49 (16%) 169 (59%) 73 (25%)
Coronary Artery Disease	561 (74%)	228 (78%)
Mean Ejection Fraction	35.6%	34%
Drug Therapy at Implant	42%	45.0%
Concomitant Surgery	0%	18.0%

Table ID1-1: Comparison of Patient Characteristics, PCD versus Ventak-P 2/1/93

The two patient groups are comparable in mean age and mean ejection fraction. Both groups had moderately depressed left ventricular function demonstrated by the mean ejection of 35.6% for the PCD Transvene System patient group and 34% for the Ventak-P Epicardial System patient group.

Analysis indicated that no statistical differences between the PCD Transvene System and Ventak-P Epicardial System patient populations except in the category of patient indication. There are more patients that had Sudden Cardiac Death as the primary indication in the PCD Transvene population than in the AICD population ($p = 0.001$).

b. Clinical Characteristics

Areas of clinical performance that were compared were implant defibrillation thresholds, incidence of

spontaneous VT/VF events, incidence of complications and patient survival. These specific areas were selected in order to evaluate the system performance in the two patient populations.

1) Implant Defibrillation Thresholds

For the purposes of the PCD Transvene System clinical study, determination of defibrillation threshold was not mandatory. However, the preferred method of evaluating defibrillation efficacy was to determine the defibrillation threshold using a testing sequence of 18J, 15J, 10J, 5J with a failure at any level causing a return to 18 J for the remaining attempts. For the purposes of this report a defibrillation threshold was defined as the energy at the lowest successful defibrillation attempt, provided a patient had a failure below their lowest defibrillation success or a success at $\leq$ 5J. The rhythm treated must have been VF to be included in the analysis.

It should be noted, that it was expected that the PCD Transvene System would have a higher mean defibrillation threshold as compared to a traditional epicardial defibrillation lead system. In a epicardial system, the increased electrode surface area would theoretically decrease defibrillation requirements.

A total of 316 patients had a defibrillation threshold determined at the time of PCD device implant. The mean defibrillation threshold (DFT) for all lead systems was 14.8J. The recommendation for VF Therapy #1 is to program the stored energy to twice the implant DFT or 18 Joules, whichever is greater. Thus an adequate defibrillation safety margin was provided when following the VF therapy programming recommendations.

In the Ventak-P Epicardial System, the mean defibrillation threshold at implant was 13.4J. Thus the two systems had similar defibrillation thresholds at implant despite the fact that one system utilized an epicardial defibrillation lead system while the other utilized a transvenous defibrillation lead system.

These data indicate that the PCD Transvene System had comparable implant defibrillation threshold performance when compared to the reported Ventak-P Epicardial System clinical experience.

2) Incidence of Spontaneous VT/VF Episodes

The incidence of spontaneous VT/VF episodes in the Ventak-P Epicardial System and PCD Transvene System patient population was evaluated by utilizing the stored episode information provided by both devices.

In the Ventak-P device, the total number of shocks delivered to the patient is provided via interrogation of the device. The PCD device provides information on the total number of VT and VF episodes detected by the PCD device and the total number of VT and VF episodes successfully treated by the PCD device as well as the number of VT/VF episodes where the PCD device was ineffective. In addition, the last 20 intervals of the last episode satisfying detection criteria along with the first 10 intervals after the last therapy delivered are recorded by the device. These data assist the physician in evaluating the frequency of VT/VF episodes, the efficacy of the PCD device programmed parameters and the need for reprogramming.

In the Ventak-P Epicardial System experience of 292 patients with a mean follow-up of 6.8 months, 137 (46.9%) received a device countershock in response to a spontaneous

ventricular tachyarrhythmia episode as defined by the Ventak-P Device detection criteria.

In the PCD Transvene System experience of 757 patients with a mean follow-up of 11.7 months, 458 patients (60.5%) have received device therapy in response to a spontaneous ventricular tachyarrhythmia episode as defined by the PCD Transvene System detection criteria.

A total of 10,027 spontaneous VT and 1982 spontaneous VF episodes have been recorded by the PCD device episode counters. Of the 9864 successfully treated spontaneous VT episodes, 91.4% were treated with one of the programmed antitachycardia pacing therapies incorporated in the PCD device. The clinical benefit of tiered therapy is the reduction of delivery of high energy shocks for the treatment of stable recurrent ventricular tachycardia that may be responsive to antitachycardia pacing.

3) Incidence of Complications

Table ID1-2 provides a comparison of reported complications and observations. The AICD clinical experience data is from the Winkle, et al Long Term Outcome with Automatic Implantable Cardioverter-Defibrillator; JACC, May 1989; 13(6); 135-161. This article was selected because it provides a detailed clinical complication experience on a large patient population, 270 patients. Note that the percentage reported in the PCD Transvene System includes **both complications and observations**. In the following table, the complications are reported for the categories of Failure to Cardiovert/Defibrillate, Pocket Infection, and Erosion. Observations are reported in the Inappropriate/Problematic VT/VF Therapy Delivery category.

PCD Transvene System Comparison of Complication/Observation Rates PCD versus AICD		
Category	**PCD%**	**AICD%**
Fail to Cardiovert/Defibrillate	2.3%	4.1%
Inappropriate/Problematic VT/VF Therapy Delivery	9.6%*	20%
Pocket Infection (explant)	2.9%	2.2%
Erosion	0.8%	0.7%

* Includes Observations only; there were no Complications in this category.

Table ID1-2: Comparison of Complication/Observation Rates: PCD Transvene System vs AICD Epicardial System - 2/1/93

The incidence of failure to cardiovert and/or defibrillate was lower in the PCD Transvene System patient population. The instances of failure to cardiovert and/or defibrillate in the PCD Transvene System patient population were associated with increased defibrillation requirements during induced episodes, none of which resulted in patient death.

The failures to cardiovert/defibrillate reported in the Winkle, et al article were associated with patch dislodgement, patch crinkling, lead conductor fracture and elevated defibrillation thresholds.

The incidence of inappropriate/problematic VT/VF therapy delivery was lower in the PCD Transvene System patient population. This is to be anticipated since the device incorporates independently programmable detection algorithms for VT and VF. The reasons for inappropriate VT/VF therapy delivery included sinus tachycardia being detected as VT or VF and atrial fibrillation with rapid ventricular response being detected as VT or VF.

The overdetection circumstances reported in Winkle, et al were nonsustained VT, VT, sinus

tachycardia, atrial fibrillation with rapid ventricular response, sensing lead fracture and pacemaker interaction. The patients with VT complained of receiving multiple shocks with limited or no symptoms. The incorporation of antitachycardia pacing in the PCD device decreases the need for delivery of cardioversion shocks for the termination of stable VT and increases patient acceptance of ICD therapy.

In the Winkle, et al experience all patients with pocket infection had the devices explanted. In the PCD Transvene System experience, the incidence of device explant secondary to pocket infection was 2.9% which was comparable to Winkle's article.

Thus, the incidence of complications and observations in the categories of ineffective VT/VF therapies, infection requiring explant and erosion was similar to that of the AICD Epicardial System. The incidence of inappropriate delivery of therapy is lower in the PCD Transvene System experience than in the AICD Epicardial System experience, which is clinically significant.

This analysis indicates that the PCD Transvene System offers clinical advantages in reducing the need for a thoracotomy for implantation and reducing the number of shocks due to successful antitachyarrhythmia pacing and inappropriate therapy incidence.

c. Survival Analysis

The Ventak-P Epicardial System produced by Cardiac Pacemaker, Inc, has obtained market approval from the U.S. FDA to date. While there are important differences in the function of the Ventak-P Epicardial System and the PCD Transvene System, the Ventak-P Epicardial system is the most comparable Market Released system. Table ID1-3 summarizes how the

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patient deaths have been classified for the PCD Transvene System and the Ventak-P epicardial System.

PCD Transvene System Comparison of Death Classification PCD Transvene System versus Ventak-P Epicardial System		
	PCD Transvene System	Ventak-P Epicardial System
Sudden Cardiac	5	4
Non-Sudden Cardiac	31	8
All Cardiac	15	6
Unknown	0	1
Total	51	19
Perioperative	5 (0.7%)	8 (2.7%)

Table ID1-3: PCD Transvene System - Death Classification- PCD Transvene VS Ventak=P - 2/1/93

A total of 51 deaths (6.7%) were reported in the PCD Transvene System patient population. Of the 35 cardiac deaths, 30 were non-sudden cardiac and 5 were sudden cardiac. Sixteen deaths were classified as noncardiac. Five of the 51 total deaths occurred within the perioperative period (death less than 30 days post implant) with a resultant perioperative mortality of 0.7%.

In the Ventak-P Epicardial System patient population a total of 19 deaths (6.5%) were reported. Of the 12 cardiac deaths, 4 were classified as sudden cardiac and 8 were classified as non-sudden cardiac. Six of the deaths were classified as noncardiac and the cause of one was unknown. Eight of the deaths occurred within the perioperative period with a resultant perioperative mortality of 2.7%. The PCD Transvene System population had a lower perioperative mortality, 0.7% vs 2.7% ($p=0.006$).

For purposes of this comparison, only the **overall** actuarial survival rate includes perioperative deaths.

All other calculations in both the PCD Transvene System and Ventak-P Epicardial System group exclude perioperative deaths.

For the Ventak-P Epicardial System, patient deaths were **censored** if the Ventak-P device had been either electively deactivated for various reasons prior to the patient's death, thus preventing the device from attempting to convert the arrhythmia or if the pulse generators were known to be nonfunctional and awaiting replacement. For purposes of this comparison, seven patient deaths were **censored** in the PCD Transvene System patient population because the devices were deactivated at the time of patient death.

Table ID1-4 contains the survival comparison of the PCD Transvene System versus the Ventak-P Epicardial System.

PCD Transvene System Survival Comparison PCD versus Ventak-P		
	PCD Transvene System	**Ventak-P Epicardial System**
Sudden Cardiac	99.7%	98.6%
Overall	94.2%	90.8%

Table ID1-3: PCD Transvene System - Survival Comparison - PCD vs Ventak-P - 2/1/93

The PCD Transvene System sudden cardiac death survival of 99.7% at one year is comparable to that of the Ventak-P Epicardial System sudden cardiac death survival rate of 98.6%. More importantly, the overall one year actuarial survival for the PCD Transvene System was 94.2% as compared to 90.8% for the Ventak-P Epicardial System. This difference was primarily due to the improvement in the reported perioperative mortality in the PCD Transvene System patient population. [Note: Confidence interval analysis was performed indicating that there was a statistical difference in the reported **Overall** mortality. The survival

probability at one year for the Transvene population was 95.3%. From the analysis run, using commercially available statistical software package (SAS), the survival standard error was also calculated. The confidence interval was calculated by taking the survival probability +/- the 1.96 (survival standard error). The survival standard error was 1.1, therefore, the confidence interval for Transvene survival at 1 year is 95.3 (b)(4) (b)(4) (b)(4)

This comparison of actuarial survival rates indicates that the projected sudden cardiac death survival of patients receiving a PCD System patient population is comparable to that reported for the Ventak-P Epicardial System. Thus, the incorporation of programmable VT/VF detection and therapy algorithms has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

In addition, the elimination of a surgical thoracotomy for implant in the PCD Transvene System has improved the perioperative mortality and overall one year survival when compared to the Ventak-P Epicardial System.

2. Comparison to PCD Epicardial Study

The PCD Epicardial System uses the same tiered therapy device that combines features of bradycardia support pacing, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. This system has incorporated programmability and multiple detection and therapeutic options that allows the titration of device therapy to a patient's specific clinical arrhythmia history.

The PCD Epicardial System requires a thoracotomy for implantation because of the need to insert epicardial patch leads. This exposes the patient to surgical risk and potentially limits the type of patient who may be considered for implant of the system. The need for a simpler and safer implantation technique is widely recognized. The

incorporation of a nonthoracotomy lead system, such as the PCD Transvene System, should decrease the potential perioperative and long term mortality and morbidity associated with current epicardial system implantation approaches.

The PCD Epicardial System and PCD Transvene System are identical except for the implanted defibrillation lead system. Thus, the performance of the PCD device, associated support equipment, is similar in the two systems and therefore a comparison of clinical experience should focus on those areas where the implanted lead system may impact clinical outcome.

This section provides a comparison of the PCD Transvene System clinical experience to the reported PCD Epicardial System clinical experience. The following areas will be discussed:

- Patient characteristics
- Implant Data
- Spontaneous VT/VF Episode Efficacy
- Complications and Observations
- Survival analysis

This analysis will show that the incorporation of a nonthoracotomy defibrillation lead system has maintained the type of therapy available for the treatment of recurrent VT/VF and decreased the potential mortality and morbidity associated with epicardial implant approaches while maintaining the positive impact of ICD therapy on VT/VF episode efficacy and patient survival.

The PCD Epicardial System clinical data was chosen as a control because the patients were being enrolled in the two studies concurrently by the same investigators, and the patient indications, implant criteria, and clinical data requirements were identical for the two patient groups.

a. Patient Characteristics

In comparing the clinical experience with the PCD Transvene System to the PCD Epicardial System

clinical experience, it is important to determine that the patients who received the device are comparable.

Table ID2-1 contains the characteristics of the 757 patients receiving the PCD Transvene System versus the characteristics of the 742 patients who received the PCD Epicardial System as of 1/5/93.

PCD Transvene System
Comparison of Patient Characteristics

	PCD Transvene System	PCD Epicardial System
Number of Patients	757	742
Mean Follow-Up Time	11.7 months	16.3 months
% Males* % Females	610 80.6% 147 19.4%	637 85.8% 105 14.2%
Mean Age	59.4 years	59.6 years
Primary Indication* SCD VT SCD/VT	 281 37.1% 377 49.8% 99 13.2%	 214 28.8% 405 54.6% 123 16.6%
Cardiovascular History Coronary Artery Disease Cardiomyopathy	 561 74.1% 238 13.1%	 569 76.7% 222 29.9%
Mean Ejection Fraction	35.6%	34.0%
Number of Drugs Failed*	2.3	3.0

* Statistically Significant

Table ID2-1: Comparison of Patient Characteristics, PCD Transvene System versus PCD Epicardial System - 2/1/93

Both groups had moderately depressed left ventricular function demonstrated by the mean ejection of 35.6% for the PCD Transvene System patient group and 34.0% for the PCD Epicardial patient group.

Analysis indicated that the PCD Transvene System patient population had a higher percentage of patients whose indication for implant was sudden cardiac death ($p = 0.002$) and higher percentage of females ($p = 0.007$). It is not expected that these differences will result in a different clinical outcome in the PCD Transvene System patient population as compared to the PCD Epicardial System. This difference in patient indication is a reflection of the physicians use of the PCD Transvene System.

It is interesting to note, that there was a statistical difference in the number of antiarrhythmic drugs tested between the two patient groups ($p = 0.001$). The PCD Transvene System patient group failed a mean of 2.3 antiarrhythmic drugs prior to implant while the PCD Epicardial System patient group failed a mean of 3.0 antiarrhythmic drugs. This difference is a reflection of the differences in the indications for implant between the two patient groups. The PCD Transvene System patient group had a higher incidence of patients whose primary indication for implant was sudden cardiac death. These patients are not required to have drug therapy screening, therefore, fewer drugs were tested in this group.

b. Implant Data

In both systems, lead system testing was performed to verify that one of the specified lead systems was capable of properly detecting and treating episodes of ventricular fibrillation and, when appropriate ventricular tachycardia. This testing included pacing and sensing thresholds during sinus rhythm, evaluation of VF electrogram amplitudes and defibrillation efficacy evaluation. The implant criteria for both systems was identical and was:

1. Successful VF termination at least 3 times in 4 attempts with an output energy of 18 Joules or less and

2. At least a 2:1 VF sensing safety margin

Pace/Sense Performance

In both the PCD Transvene and PCD Epicardial Systems, sensing is performed in a standard bipolar configuration and pacing is performed in the integrated bipolar configuration. The pace/sense implant criteria for both systems was:

Pacing Threshold:	$\leq$ 1.5V @ 0.5 ms
R-Wave Amplitude:	$\geq$ 5 mV
Slew Rate:	$\geq$ 0.75 volt/sec
Resistance:	200 - 880 ohms

Table ID2-2 provides a comparison of the mean pace/sense values obtained at the time of implant for the PCD Transvene and Epicardial Systems. It should be noted that the pace/sense values presented for the PCD Epicardial System are for the Model 7217B PCD Device.

PCD Transvene System
Performance Comparison
Implant Pace/Sense Parameters

Parameter	PCD Transvene System	PCD Epicardial System
Pacing Threshold*	0.87 V (0.1-3.6V)	0.98 V (0.2-5.3 V)
R Wave Amplitude*	14.2 mV (1.3-32 mV)	13.5 mV (2.2-37.2 mV)
Slew Rate*	1.66 v/S (0.25-9.8 v/S)	1.38 v/S (0.15-7.2 v/S)
Resistance*	575 ohms (264-1381 ohms)	438 ohms (157-1206)

* Statistically Significant

Table ID2-2: PCD Transvene System: Comparison of Implant Pace/Sense Parameters - 2/1/93

The implant pace/sense parameters obtained for the PCD Transvene System indicates that the lead system provided adequate pacing and safety margins. There was a statistically significant difference in all of the implant pace/sense parameters ($p = 0.001$). This is anticipated because

endocardial pace/sense parameters are better than epicardial values for bradycardia pacing electrode systems.

Electrogram amplitudes were evaluated at follow-up evaluations of both systems to evaluate the performance of the pace/sense lead system and assure adequate safety margin for detection of both baseline rhythms and ventricular tachyarrhythmias. In addition, pacing thresholds were also evaluated at follow-up evaluations to assure an adequate safety margin for capture during both bradycardia and antitachycardia pacing therapies. A comparison of the chronic pace/sense performance for the two systems is presented in Table ID2-3. It should be noted that there was no statistical difference in the chronic pace/sense performance of the two systems.

PCD Transvene System
Performance Comparison
Chronic Pace/Sense Parameters

Parameter	PCD Transvene System	PCD Epicardial System
Electrogram Amplitude	10.0 mV (0.5 - 25 mV)	9.5 mV (0.5 - 40 mV)
Pulse Width Threshold	0.24 ms (0.03-1.59 ms)	0.24 ms (0.03-1.59 ms)

Table ID2-3: PCD Transvene System: Comparison of Chronic Pace/Sense Parameters - 2/1/93

The incidence of loss of capture requiring lead system modification in the PCD Transvene System was 0.8% while the incidence in the PCD Epicardial System was 2.0%. There were no reports of undersensing requiring lead modification in the PCD Transvene System while the incidence in the PCD Epicardial System was 0.8%.

This comparison of implant and chronic pace/sense data performance indicates that the performance of the PCD Transvene System is similar to that reported with the PCD Epicardial System and potentially may be improved over the PCD Epicardial system. The

PCD Transvene System provides appropriate acute and chronic safety margins for sensing of sinus rhythm and ventricular tachyarrhythmia as well as appropriate safety margins for pacing therapy.

Implant Defibrillation Thresholds

For the purposes of both systems, determination of defibrillation threshold was not mandatory. However, the preferred method of evaluating defibrillation efficacy was to determine the defibrillation threshold using a testing sequence of 18J, 15J, 10J, 5J with a failure at any level causing a return to 18 J for the remaining attempts.

A defibrillation threshold was defined as the energy at the lowest successful defibrillation attempt, provided a patient had a failure below their lowest defibrillation success or a success at $\leq$ 5J. The rhythm treated must have been VF to be included in the analysis.

Table ID2-4 provides a comparison of defibrillation thresholds determined at implant for the PCD Transvene and PCD Epicardial Systems.

PCD Transvene System Performance Comparison Implant Defibrillation Thresholds	
System	**Mean DFT**
PCD Transvene System*	14.8J
PCD Epicardial System	9.8J

(b)(4) (b)(4)

Table ID2-4: PCD Transvene System: Comparison of Implant DFT - 2/1/93

The PCD Transvene System did have a significantly higher mean implant defibrillation threshold (b)(4) (b)(4) It should be noted, that it was expected that the PCD Transvene System would have a higher mean defibrillation threshold as compared to a traditional epicardial defibrillation lead system. In a traditional epicardial system, the

increased electrode surface area would theoretically decrease defibrillation requirements.

The programmed defibrillation pathways for the two patient populations is presented in Table ID2-5. The implanted PCD Transvene Systems are almost exclusively three lead systems and this explains the decreased use of SINGLE pathway. The use of SIMULTANEOUS pathway is higher in the PCD Transvene System and indicates that in a group of patients the incorporation of multiple defibrillation pathways allowed an increase in the ability to meet the PCD Transvene System implant criteria. Most of the PCD Epicardial System implants used a two patch system resulting in the increased use of the SINGLE pathway.

PCD Transvene System Performance Comparison Programmed Defibrillation Pathway		
Defibrillation Pathway	**PCD Transvene System**	**PCD Epicardial System**
Sequential	574 (75.3%)	251 (33.0%)
Simultaneous	178 (23.4%)	14 (1.8%)
Single	10 (1.3%)	496 (65.2%)

Table ID2-5: PCD Transvene System: Comparison of Programmed Defibrillation Pathway - 2/1/93

The differences in the programmed status of the PCD device in the PCD Transvene System are a reflection of the type of patients who received the device and the defibrillation energy requirements for each lead system. It is important to note that the PCD device performed safely and effectively in both patient populations.

c. Spontaneous VT/VF Efficacy

The primary benefits from the use of the PCD System center on the detection and termination of life-threatening ventricular tachyarrhythmias. An additional benefit of the PCD Transvene System is the elimination of the need for a thoracotomy for

implantation of the defibrillation lead system and the resultant decrease in potential patient morbidity and mortality associated with a thoracotomy. This clinical benefit should not be gained at the expense of providing effective termination of spontaneous VT and VF episodes. Table ID2-6 provides a comparison of the efficacy of the PCD Transvene and PCD Epicardial System in treating spontaneous episodes of VT and VF.

PCD Transvene System Performance Comparison		
Spontaneous VT Episodes		
	PCD Transvene System	**PCD Epicardial System**
Mean Follow-Up	11.7 months	16.3 months
Number of Patients with VT Episodes	316	386
Number of Episodes	10,027	20,061
% Overall Efficacy	9,864/10,027 98.4%	19,726/20,061 98.3%
% Unsuccessful Termination (VT)	68/10,027 0.7%	150/20,061 0.8%
% Unsuccessful Termination (AF,ST)	95/10,027 0.9%	185/20,061 0.9%
Spontaneous VF Episodes		
	PCD Transvene System	**PCD Epicardial System**
Mean Follow-Up	11.7 months	16.3 months
Number of Patients with VF Episodes	317	342
Number of Episodes	1982	2,636
% Overall Efficacy	1951/1982 98.4%	2601/2636 98.7%
% Unsuccessful Termination (VF)	5/1982 0.3%	15/2636 0.5%
% Unsuccessful Termination (AF,ST, Other)	26/1982 1.3%	24/2636 0.8%

Table ID2-6: PCD Transvene System: Comparison of Spontaneous VT/VF Episode Efficacy - 2/1/93

The overall success rate of the PCD Transvene System in terminating spontaneous episodes of VT or VF is 98.5%. This success rate compares very favorably with the overall success rate of the PCD Epicardial System which was 98.4%. Therefore, the PCD Transvene System offers the potential of decreased patient morbidity and mortality without decreasing the treatment efficacy of spontaneous VT/VF episodes.

d. Complications and Observations

A comparison of the reported complications and observations was made between the PCD Transvene System and the PCD Epicardial System. The PCD Epicardial System patient population used for comparison included clinical experience as of January 5, 1992 with 742 patients and a mean implant duration of 16.3 months. These two patient groups are similar in the patient demographics and indication for implant of the PCD System. In the PCD Transvene System patient population, 19.4% of the patients experienced a clinical complication and 23.8% of the patients experienced a clinical observation. In the PCD Epicardial System, 14.2% of the patients experienced a clinical complication and 32.9% of the patients experienced a clinical observation.

Table ID2-7 and ID2-8 provide a comparison of the reported complications/observations and their incidence in the two patient populations.

PCD Transvene System PCD Transvene System versus PCD Epicardial System Reported Complications		
Reported Complications	**PCD Transvene System (N = 757)**	**PCD Epicardial System (N = 742)**
Increased Defibrillation Requirements	1.2%	0.5%
Inappropriate Therapy	-	2.2%
Pace/Sense Related	0.8%	3.5%
Infection Related - Explant	2.9%	2.3%
Lead Related	15.1%	3.0%
Device Related	0.5%	0.9%

Table ID2-7: Reported Complications: PCD Transvene System versus PCD Epicardial System - 2/1/93

PCD Transvene System PCD Transvene System versus PCD Epicardial System Reported Observations		
Reported Observations	**PCD Transvene System (N = 757)**	**PCD Epicardial System (N = 742)**
Ineffective Therapy	1.1%	1.1%
Inappropriate Therapy	9.6%	13.6%
Pace/Sense Related	9.0%	14.0%
Infection Related	5.3%	2.6%
Lead Related	2.3%	1.2%
Device Related	-	-

Table ID2-8: Reported Observations: PCD Transvene System versus PCD Epicardial System - 2/1/93

e. Survival Analysis

Despite their excellent clinical performance, epicardial defibrillation lead system have important limitations. The requirement for direct thoracic access contributes significantly to patient morbidity and mortality, patient discomfort and prolonged hospitalization. The availability of reliable nonthoracotomy lead systems should provide

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positive clinical impact on these issues while not negatively impacting patient survival. Therefore, a comparison of the one year actuarial survival rates for the PCD Transvene and Epicardial System was performed.

Table ID2-9 provides a summary of the patient deaths reported in the two patient populations by classification. As a reference, the mean follow-up time for the PCD Transvene System patient population was 11.7 months while for the PCD Epicardial System it was 16.3 months. Patients with the device programmed OFF and perioperative deaths are not mutually exclusive.

PCD Transvene System Death Classifications PCD Transvene System versus PCD Epicardial System		
Death Classification	**PCD Transvene System (N=757)**	**PCD Epicardial System (N=742)**
Sudden Cardiac	5 0.7%	24 3.2%
# Off	1 0.1%	3 0.4%
# Perioperative	2 0.3%	9 1.2%
Non-Sudden Cardiac	31 4.1%	54 7.3%
# Off	4 0.5%	12 1.6%
# Perioperative	2 0.3%	18 2.4%
All Cardiac	36 4.8%	78 10.5%
# Off	5 0.7%	15 2.0%
# Perioperative	4 0.5%	27 3.6%
Noncardiac	15 2.0%	34 4.6%
# Off	2 0.3%	7 0.9%
# Perioperative	1 0.1%	12 1.6%
Total	51 6.7%	113 15.2%
# Off	7 0.9%	23 3.1%
# Perioperative	5 0.7%	39 5.3%

Table ID2-9: Death Classifications: PCD Transvene System versus PCD Epicardial System - 2/1/93

Table ID2-10 provides a comparison of actuarial survival rates between the PCD Transvene and PCD Epicardial patient populations. The actuarial survival projections include perioperative deaths only in the calculation of

survival from death due to all causes (shown in table row labelled **Overall**). Perioperative mortality includes those deaths which occur in the first thirty days post implant of the PCD System.

PCD Transvene System Comparison of Actuarial Survival PCD Transvene System versus PCD Epicardial System			
One Year Survival	**PCD Transvene System**	**PCD Epicardial System**	**P-Value**
Number of Patients	757	742	-
Sudden Cardiac	99.5%	98.9%	0.197
Non-Sudden Cardiac	96.2%	96.7%	0.542
All Cardiac	95.8%	95.7%	0.992
Noncardiac	98.1%	98.0%	0.820
Overall*	93.3%	88.6%	0.004

* **Statistically Significant** $p \leq 0.05$

Table ID2-10: Comparison of Actuarial Survival: PCD Transvene System versus PCD Epicardial System - 2/1/93

There was a significant increase in overall survival in the patients receiving a PCD Transvene System. As previously noted, the Overall one year actuarial survival includes death from all causes. The overall one year survival for patients receiving the PCD Transvene System was 93.3%. This is significantly improved as compared to the overall one year actuarial survival for the PCD Epicardial System (88.6%) [p=0.004]. This improvement in overall survival is primarily due to the marked improvement in perioperative mortality, the PCD Transvene System having a 0.7% (5/757) perioperative mortality versus the a perioperative mortality of 5.3% (39/742) in the PCD Epicardial System. This improvement in perioperative mortality is primarily due to the elimination of the need for a thoracotomy and its associated morbidity and mortality.

E. Transvene PCD System Performance

1. Explants; Leads and PCD Devices

Transvene Lead Performance

The Transvene Lead System consists of a Right Ventricular Lead, a Coronary Sinus/Superior Vena Cava lead, and a Subcutaneous Patch lead. There have been a total of 757 Right Ventricular leads (15 with the SP2100 and 742 with the Model 6884/6966), 796 Coronary Sinus/Superior Vena Cava leads (Model 6881/6963), and 718 Subcutaneous Patch leads (Models 6895/10317/6999) implanted with a cumulative implant duration of 8894.8 months. The reported incidence of fracture for the RV lead is 0.9% (7/757) and 0.3% (2/757) for the SQ lead.

A Model 6884, screw-in, right ventricular, pace/sense, cardioversion/ defibrillation lead was returned to Medtronic 27 months post implant. The lead was returned to Medtronic following explant from a patient that was undergoing a heart/lung transplant. Note that the lead had been fully functional while implanted and was found to be fully functional upon explant.

Upon undergoing further analysis at Medtronic, some MIO (metal ion oxidation) was observed on the lumen of the middle insulation approximately 20 cm proximal of the pacing tip electrode, and on the outside of the inner insulation. The MIO was further characterized to be "cosmetic" in that it had not functionally affected the lead in any way. Cosmetic MIO is defined as any crack that has not breached the insulation.

Initial analysis indicated that the presence of the MIO was in the clavicular region of the body; i.e., the location, 20 cm proximal of the tip, would be in the first rib clavicle region of a small adult. There was no evidence, however, of conductor coil fracture and the lead was fully functional. Given the Model 6884 lead is generally implanted via subclavian vein insertion, this type of observation may occasionally be expected. However, subsequent analysis of the patient X-rays showed that the area of MIO was actually in the right ventricle. The patient's right ventricle

was extremely dilated, secondary to pulmonary hypertension. Therefore, 20 cm from the proximal tip electrode located the area of MIO at the point of maximum curvature of the lead, in the right ventricle, rather than in the clavicular region.

Detailed Analysis Results

Visual/Microscopic

Shallow (cosmetic) environmental stress cracking (ESC) was visible. No coil deformation was visible in the first rib/clavicle region. Possible MIO was visible 20 cm proximal of the electrode tip extending approximately 0.5 cm on the middle insulation. Possible MIO was also visible on the innermost insulation starting at 19.3 cm proximal of the electrode tip and extending 5.4 cm proximally.

Scanning Electron Microscopy

MIO was observed on the lumen of the middle insulation and on the outside of the innermost insulation. The MIO penetration was less than five percent of the insulation wall thickness. In addition to the insulation, both the middle and inner coils were evaluated up to 2500 times magnification. There were no anomalies apparent on the inside or outside of the middle coil in the region of the MIO. The innermost coil showed no signs of crush or fatigue in the region of the MIO.

FTIR-ATR

FTIR spectra were obtained for a control area (no MIO) of the inner tubing and the cracked area of the tubing. Relative ratios of key bonds were calculated using the absorption intensities. These ratios indicated that the ether segments were oxidized in the polyurethane, which is characteristic of MIO. In addition, peaks appeared, indicative of carboxylic acids or esters (oxidation byproducts).

Discussion

Contrary to the initial dimensional analysis of this lead that indicated the area of MIO was located to the clavicular region of implant, review of the patient's X-rays revealed that the heart was significantly enlarged due to the advanced disease state. Subsequently, a significant portion of the insulated lead body was located in the heart, including the portion with cosmetic MIO. Typically, 20 cm proximal of the tip electrode approximates the clavicular region.

Consistent with our previous analysis of MIO relative to the 6884/6966 lead, the observed MIO did not, in any way, affect the clinical performance of this lead. Patient data analysis shows that the implanted lead system, inclusive of the 6884 lead, performed appropriately. Of six spontaneous VT/VF episodes reported (4VT/2VF), all were appropriately detected and treated via the implanted PCD Transvene system.

In addition, the presence of MIO on the middle insulation is not entirely unexpected (reference February 18, 1993, Medtronic/FDA meeting). If the middle insulation had been degraded to the point of electrically shorting the sensing ring (middle conductor coil) to the common defibrillation electrode (middle coil), an integrated bipolar sensing system would, in essence, be created. In this type of system, sensing occurs between the unipolar pacing tip and the common defibrillation electrode, versus standard, or true, bipolar sensing between the pace/sense tip and the ring electrodes. This type of sensing system is identical to the CPI Endotak configuration, as well as Medtronic's earlier design of a Transvene RV lead, i.e., the Model SP2100. These types of integrated systems have been shown to be clinically acceptable. Note that canine testing of a shorted, RV cardioversion/defibrillation lead, indicated that this type of failure does not result in the lack of therapy delivery.

If the innermost insulation had degraded such that the pacing tip electrode shorted, this could manifest as intermittent sensing of the brady pace/sense function of the lead. This type of anomalous system performance is expected to be observed at follow-up sessions, given the

frequent monitoring of patients (every three months) or as necessary when the patient experiences VT/VF episodes or anything unusual. Similar to brady pacing patients, problems related to pace/sense performance are typically observed at the time of follow-up (pace/sense threshold measurements are standard follow-up procedure for both brady and tachy lead systems) and/or when the patient reports to his/her physician for any unusual events, e.g., intermittent pacing/sensing.

The extensive dilatation of the right ventricle in which this lead was implanted resulted in a large portion of insulated lead body being in the right ventricle, as opposed to primarily just the cardioversion/defibrillation electrode coil. Subsequently, this lead may have been subject to more flexing in the heart than what is typical for the RV lead. Note: this was demonstrated in the videotape that was presented to FDA at the February 18, 1993, Medtronic/FDA meeting.

Clinical data from brady pacing leads indicates that the portion of the lead subject to the flexing motion in the heart may be related to the occurrence of MIO in brady lead bodies. Brady pacing leads, proximal to the tip/ring electrodes are subject to more flexing motion, relative to a cardioversion/defibrillation RV lead, while contained in the heart. On the other hand, cardioversion/defibrillation leads, like the 6884/6966, are comprised of a comparatively stiff portion proximal to the tip/ring electrode. This length of defibrillation electrode, 5 cm, appears to flex less than a typical brady pacing lead while in the heart, as a result of greater stiffness. However, in the extremely hypertrophic heart, as was the case with this particular RV lead, the lead may be subject to more flexing, similar to that of a brady pacing lead.

Conclusions

As noted, Medtronic cannot assure that MIO, or other lead failure mechanisms will not occur in the 6884/6966 lead. However, one should consider the actual benefits of the lead versus the **potential** for MIO occurrence. Specifically, clinical data to date for the Transvene system show that one year actuarial survival from SCD is 99.5 percent and

the average hospital stay for Transvene implant is only seven days (versus ten for an epicardial system)*. Regarding the potential for MIO occurrence, analysis shows this would result in a bipolar integrated sensing system, or in an intermittent pace/sense system. Integrated sensing has been shown to be clinically acceptable, and intermittent pacing/sensing is assessed as part of standard follow-up procedures. Additionally, with postmarket surveillance mechanisms in place, such as returned product analysis and chronic lead monitoring, Medtronic is well positioned to appropriately evaluate and manage potential failure mechanisms of implantable cardiac leads. We are committed to these surveillance mechanisms in the interest of delivering optimal implantable technology products to the health care market.

Based on the clinical data collected, the Transvene leads have performed safely and reliably.

PCD Devices

In the 762 implants, a total of 63 units (8.3%) were explanted secondary to patient deaths, infection, heart transplant, low battery voltage measurement and PCD Device performance issues. Table IE1-1 provides an overview of the units explanted, and returned to Medtronic for analysis and reason for explant.

PCD Transvene System Reasons for PCD Device Explant n = 762		
Reason	**All Models**	
	Explanted	Received for analysis
Patient Death	22	17
Infection	22	10
Cardiac Transplant	9	5
Low Battery Voltage Measurement	1	1
PCD Device Performance Issues	4	4
L23	1	1
Lead Issues	4	4
Total	63	42

Table IE1-1 Reasons for PCD Device Explant - 2/1/93

The investigational plan requests that if the patient expires during the course of the clinical study that the PCD device be explanted and returned to Medtronic for analysis. There were 51 reported patient deaths and 22 devices were explanted. Seventeen have been received at Medtronic for analysis. In the 29 deaths where the device was not explanted, the patients expired and were buried before the devices could be explanted.

Results of analysis performed on the 42 explanted devices is presented in Table IE1-2.

PCD Transvene System Final Analysis on Explanted PCD Devices (N = 762)	
Within Normal Specifications	36
Hermetic Leakage at IC	1
Random Component Failure	2
Shorted on Pulse 2 Output	2
L23	1
Analysis Pending	0
Total	42

Table IE1-2: Final Analysis on Explanted PCD Devices - 2/1/93

Of the 42 devices explanted, final analysis on 36 units indicated that the devices were functioning within normal specifications.

Six PCD Devices were explanted for the following device performance issues:

- explanted due to a Power On Reset (POR) condition that was not related to the delivery of external defibrillation or cautery (N = 1);
- explanted for lower than expected battery voltage for time in service, includes L23 (N = 2);
- explanted secondary to failure to appropriately synchronize and deliver cardioversion therapy for an induced VT episode (N = 1); and
- explanted post inappropriate delivery of VF therapy during a manual capacitor charge time (N = 2).

These devices are discussed in detail in the discussion that follows.

In the case of the device explanted for PCD Device performance issue (b)(4) (b)(4) the device experienced a Power On Reset (POR) condition that was not related to

the delivery of external defibrillation or electrocautery. Under certain conditions, the use of direct defibrillation or electrosurgical cautery in the vicinity of a Model 7217B PCD System (i.e., device and electrodes) may cause the device to be set to its reset parameter values (VT/VF detection and therapies disabled and nominal VVI pacing parameters). In the case of this patient, the POR condition occurred during the pre-hospital discharge evaluation and the patient was under no increased risk.

Since external defibrillation or electrocautery had not been used near the device, it was recommended that the device be explanted. The patient received a second PCD Device without difficulties. The explanted PCD Device underwent initial evaluation and was found to be performing within specifications. Additional testing is currently ongoing.

Analysis of the device which had the documented short on the Pulse 2 output was found in a device which was explanted secondary to patient death. The death was classified as nonsudden and not related to the implanted PCD Transvene System. It appears that this diode failed post explant of the system probably due to electrocautery being used at the time of explant and was not related to the patient's death.

There was one device (b)(4) that was explanted due to lower than expected battery voltage for time in service. Analysis indicated that hermetic leakage at the input to one of the integrated circuits lead to a voltage drop across a resistor where the voltage measurement is taken. Thus the actual battery voltage was appropriate but the telemetry reading was incorrectly low.

There have been no reports of lower than expected battery voltage for time in service due to failure in an integrated circuit which increases current drain or leakage of tantalum capacitors on the printed circuit board as reported in the PCD Epicardial System experience.

None of these issues are related to the PCD device battery performance. The battery has performed according to specifications and there is no clinical data indicating otherwise.

In the case of the PCD Device (b)(4) which did not appropriately synchronize cardioversion therapy, during the pre-hospital discharge electrophysiology study, VT was induced and cardioversion therapy failed to appropriately synchronize and deliver therapy for the induced episode. The PCD Device was explanted and the patient received a second device without difficulties. Analysis of the explanted PCD Device indicated a random device failure. The manufacturing process was modified to incorporate a screening process to identify any further devices which may exhibit this behavior.

In the PCD Device (b)(4) in which VF therapy was delivered during a capacitor charge time, appropriate function of the Model 7217B PCD Device was documented at the time of implant. At the time of the one month follow-up, the device was interrogated and there were no spontaneous episodes between hospital discharge and the one month follow-up. During the monitor, the capacitors were being charged according to protocol and the patient indicated she felt a sensation in her abdomen. Subsequently, the PCD device did not respond to telemetry.

The patient was monitored again in an effort to assess telemetry. Another programmer was used and various radiofrequency sensitivities were used in attempts to gain telemetry. Still there was no response. The implanted system was assessed via x-ray and device (leads) dislodgement was not seen. Alternative implant, e.g., another commercially available defibrillator, was not considered an option as the Medtronic lead connections were not known to be compatible with other manufacturer's devices. The PCD Device was explanted and a second Model 7217B PCD device was implanted without difficulty. This patient has done well since the second implant procedure. No further device performance issues such as this one have been reported in this patient or other implanted devices.

Analysis of the explanted unit indicated that arcing occurred between the conductors inside the hermetically enclosed brazed ring of the high power hybrid. As a result, high voltage was momentarily applied to the low power circuitry, including the low power hybrid. This low power

hybrid lost function including the capability to pace and transmit telemetry due to excessive voltage applied. The mechanism that initiated the arcing could not be identified.

Even though the arcing mechanism could not be identified, it is important to note that the hybrid manufacturing procedure has processing steps to ensure that arcing does not occur. Traceability data on this unit indicated there were no processing anomalies related to this hybrid.

Since this was the only device that exhibited this type of failure in the field and the hybrid manufacturing process has demonstrated that it will screen out infant mortality, this is considered a random component failure.

F. Clinical Conclusions

The overall clinical experience with the PCD Transvene System indicates that the system performed according to design and specification. The reported clinical complications and patient deaths are appropriately addressed in the required labelling for the system and the patient selection criteria for implant of the device is appropriate.

The following can be drawn from this analysis of the data collected in this clinical study from the 757 patients with a mean follow-up of 11.7 months:

Patient Deaths

- The projected one year survival probabilities for Sudden Cardiac Death, Non-Sudden Cardiac Death, all Cardiac Deaths and Noncardiac Death were found to be 99.5%, 96.2%, 95.8%, and 98.1%, respectively.

  The incorporation of programmable VT/VF detection and therapies has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

- The sudden cardiac death survival of 99.5% at one year is comparable to that of the AICD patient population 98.0%.

- There have been no deaths due to a PCD Device malfunction.

Complications/Observations

- Complications were reported in 19.4% of the patient population and observations were reported in 23.8% of the patient population.

- The incidence of complications was comparable to that of the market released AICD system in the categories of ineffective VT/VF therapy, pocket infection, and pocket erosion and was lower than the AICD in the category of inappropriate delivery of VT/VF therapy.

Patient Indications

- All of the 757 patients who received a 3 lead system in this clinical evaluation met at least one of the primary indications. Sudden cardiac death (SCD) was the primary indication in 37.1% of the patients, recurrent ventricular tachycardia (VT) was the primary indication in 49.8 % of the patients and SCD/VT was the primary indication in 13.1% of the patients.

- The number of patients (60.5%) receiving VT/VF therapy for spontaneous episodes of ventricular arrhythmias supports the conclusion that the patient selection criteria are appropriate and that the PCD Transvene System was implanted in patients who benefit from this therapy.

- The one year sudden cardiac death survival rates for the SCD patient group was 100.0%, for the VT patient group 99.4% and the SCD/VT patient group 98.6%.

VT/VF Detection and Therapy Performance

- The PCD Transvene System properly detects and treats VT as demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VT was 98.4%.

- The PCD Transvene System properly detects and treats VF as demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VF was 98.4%.

- There were no reported patient deaths due to the nondetection of a spontaneous VT or VF episode by the PCD Transvene System.

PCD Transvene System Performance

- The PCD Transvene System components (Model 7216A/7217B and Model 6884/6966, 6881/6963, 6895/6999 Transvene leads) have performed according to design and specification and are, therefore, considered safe and effective in the indicated patient population.

Medtronic asserts and the PCD Transvene investigators unanimously agree that the findings of the clinical study support the conclusion that the Medtronic Tachyarrhythmia Control System and the Transvene Cardioversion and Defibrillation Electrodes are safe and effective in the indicated patient population.

IV. Summary of Additional Implants

A. Overview

This overview covers a total of 1335 implants in 1330 patients of the PCD Device with the Transvene Defibrillation Lead System. The patients included in this report includes the 757 patients described in the original PMA application and an additional 573 patients that have been implanted in the U.S. from 6/25/92 to 2/1/93. The first implant occurred internationally on October 20, 1989, and the first implant in the U.S. occurred on October 16, 1990.

The mean implant duration for this patient population is 8.0 months and ranges from implant to 37.4 months. The cumulative implant duration is 10,653.7 months.

The patient population (N = 1330) enrolled in the clinical trial was predominately male (81.6%) with a mean age of 60.4 years. In half of the patients (54.5%), the primary indication for implant was recurrent, sustained ventricular tachycardia without an episode of sudden cardiac death. Sudden Cardiac Death was the primary indication for 34.7% of the patients and SCD in combination with recurrent, sustained VT was the primary indication in 10.8%. Coronary artery disease was the primary heart disease in 76.2% of the patient population with a mean reported ejection fraction of 34.3% Table IVA-1 provides a data summary on these patients. Although there is a slightly higher percentage of patients with the primary indication of VT, 54.5% vs 49.8% (PMA patient population), there are no substantial differences or trends noted from the original PMA population.

PCD Transvene System Data Summary of Updated Population N = 1330			
Number of Patients	757	573	1330
Device Months Follow-up	8894.8	1758.9	10,653.7 mo
Mean Follow-up Time	11.7 mo	3.1 mo	8.0 mo
Maximum Follow-up Time	37.4 mo	12.5 mo	37.4 mo
Number, % Male Number, % Female	610 80.6% 147 19.4%	475 82.9% 98 17.1%	1085 81.6% 245 18.4%
Mean Age	59.4 yrs	61.8 yrs	60.4 yrs
Primary Indication: SCD VT SCD/VT	 281 37.1% 377 49.8% 99 13.1%	 182 31.8% 347 60.6% 44 7.6%	 463 34.8% 724 54.4% 143 10.8%
Coronary Artery Disease	561 74.1%	453 79.1%	1014 73.4%
Mean Ejection Fraction	688 35.6%	506 32.5%	1194 34.3%
Defibrillation Pathway: Sequential Simultaneous Single	 574 75.3% 178 23.4% 10 1.3%	 406 70.9% 163 28.4% 4 0.7%	 980 73.4% 341 25.5% 14 1.1%
Mean LED	16.0J (N = 702)	17.0J (N = 534)	16.4J (N = 1236)
Mean DFT	14.8J (N = 316)	16.4J (N = 180)	15.4J (N = 496)
Spontaneous VT: Number of Patients Number of Episodes % Success	 316 9864/10027 98.4%	 108 1487/1550 96.0%	 424 11577 98.1%
Spontaneous VF: Number of Patients Number of Episodes % Success	 317 1951/1982 98.4%	 110 468/471 99.4%	 427 2453 98.6%
One Year SCD Survival	99.5%	98.3%	99.3%
Overall Survival	93.3%	93.4%	93.0%

Table 8-1: PCD Transvene System: Data Summary - Updated Pts. (1330) - 2/1/93

B. Complications and Observations

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following previously described definitions:

COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

Of the 1330 patients, as of February 1, 1993, there have been a total of 225 complications reported in 195 patients and 275 observations reported in 228 patients in the PCD Transvene System patient population. Thus, 14.7% (195/1330) of the patients had a clinical event which was categorized as a complication and 17.1% (228/1330) of the patients had a clinical event which was categorized as an observation.

Table IVB-2 and IVB-3 summarize the reported PCD Transvene System complications and observations by category, respectively. In almost all categories, the percentage of patients in which a complication or observation was reported has decreased compared to the original PMA patient population of 757. The percentage of patients with lead dislodgements reported has substantially decreased from 12% with a complication to 8.8% and 1.6% with an observation to 0.9%. No new categories of complications or observations were reported. The reported complications and observations are recognized clinical events that may occur with **any** of the current ICD devices. These complications and observations are discussed in the PCD device and Transvene manual. **None of the reported complications or observations have resulted in a patient death.**

PCD Transvene System Reported Complications By Category			
Category	757	573	1330
	Num (% of Pts)	Num (% of Pts)	Num (% of Pts)
Increased Defibrillation Requirements	9 (1.2%)	5 (0.9%)	14 (1.1%)
Inappropriate VF Therapy Delivery	-	-	-
Inappropriate VT Therapy Delivery	-	-	-
Loss of Capture	6 (0.8%)	-	6 (0.5%)
Oversensing	-	1 (0.2%)	1 (0.1%)
Undersensing	-	-	-
Skin Erosion	5 (0.7%)	-	5 (0.4%)
Pocket Infection	24 (3.2%)	6 (1.0%)	30 (2.3%)
Seroma	6 (0.8%)	4 (0.7%)	10 (0.8%)
Hematoma	6 (0.8%)	6 (1.0%)	12 (0.9%)
Pneumothorax	2 (0.3%)	-	2 (0.2%)
Pacemaker Syndrome	-	-	-
Perforation	6 (0.8%)	1 (0.2%)	7 (0.5%)
Subclavian Vein Thrombosis	1 (0.1%)	-	1 (0.1%)
Lead Fracture	9 (1.2%)	-	9 (0.7%)
Subcutaneous Patch Crinkling	7 (0.9%)	-	7 (0.5%)
Early Device Explant	4 (0.5%)	-	4 (0.3%)
Total Lead Dislodgement (n = 1330)	91 (12.0%)	26 (4.5%)	117 (8.8%)
Total	176	49	225

Table 8-2: PCD Transvene System: Reported Complications/ Observations (n = 1330) - 2/1/93

PCD Transvene System Reported Observations By Category			
Category	**757**	**573**	**1330**
	Num (% of Pts)	**Num (% of Pts)**	**Num (% of Pts)**
Increased Defibrillation Requirements	8 (1.1%)	1 (0.2)	9 (0.7%)
Inappropriate VF Therapy Delivery	12 (1.6%)	3 (0.5%)	15 (1.1%)
Inappropriate VT Therapy Delivery	59 (7.8%)	9 (1.6%)	68 (5.1%)
Loss of Capture	14 (1.8%)	2 (0.3%)	16 (1.2%)
Oversensing	54 (7.1%)	29 (5.1%)	83 (6.2%)
Undersensing	-	-	-
Skin Erosion	1 (0.1%)	-	1 (0.1%)
Pocket Infection	10 (1.3%)	2 (0.3%)	12 (0.9%)
Seroma	14 (1.8%)	6 (1.0%)	20 (1.5%)
Hematoma	17 (2.2%)	6 (1.0%)	23 (1.7%)
Pneumothorax	1 (0.1%)	-	1 (0.1%)
Pacemaker Syndrome	2 (0.3%)	-	2 (0.2%)
Perforation	-	-	-
Subclavian Vein Thrombosis	3 (0.4%)	3 (0.5%)	6 (0.5%)
Lead Fracture	-	-	-
Subcutaneous Patch Crinkling	5 (0.7%)	-	5 (0.4%)
Early Device Explant	-	-	-
Total Lead Dislodgement	12 (1.6%)	-	12 (0.9%)
Total	**212**	**61**	**273**

Table 8-2: PCD Transvene System: Reported Observations - 2/1/93

Table IVB-4 contains a description of the lead dislodgements that have occurred in less than 30 days and in greater than 30 days. As noted earlier, the percentage of patients in which a complication or observation regarding lead dislodgement was reported has decreased from the original PMA patient population of 757.

PCD Transvene System
Reported Complications/Observations
Lead Dislodgements <30 and >30 days (N=1330)

Category	Complications		Observations	
	Num (% of Pts)		Num (% of Pts)	
	<30 days	>30 days	<30 days	>30 days
RV Lead Dislodgement n=1314	19 (1.4%)	13 (1.0%)	0 (0)	1 (0.1%)
CS Lead Dislodgement n= 387	19 (4.9%)	11 (2.8%)	2 (0.5%)	2 (0.5%)
SVC Lead Dislodgement n=989	16 (1.9%)	36 (3.6%)	1 (0.1%)	6 (0.6%)
Total Dislodgement n=1330	57 (4.3%)	60 (4.5%)	3 (0.2%)	9 (0.7%)

Table 8-3: PCD Transvene System: Lead Dislodgements <30/>30 days (n=1330) - 2/1/93

There have been a total of 60 lead dislodgements reported in patients at greater than 30 days. None of the lead dislodgements resulted in an ineffective therapy for a spontaneous VT of VF episode or patient death. Lead dislodgements were documented by fluoroscopic examination during electrophysiologic evaluation, chest x-ray obtained during routine follow-up, or during pacing/sensing threshold evaluation during routine follow-up. In all 60 cases, reoperation was required to reposition the lead and reestablish an effective defibrillation lead system.

Lead dislodgements are not specific to the PCD® Transvene™ System and have been reported with dual chamber pacemakers and the current market released implantable cardioverter defibrillator (ICD) system. The early history of dual chamber pacemakers witnessed a high lead dislodgement rate of at least 20% (Smyth, PND, et al. Permanent perivenous atrial sensing and pacing with a new J-shaped lead. J Thoracic Cardiovascular Surgery. 1976;72:565-570). Winkle, et al reported that the incidence of dislodgement of the superior vena cava spring leads

with the current market release ICD system to be 6.3%. (Winkle, et al. Automatic Implantable Cardioverter-Defibrillator: Efficacy, Complications, and Survival in Patients with Malignant Ventricular Arrhythmias. JACC. June 1988; Vol.11, No.6:1278-86).

Patient Deaths

The positive impact of implantable cardioverter defibrillator (ICD) therapy on sudden cardiac death mortality has been well documented in the medical literature. The use of device therapy for the treatment of recurrent ventricular arrhythmias has become an accepted and important clinical tool. An analysis of the sudden cardiac death survival in the PCD Transvene System patient population was performed.

For purposes of the clinical study, each of the patient deaths was categorized using the following definitions:

Non-Cardiac:	Deaths that occurred where the primary cause of death was determined to be non cardiac in nature, e.g. stroke, cancer, etc.
Cardiac:	Deaths that occurred where the primary cause of death was determined to be cardiac in nature.
Non-Sudden:	Deaths that occur greater than one hour after the onset of symptoms.
Sudden:	Deaths that occur within one hour of the onset of symptoms or where the death is unwitnessed. Sudden cardiac deaths were also categorized as being **Witnessed** or **Unwitnessed**.
Perioperative:	Deaths that occur within thirty days of implant.
System Related:	A death which results from a malfunction (operation not according to design specification) of a PCD System component, or as a result of a device induced arrhythmia, or an interaction between a PCD System component and the patient.
Procedure Related:	A death which occurs as a result of a procedure required to implant, follow or test a PCD System.

All deaths and significant complications have been and will continue to be reviewed by a committee comprised of PCD Transvene System investigators and other physicians. Two committees (Clinical Event Review Committees) have been formed, one to review North American deaths and complications, and the other to review European clinical events. The primary purpose of these reviews was to determine whether the PCD System was related to the deaths or significant complications that have occurred and, if so, what changes may be required to prevent such events in the future.

There have been a total of 68 patient deaths reported in the PCD Transvene System patient population. Table IVC-1 summarizes how these patient deaths have been classified.

PCD Transvene System
Summary of Death Classifications
(n = 1330)

Classifications	n=757	n=573	Total # of Deaths
Sudden Cardiac	5	5	10
Non-Sudden Cardiac	31	7	38
Noncardiac	15	5	20
TOTAL	51	17	68

Table 8-4: PCD Transvene System - Summary of Death Classifications (n=1330) - 2/1/93

None of the patient deaths were attributed to a malfunction of the PCD Transvene System.

Actuarial survival analysis on the PCD Transvene System was done on all patients who were either evaluated for implantation or in whom the device was implanted. Thus, the analysis is done from the perspective of **intention to treat**. Those patients in whom the PCD Device was OFF at the time of death or in whom no device was implanted <u>are</u> included in the survival analysis. Those patients that were screened for a PCD Transvene System but failed to receive a Transvene system are not included in this analysis.

Projected one year survival calculations for the various death classifications are provided in Table IVC-2. **The actuarial projections include perioperative deaths only in the calculation of one year survival from death due to all causes (shown in the row labelled Overall).** The perioperative death rate defined as deaths which occurred within thirty days of implant was 0.8% (10/1330) which is considerably less than the perioperative mortality for the PCD System with Epicardial leads (5.3% - 39/742).

PCD Transvene System One Year Actuarial Survival			
	757	**573**	**1330**
Sudden Cardiac Death	99.5%	98.3%	99.3%
Non-Sudden Cardiac	96.2%	97.7%	96.3%
All Cardiac	95.8%	96.0%	95.6%
Noncardiac	98.1%	98.3%	98.1%
Perioperative	0.7%	0.9%	0.8%
Overall	93.3%	93.4%	93.0%

Table 8-5: PCD Transvene System - One Year Actuarial Survival - 2/1/93

The positive impact of the PCD Transvene System on patient mortality is clearly obvious from this analysis. The sudden cardiac death survival rate the total patient group (n = 1330) is 99.3%. This is a marked improvement when compared with the reported survival of similar patient groups treated with drug therapy alone of between 34% and 73% at one year.

In conclusion, the data above for the 1330 patients implanted and followed through 2-1-93 is similar to the 757 PMA patient population as expected. Although lead dislodgement is not an unexpected complication and patients are routinely evaluated during follow-up procedures at follow-up visits, in order to minimize the incidence of lead dislodgement, the dual anchoring sleeve has been introduced and the incidence of lead dislodgement has drastically decreased. The one year actuarial survival results continue to be stable, above 99% for SCD and efficacy rates continue at greater than 98%.

AA DCRND PE

P 015/S000

9-Jul-1993

mfc

FROM:	LETTER DATE	LOGIN DATE	DUE DATE
MEDTRONIC INC. ATTN: JENNIFER M. MARRONE 7000 CENTRAL AVENUE, N.E. MINNEAPOLIS,, MN 554323576	07/08/93	07/09/93	/ /
	DOCUMENT: PMA	CONTROL # P920015/S000 AMENDMENT	

SUBJECT:
MEDTRONIC(R) TRANSVENE LEAD SYSTEM

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Medtronic

Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576
Telephone: (612) 574-4000
Cable: Medtronic Telex: 29-0598
FAX: (612) 574-4879

July 8, 1993

SENT VIA FEDERAL EXPRESS

MS. DORIS TERRY
Office of Device Evaluation (HFZ-450)
Center for Devices and Radiological Health
Food and Drug Administration - Room 170L
1390 Piccard Drive
Rockville, MD 20850

P920015
AC2V)

Dear Doris:

Enclosed please find a copy of the Transvene PMA Amendment (Volumes 1 and 2) dated March 26, 1993 and also the Transvene PMA Amendment dated June 1, 1993.

Sincerely yours,

MEDTRONIC, INC.

Heather Rohweder

Heather Rohweder
Senior Secretary
Cardiac Pacing Business
(612) 574-3289
(612) 574-6424 FAX

Enclosure

HFZ-450/ODE/DMC
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2

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3-Nov-1993

Yes

FROM: MEDTRONIC INC. ATTN: JENNIFER M. MARRONE 7000 CENTRAL AVENUE, N.E. MINNEAPOLIS,, MN 554323576	LETTER DATE 11/02/93	LOGIN DATE 11/03/93	DUE DATE / /
	DOCUMENT: PMA	CONTROL # P920015/S000 AMENDMENT	

SUBJECT:
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Medtronic

Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576
Telephone: (612) 574-4000
Cable: Medtronic Telex: 29-0598

November 2, 1993

Office of Device Evaluation
PMA Documentation Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

Re: PMA Amendment to the Medtronic® TRANSVENE® Lead System (Document Control Number P920015) /A-2V1
Response to FDA Approvable Letter of September 23, 1993

The purpose of this PMA Amendment is to document additional modifications to the TRANSVENE® Lead System Labelling. These changes are the result of further discussions between FDA and Medtronic.

Copies of the final proposed labeling (technical manuals and package labels) for the TRANSVENE® lead system (reference Attachment A) and the PCD® Device (reference Attachment B) are provided. (Note: The PCD® Technical Manual is synonymous with the term Physician's Manual.)

Via this amendment, we are also informing the Agency that there is no new safety and effectiveness information learned about the device (system) from the ongoing clinical study that could reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling.

Three copies of this submission are provided in accordance with 21 CFR Part 814.44(e)(2). It contains confidential and commercial trade secret information and we request that it be given the maximum protection provided by the law. If additional information is required, please contact Dennis Connolly at (612) 574-4696.

Sincerely,

MEDTRONIC, INC.

Charles H. Swanson, PhD.
Vice President, Regulatory Affairs
Cardiac Pacing Business
Tel: (612 574-3409
Fax: (612) 574-6424

Attachment

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FDA/CDRH/ODE/DMC

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Attachment B: PCD® Technical Manual

A

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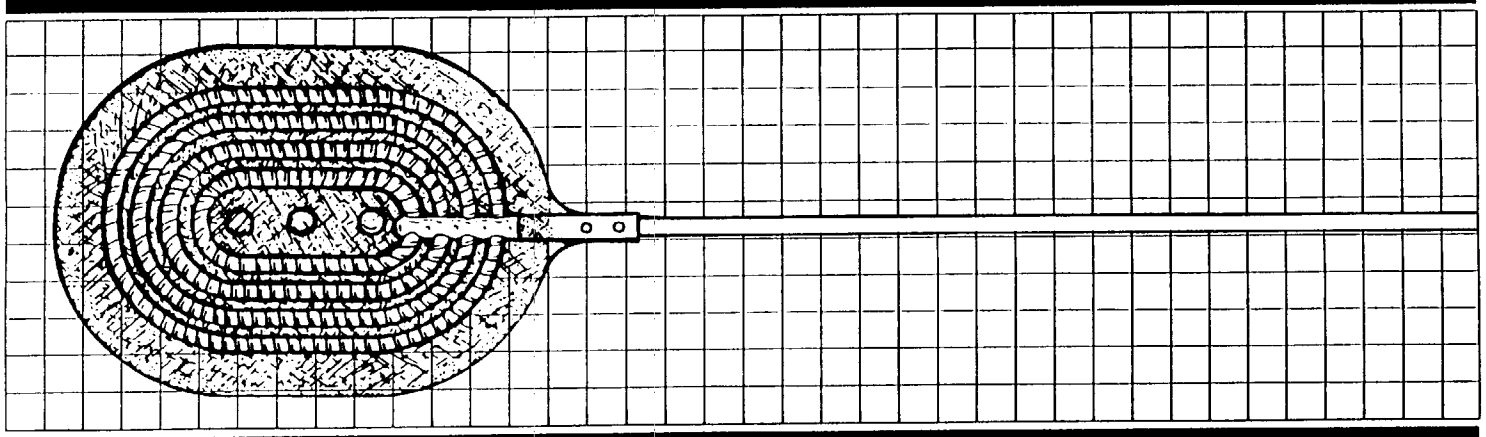
Medtronic

TRANSVENE®-SQ 6999

Unipolar, Subcutaneous, Oval Patch Lead



Technical Manual

TECHNICAL MANUAL

TRANSVENE®-SQ UNIPOLAR, SUBCUTANEOUS, OVAL PATCH LEAD FOR CARDIOVERSION AND DEFIBRILLATION

MODEL 6999

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DESCRIPTION

The Medtronic® TRANSVENE®-SQ Model 6999 Unipolar, Subcutaneous, Oval Patch Lead is designed for the delivery of cardioversion and defibrillation therapies.

The lead features a low resistance conductor coil and platinum alloy electrode coils for cardioversion and defibrillation therapies. The outer edge of the lead is used for suturing. The lead also has a 6.5 mm unipolar connector.

There are 3 nodes on one side of the patch, and 2 nodes at the junction of the lead body and patch electrode. These nodes are intended to mark the insulated side of the patch electrode.

INDICATIONS FOR USE

modified

The Medtronic® TRANSVENE®-SQ Model 6999 is intended for single long-term use only with a compatible Medtronic implantable tachyarrhythmia control device along with at least one other Medtronic defibrillation lead.

added Remand

~~**NOTE:** The Model 6999 TRANSVENE®-SQ patch lead is not intended for epicardial or pericardial placement.~~

The lead has application for patients in which implantable tachyarrhythmia cardioversion or defibrillation systems are indicated. Current medical research indicates that such patients should:

- have survived at least one episode of a cardiac arrest, presumably due to a ventricular tachyarrhythmia as evidenced by resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; OR
- in the absence of a prior cardiac arrest, have poorly tolerated sustained VT and/or VF, which occurs spontaneously or can be induced despite the best antiarrhythmic drug therapy.

The natural history of patients with hemodynamically stable sustained VT is not well defined. While this patient population was included in the TRANSVENE® Lead clinical study, the study objectives did not include stratification of this specific patient group.

modified

Prior to TRANSVENE® implant, it is strongly recommended that patients undergo a complete cardiac evaluation, which should include extensive electrophysiologic testing. Also, extensive electrophysiologic evaluation and testing of the

safety and efficacy of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the TRANSVENE® system.

CONTENTS OF PACKAGE

The leads are supplied sterile. Each package contains:

- 1 TRANSVENE®-SQ lead
- End Cap
- Product literature

CONTRAINDICATIONS

The TRANSVENE® system is contraindicated for patients.

- with transient ventricular tachyarrhythmias due to reversible causes, e.g., drug intoxication, electrolyte imbalance, sepsis, or hypoxia.
- with transient ventricular tachyarrhythmias due to other factors, e.g., myocardial infarction and electrocution.

The TRANSVENE® system is contraindicated for the sole use of detection and treatment of atrial arrhythmias.

~~The TRANSVENE® lead system is contraindicated for use in any system other than a Medtronic implantable~~ tachyarrhythmia control device system for which it has been tested. Refer to the appropriate Medtronic technical manual for the contraindications to the ICD system.

WARNINGS

Use only battery-powered equipment during lead implantation and testing to protect against fibrillation that may be caused by alternating currents. Line-powered equipment used in the vicinity of the patient must be properly grounded. Lead connector pins must be insulated from any leakage currents that may arise from line-powered equipment.

See also the section titled "General Warning."

Do not attempt to use the TRANSVENE® lead system with any device other than a Medtronic implantable tachyarrhythmia control device for which it has been tested. While there has been no testing of the TRANSVENE® leads with a non-Medtronic device, the potential adverse consequences of using such a combination may include, but are not limited to, undersensing cardiac activity and failure to deliver necessary therapy.

The Model 6999 TRANSVENE® SQ patch lead is not intended for epicardial or pericardial placement since testing has not been performed to determine if epicardial or pericardial use is safe or effective.

Placement of a patch electrode over nerve tissue may result in nerve damage.

The Model 6999 TRANSVENE® leads have palpable nodes on the insulation side of the patch which must face the skin surface to assure the electrode surface is facing the heart. If the insulation side of the patch is facing the heart cardioversion/defibrillation energy maybe inadequate to reliably convert arrhythmias.

If patients do not meet the implant criteria (demonstration of a 10 Joule safety margin) for a transvenous lead system, physicians should consider implanting an epicardial cardioversion/defibrillation lead system. If an epicardial system is to be implanted after testing a transvenous system, consider performing the procedure at a later date. The Transvene® clinical study showed a 9.3% perioperative death rate for patients failing the implant criteria for a Transvene® system and receiving an epicardial system. This compares to 0.7% for those patients receiving a Transvene® system without the additional epicardial surgical procedure.

PRECAUTIONS

Necessary Hospital Equipment

Defibrillation equipment should be kept nearby for immediate use during the acute lead system testing, implantation procedure, or whenever arrhythmias are possible or intentionally induced during post-implant testing.

Inspecting the Package

Carefully inspect the lead sterile package prior to opening; if the seal or package is damaged, contact your local Medtronic representative.

Handling the Lead

Leads should be handled with great care at all times. **Any severe bending, kinking, stretching, or handling with surgical instruments may cause permanent damage to the lead.**

Lead insulators attract small particles such as lint and dust. Therefore, protect the lead from materials shedding these substances. Handle the lead with sterile gloves that have been wiped with a sterile moist sponge or equivalent.

Do not immerse leads in mineral oil, silicone oil, or any other liquid.

Chronic Repositioning

Chronic repositioning or removal of the lead may be difficult because of the fibrotic tissue. **However, if a lead must be removed or repositioned, proceed with extreme caution.** If a lead is abandoned, it should be capped to avoid transmitting electrical signals. Return all removed or unused leads or portions thereof to Medtronic.

See additional cautions in the section titled "Suggested Implantation Procedure."

Resterilization

For resterilization use ethylene oxide only. Do not resterilize more than one time.

Implant Technique

Do not use surgical instruments to grasp the lead or connector pin when tunneling.

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POTENTIAL ADVERSE EFFECTS

The potential adverse effects related to the use of subcutaneous patch leads include, but are not limited to, the following patient-related conditions: serous fluid accumulation around the patch; infection; and bleeding after placement, after repositioning, or if sutures tear out.

Other potential adverse effects related to the lead system, but are not limited to the following: lead displacement, lead conductor or electrode fracture, insulation failure, and poor connection which may lead to loss of cardioversion and defibrillation therapies.

ENSURING PRODUCT INTEGRITY

Carefully inspect the sterile package before opening. It is not recommended that you use the product after its expiration date.

If the integrity of the sterile package has been compromised prior to the product expiration date, place the contents in a gas-permeable bag and resterilize them with ethylene oxide as described below.

CAUTION: Use ethylene oxide only. Do not resterilize more than one time.

The process should not exceed temperatures of 55°C (130°F). Allow proper aeration of ethylene oxide residues prior to implantation. Use an acceptable method to determine sterilizer effectiveness, such as a biological indicator.

Due to the variability between sterilizers, precise sterilization instructions cannot be provided. Contact your sterilizer manufacturer for more information regarding sterilization procedures.

SUGGESTED IMPLANTATION PROCEDURE

General Instructions

The implantation procedure generally includes selecting an insertion site; positioning the lead; taking electrical and defibrillation efficacy measurements; tunneling the lead; connecting the lead to the pulse generator; and closing the pocket.

Proper surgical procedures and sterile techniques are the responsibility of the medical professional. The implant procedures described in this manual are furnished for information only. Each physician must apply the information in these instructions according to professional medical training and experience.

Opening the Package

Open the package according to the instructions and inspect the lead.

Positioning a Lead

The recommended starting position for the TRANSVENE®-SQ subcutaneous patch lead is along the left chest near the heart. The patch may be repositioned, if necessary, to meet the implant defibrillation efficacy criteria.

The subcutaneous patch should be placed subcutaneously, submuscularly, or directly on the periosteum of the ribs.

Place sutures through the outer edge of the patch electrode. It is recommended that two or more sutures be used for fixation.

CAUTION: The patch must be placed such that the nodes are facing away from the heart (Figure 1).

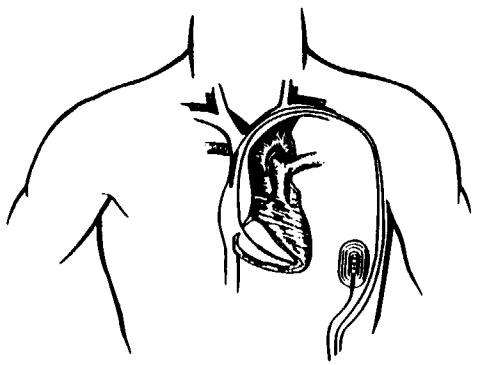


Figure 1. Positioning a Patch Lead

Taking Electrical Measurements and Defibrillation Efficacy Measurements

Initial electrical measurements may deviate from the recommendations because of acute cellular trauma. If this occurs, wait five to fifteen minutes and repeat the testing procedure. Values may vary depending upon lead type, pulse generator settings, cardiac tissue condition, and drug interactions. If electrical measurements do not stabilize to acceptable levels, it may be necessary to reposition the lead and repeat the testing procedure.

To demonstrate reliable defibrillation efficacy with acute or chronic leads, it is recommended that VF be initiated and terminated either two consecutive times at a stored energy of 24 joules or less, or 3 out of 4 times at a stored energy of 24 joules or less. If more than one of the four VF inductions are not terminated by the ETCD and lead system, the decision to implant the PCD device should be re-evaluated.

In order to keep patient morbidity and mortality to a minimum, patients should be rescued promptly with an external device if the lead system and ETCD fails to terminate the VF episode and at least 5 minutes should elapse between VF inductions.

For more information on obtaining electrical measurements, consult the technical manual supplied with the testing device.

Recommended Pacing/Sensing Measurements at Implant
(when using a pacing system analyzer)

Measurements Required	Acute Lead System	Chronic Lead System
Capture threshold (at 0.5 ms pulse width)	≤ 1.0 V	≤ 3.0 V
Impedance	200 - 800 ohms	200 - 800 ohms
Filtered R-wave amplitude	≥ 5 mV (during sinus rhythm)	≥ 3 mV (during sinus rhythm)
Slew rate	≥ 0.75 V/s	≥ 0.45 V/s

Tunneling the Lead

Before tunneling the lead connector, record each lead's serial number along with the function of the lead. Use of a chest tube is suggested in tunneling the lead connector to the pulse generator to prevent damage to the lead. Tunnel the lead subcutaneously to the pulse generator pocket.

CAUTION: Do not use surgical instruments to grasp the lead or connector pin when tunneling.

Connecting the Lead to a Tachyarrhythmia Device

Refer to Figures 2a and 2b for instructions and illustrations showing lead connections to the Medtronic® PCD® Tachyarrhythmia Control Device Model 7217B.

Insert the lead connector into the connector block. Refer to the PCD® Tachyarrhythmia Control Device technical manual for the use of setscrews and setscrew tools.

Before closing the pocket, verify sensing, pacing, and defibrillation efficacy.

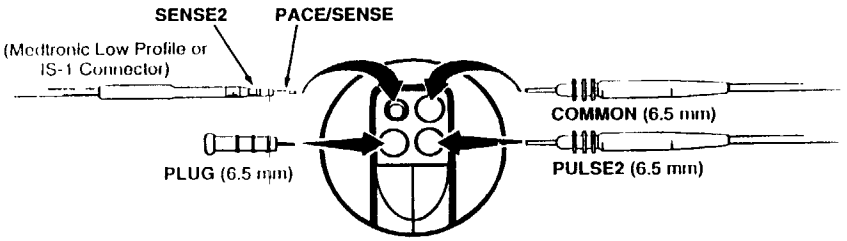
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillation Electrodes	Two-Electrode System Connection Diagram
Medtronic® Model 7217B PCD® Device	2	**PACE/SENSE, SENSE2** Insert the Pace/Sense lead connector of the TRANSVENE®-RV into the PACE/SENSE, SENSE2 port. **COMMON** Insert the unipolar lead connector of the TRANSVENE®-RV, -SVC, or -SQ into the COMMON port.  **PULSE1** Insert the connector plug packaged with the pulse generator into the PULSE1 port. **PULSE2** Insert the lead connector of the TRANSVENE®-RV, -SVC, or -SQ lead into the PULSE2 port.

Figure 2a. Connections for two-electrode system leads (single pulse) into the Medtronic® PCD® Tachyarrhythmia Control Device Model 7217B.

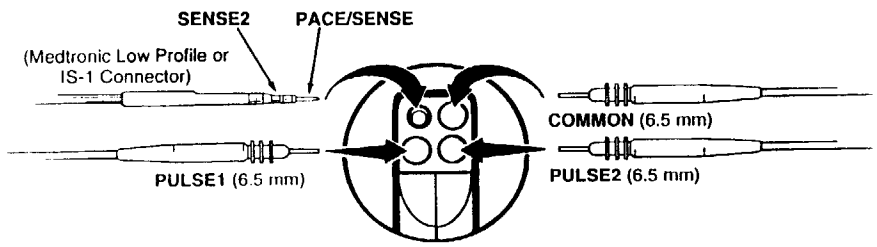
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillation Electrodes	Three-Electrode System Connection Diagram
Medtronic® Model 7217B PCD® Device	3	**PACE/SENSE, SENSE2** Insert the Pace/Sense lead connector of the TRANSVENE®-RV into the PACE/SENSE, SENSE2 port. **COMMON** Insert the unipolar lead connector of the TRANSVENE®-RV, -SVC, or -SQ into the COMMON port.  **PULSE1** Insert the lead connector of the TRANSVENE®-RV, -SVC, or -SQ lead into the PULSE1 port. **PULSE2** Insert the lead connector of the TRANSVENE®-RV, -SVC, or -SQ lead into the PULSE2 port.

Figure 2b. Connections for three electrode system leads (simultaneous or sequential pulse) into the Medtronic® PCD® Tachyarrhythmia Control Device Model 7217B.

Closing the Pocket

To prevent undesirable twisting of the lead body, wrap the excess lead length loosely under the pulse generator and place both into the subcutaneous pocket (Figure 3). Ensure that the leads do not leave the pulse generator at an acute angle. Sharp angles place undue stress on the lead conductor and insulation.

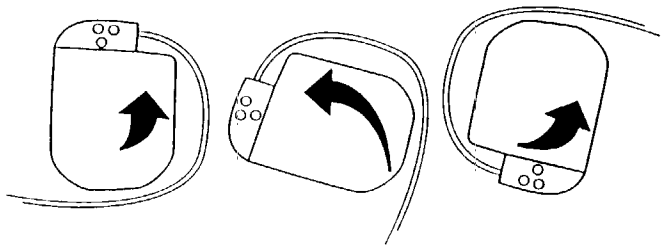


Figure 3. While rotating the pulse generator, loosely wrap the excess lead length and place it under the pulse generator.

To reduce the potential for abrasion on the lead body, it is recommended that the PCD be placed in a Parsonnet pouch.

When placing the pulse generator and leads into the subcutaneous pocket:

- Do NOT coil the lead. Coiling the lead can twist the lead body and may result in lead dislodgement (Figure 4).
- Do NOT grip the lead or pulse generator with surgical instruments.

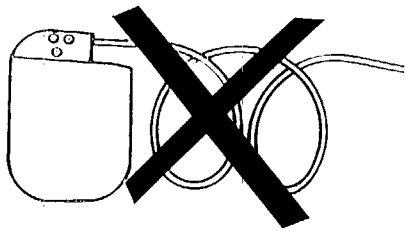


Figure 4. Do not coil or twist the lead body.

Post-Implant Evaluation

After implantation, monitor the patient's electrocardiogram continuously. If a lead dislodges, it usually occurs during the immediate postoperative period.

The patient should have X-rays and pacing/sensing thresholds taken every three months for the first year after implant and every six months thereafter to verify proper lead position and to check for conductor fractures.

In the event of a patient death, all implanted leads and devices should be explanted and returned to Medtronic with a completed PCD® Product Information Report. Any questions on product handling procedures can be addressed by calling 1-800-PCD-INFO.

SPECIFICATIONS (Nominal)

PARAMETER	MODEL 6999
Type	Unipolar
Position	Subcutaneous chest wall
Fixation	Sutures (may be placed through the outer edge of the patch body)
Length	50 cm
Connector	6.5 mm
Materials	Conductor: Multifilar MP35N Composite Insulator: Silicone Electrode: Platinum Alloy

PARAMETER	MODEL 6999
Number of Electrode Coils	4
Electrode Surface Area	660 mm^2
Body Diameter	2.5 mm
Patch Dimensions	8.0 cm x 11.0 cm
Silicone Patch Area	50 cm^2
Unipolar Resistance	1.2 ohms

GENERAL WARNING

Medtronic® implantable leads are implanted in the extremely hostile environment of the human body. Leads are necessarily very small in diameter and must still be very flexible, which unavoidably reduces their potential performance or longevity. Leads may fail to function for a variety of causes, including, but not limited to: medical complications, body rejection phenomena, allergic reaction, fibrotic tissue, or failure of leads by breakage or by breach of their insulation covering. In addition, despite the exercise of all due care in design, component selection, manufacture, and testing prior to sale, leads may be easily damaged before, during, or after insertion by improper handling or other intervening acts. Consequently, no representation or warranty is made that failure or cessation of function of leads will not occur or that the body will not react adversely to the implantation of leads or that medical complications will not follow the implantation of leads or that the lead will, in all cases, restore adequate cardiac function.

For complete warranty information, see the accompanying card enclosed in the package.

SERVICE

Medtronic employs highly trained representatives and engineers located throughout the world to serve you and, upon request, to provide training to qualified hospital personnel in the use of Medtronic products. In addition, Medtronic maintains a professional staff of consultants to provide technical and medical consultation to product users. For supplemental information, contact your local Medtronic representative, or call or write Medtronic at the appropriate address or telephone number listed on the back cover.

Europe

Medtronic Europe
Immeuble Myron
6, avenue E. van Nieuwenhuyse
B-1160, Brussels
Belgium
Telephone: (32-2) 676 08 11
FAX: (32-2) 676 08 15

Asia-Pacific

Japan
Medtronic Asia-Pacific
Shuwa Kioi-cho Park Building, 5F
3-6 Kioi-cho, Chiyoda-ku
Tokyo 102, Japan
Telephone: (81-3) 3230-2701
FAX: (81-3) 3230-0446

Australia
Medtronic Australasia Pty. Ltd.
22 Clarke Street
Crows Nest, Sydney, N.S.W., 2065
Australia
Telephone: (61) 2 437-6066
FAX: (61) 2 437-6869

Asia
Medtronic International Ltd.
2002 C C Wu Building
308 Hennessey Road,
Wanchai
Hong Kong, B.C.C.
Telephone: (852-5) 891-4068
FAX: (852) 891-6830

Latin America

Medtronic, Inc.
450 Fairway Drive
Suite 103
Deerfield Beach, FL 33441
U.S.A.
Telephone: (305) 428-8556
FAX: (305) 428-8984

North America

Canada
Medtronic of Canada Ltd.
6733 Kitimat Road
Mississauga, Ontario L5N 1W3
Canada
Telephone: (905) 826–6020
FAX: (905) 826-6620
Toll-free: 1-800-268-5346
(24-hour consultation service)

United States
Medtronic, Inc.
7000 Central Avenue, NE
Minneapolis, MN 55432-3576
U.S.A.
Telephone: (612) 574-4000
FAX: (612) 574-4879
Toll-free: 1-800-328-2518
(24-hour consultation service)

Medtronic

October 1993
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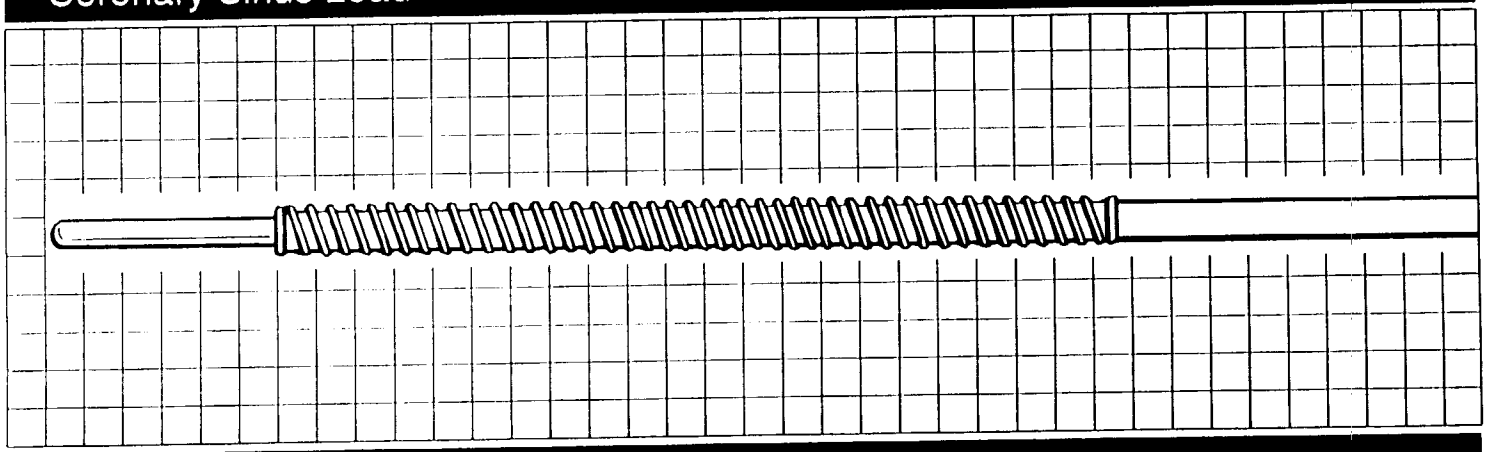
Medtronic

TRANSVENE®-SVC 6963

Unipolar, Endocardial, Superior Vena Cava or Coronary Sinus Lead



Technical Manual

TECHNICAL MANUAL

TRANSVENE®-SVC UNIPOLAR, ENDOCARDIAL, SUPERIOR VENA CAVA OR CORONARY SINUS LEAD FOR CARDIOVERSION AND DEFIBRILLATION

MODEL 6963

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DESCRIPTION

The Medtronic® TRANSVENE®-SVC Model 6963 Unipolar, Endocardial, Superior Vena Cava or Coronary Sinus Lead is designed for the delivery of cardioversion and defibrillation therapies.

Silicone insulation surrounds the low resistance conductor coil and the coil electrode is a platinum alloy. The lead also has a 6.5 mm connector.

INDICATIONS FOR USE

The Medtronic® TRANSVENE®-SVC Model 6963 is intended for single long-term use in the superior vena cava or coronary sinus and is designed to be used only with a compatible Medtronic implantable tachyarrhythmia control device along with at least one other Medtronic defibrillation lead.

The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated. Current medical research indicates that such patients should:

- have survived at least one episode of a cardiac arrest, presumably due to a ventricular tachyarrhythmia as evidenced by resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; OR
- in the absence of a prior cardiac arrest, have poorly tolerated sustained VT and/or VF, which occurs spontaneously or can be induced despite the best antiarrhythmic drug therapy.

The natural history of patients with hemodynamically stable sustained VT is not well defined. While this patient population was included in the TRANSVENE® Lead clinical study, the study objectives did not include stratification of this specific patient group.

Prior to TRANSVENE® implant, it is strongly recommended that patients undergo a complete cardiac evaluation, which should include extensive electrophysiologic testing. Also, extensive electrophysiologic evaluation and testing of the safety and efficacy of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the TRANSVENE® system.

CONTENTS OF PACKAGE

The leads are supplied sterile. Each package contains:

- 1 TRANSVENE®-SVC lead with two non-radiopaque anchoring sleeves, stylet, and stylet guide
- 1 vein lifter
- Extra stylets
- Product literature
- End Cap

CONTRAINDICATIONS

The TRANSVENE® system is contraindicated for patients:

- with transient ventricular tachyarrhythmias due to reversible causes, e.g., drug intoxication, electrolyte imbalance, sepsis, or hypoxia.
- with transient ventricular tachyarrhythmias due to other factors, e.g., myocardial infarction and electrocution.

The TRANSVENE® system is contraindicated for the sole use of detection and treatment of atrial arrhythmias.

The TRANSVENE® lead system is contraindicated for use in any system other than a Medtronic implantable tachyarrhythmia control device system for which it has been tested. Refer to the appropriate Medtronic technical manual for the contraindications to the ICD system.

WARNINGS

Use only battery-powered equipment during lead implantation and testing to protect against fibrillation that may be caused by alternating currents. Line-powered equipment used in the vicinity of the patient must be properly grounded. Lead connector pins must be insulated from any leakage currents that may arise from line-powered equipment.

See also the section titled "General Warning."

PRECAUTIONS

Necessary Hospital Equipment

Defibrillation equipment should be kept nearby for immediate use during the acute lead system testing, implantation procedure, or whenever arrhythmias are possible or intentionally induced during post-implant testing.

Do not attempt to use the TRANSVENE® lead system with any device other than a Medtronic implantable tachyarrhythmia control device for which it has been tested. While there has been no testing of the TRANSVENE® leads with a non-Medtronic device, the potential adverse consequences of using such a combination may include, but are not limited to, undersensing cardiac activity and failure to deliver necessary therapy.

Two anchoring sleeves are provided with the lead. Both anchoring sleeves should be used as described in the section of this manual "Anchoring the Lead" to assure adequate fixation.

If patients do not meet the implant criteria (demonstration of a 10 Joule safety margin) for a transvenous lead system, physicians should consider implanting an epicardial cardioversion/defibrillation lead system. If an epicardial system is to be implanted after testing a transvenous system, consider performing the procedure at a later date. The Transvene® clinical study showed a 9.3% perioperative death rate for patients failing the implant criteria for a Transvene® system and receiving an epicardial system. This compares to 0.7% for those patients receiving a Transvene® system without the additional epicardial surgical procedure.

Avoid placing the lead under extreme tension of angulation to prevent lead dislodgement and possible lead fracture. Do not grip the lead with surgical instruments.

Inspecting the Package

Carefully inspect the lead sterile package prior to opening; if the seal or package is damaged, contact your local Medtronic representative.

Handling the Lead

Leads should be handled with great care at all times. **Any severe bending, kinking, stretching, or handling with surgical instruments may cause permanent damage to the lead.**

Lead insulators attract small particles such as lint and dust. Therefore, protect the lead from materials shedding these substances. Handle the lead with sterile gloves that have been wiped with a sterile moist sponge or equivalent.

Do not immerse leads in mineral oil, silicone oil, or any other liquid.

Using an Anchoring Sleeve

Always use an anchoring sleeve with all leads to secure the lead from moving and to protect the lead insulation and conductor coil from damage. A second anchoring sleeve is provided for additional fixation.

Insertion Site
Given the body diameter of transvenous defibrillation leads, insertion via a subclavian approach should be done as far lateral as possible to avoid clamping the lead body between the clavicle and the first rib. Clamping the lead can eventually cause the conductor to fracture, can cause damage to the insulation, or can cause other damage to the lead. This can result in complications such as loss of detection, loss of pacing therapies, or loss of cardioversion/defibrillation therapy. Certain anatomical abnormalities, such as thoracic outlet syndrome, can also precipitate pinching and subsequent fracture of the lead. If the subclavian approach is required, avoid techniques that can damage the lead. Specifically, do not force the lead if significant resistance is encountered. Do not use techniques such as adjusting the patient's posture (i.e. raising the arm or putting a towel behind the person's back) to facilitate the passage of the lead. If resistance is encountered, it is recommended that an alternate venous entry site be used, e.g. the cephalic vein.

Implant Technique
Avoid placing the lead under extreme tension or angulation to prevent dislodgement and possible lead fracture. Do not grip the lead with surgical instruments.

Do not use the anchoring sleeve for suturing.

Do not use surgical instruments to grasp the lead or connector pin when

Chronic Repositioning

Chronic repositioning or removal of the lead may be difficult because of the fibrotic tissue. **However, if a lead must be removed or repositioned, proceed with extreme caution.** If a lead is abandoned, it should be capped to avoid transmitting electrical signals. Return all removed or unused leads or portions thereof to Medtronic.

See additional cautions in the section titled "Suggested Implantation Procedure."

POTENTIAL ADVERSE EFFECTS

The potential adverse effects related to the use of endocardial leads include, but are not limited to, the following patient-related conditions: fibrillation or other arrhythmias, air embolism, cardiac perforation, heart wall rupture, cardiac tamponade, infection, endocarditis, constrictive pericarditis, pneumothorax, hemothorax, and tissue necrosis.

Other potential adverse effects related to the lead system, but are not limited to the following: lead dislodgement, lead conductor or electrode fracture, insulation failure, and poor connection which may lead to loss of detection, cardioversion, and defibrillation therapies.

Resterilization
For resterilization use ethylene oxide only. Do not resterilize more than one time.

Stylet Usage
To avoid damage to the lead or body tissue, do not use excessive force or surgical instruments to insert a stylet into the lead. When handling a stylet, avoid overbending, kinking, or blood contact.

Repeated insertions of a stylet increases the chance that blood or other fluids may accumulate on it, which may cause difficulty in passing the stylet through the lead and may cause damage to the lead.

To avoid damage to the stylet, do not use a sharp object to impart a curve to the distal end.

Always remove the stylet before connecting the lead to the pulse generator. Failure to remove the stylet may result in lead failure.

ENSURING PRODUCT INTEGRITY

Carefully inspect the sterile package before opening. It is not recommended that you use the product after its expiration date.

If the integrity of the sterile package has been compromised prior to the product expiration date, place the contents in a gas-permeable bag and resterilize them with ethylene oxide as described below.

CAUTION: Use ethylene oxide only. Do not resterilize more than one time.

The process should not exceed temperatures of 55°C (130°F). Allow proper aeration of ethylene oxide residues prior to implantation. Use an acceptable method to determine sterilizer effectiveness, such as a biological indicator.

Due to the variability between sterilizers, precise sterilization instructions cannot be provided. Contact your sterilizer manufacturer for more information regarding sterilization procedures.

SUGGESTED IMPLANTATION PROCEDURE

General Instructions

The implantation procedure generally includes using a stylet guide, stylets, and a vein lifter; selecting an insertion site; positioning the lead; taking electrical and defibrillation efficacy measurements; anchoring the lead; tunneling the lead; connecting the lead to the pulse generator; and closing the pocket.

Proper surgical procedures and sterile techniques are the responsibility of the medical professional. The implant procedures described in this manual are furnished for information only. Each physician must apply the information in these instructions according to professional medical training and experience.

Opening the Package

Open the package according to the instructions. Inspect the lead. Remove the disc from the distal end of the lead. Verify that two anchoring sleeves are present.

Using the Stylet Guide and Stylets

The lead is packaged with a stylet guide attached and a stylet already inserted. Use of the stylet guide is optional. An attached stylet guide may be removed by gently pulling it off. To attach a stylet guide, gently push it as far as possible onto the connector pin that accepts the stylet (Figure 1).

A stylet provides additional stiffness and controlled flexibility for maneuvering the lead into position. Stylets vary in stiffness for different lead and stylet flexibility. Each stylet knob is etched with the stylet diameter and length.

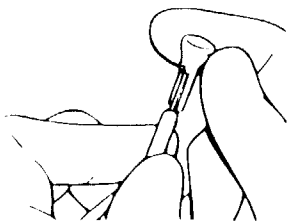

Figure 1. Stylet guide attachment.

If a slight curve is needed for the stylet, refer to instructions in the section titled "Positioning a Lead."

CAUTION: To avoid damage to the lead or body tissue, do not use excessive force or surgical instruments to insert a stylet into the lead. When handling a stylet, avoid overbending, kinking, or blood contact.

CAUTION: Repeated insertions of a stylet increases the chance that blood or other fluids may accumulate on it, which may cause difficulty in passing the stylet through the lead and may cause damage to the lead.

Selecting an Insertion Site

The lead may be inserted by venotomy through several different venous routes, including the right or left cephalic vein or the external or internal jugular vein. In general, a left venous entry site will aid in maneuvering the lead into the coronary sinus orifice.

CAUTION: Given the body diameter of transvenous defibrillation leads, insertion via a subclavian approach should be done as far lateral as possible to avoid clamping the lead body between the clavicle and the first rib (Figure 2). Clamping the lead can eventually cause the conductor to fracture, can cause damage to the insulation, or can cause other damage to the lead. This can result in complications such as loss of detection, loss of pacing

therapies, or loss of cardioversion/defibrillation therapy. Certain anatomical abnormalities, such as thoracic outlet syndrome, can also precipitate pinching and subsequent fracture of the lead. If the subclavian approach is required, avoid techniques that can damage the lead. Specifically, do not force the lead if significant resistance is encountered. Do not use techniques such as adjusting the patient's posture (i.e., raising the arm or putting a towel behind the person's back) to facilitate the passage of the lead. If resistance is encountered, it is recommended that an alternate venous entry site be used, e.g., the cephalic vein.

Use fluoroscopy to facilitate accurate lead placement.

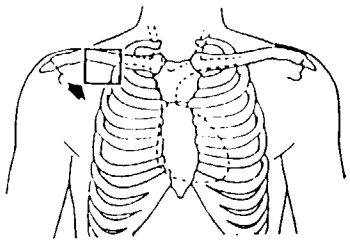

Figure 2. Insertion site.

Using a Vein Lifter

A vein lifter facilitates lead introduction. Insert its tapered end into the incised vein and gently push the lead tip underneath and into the vein (Figure 3). During insertion of the lead into the vein, make sure the anchoring sleeves do not slide off the distal end of the lead.

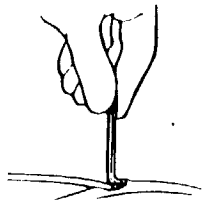

Figure 3. Using the vein lifter.

CAUTION: Avoid placing the lead under extreme tension or angulation to prevent lead dislodgement and possible lead fracture. **Do not grip the lead with surgical instruments.**

Positioning a Lead

For added control in maneuvering the lead tip, the distal end of the lead may be slightly curved by inserting a gently curved stylet as shown in Figure 4. A possible angle of curvature is illustrated in Figures 5 and 6.

CAUTION: To avoid damage to the stylet, do not use a sharp object to impart a curve to the distal end (Figure 4).

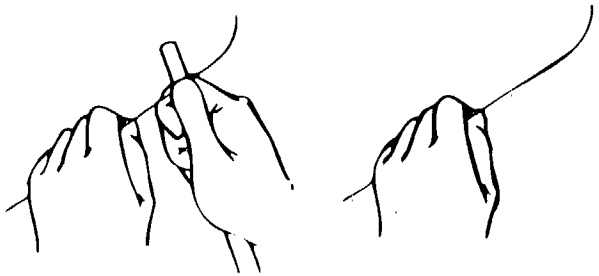

Figure 4. Imparting a curve to the stylet.

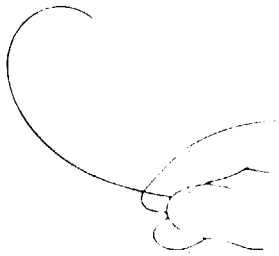

Figure 5. Bend the stylet into a gentle spiral. This gives the lead a gentle curve upward, to the left, and posterior.

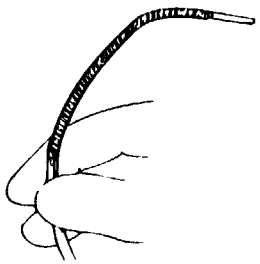

Figure 6. The curve in the stylet is designed to facilitate passage of the lead across the superior surface of the tricuspid valve. The second bend helps to position the lead to the left and posterior toward the coronary sinus ostium.

The electrode may be placed in either the superior vena cava or the coronary sinus.

If placing the electrode in the superior vena cava, advance the tip so that the distal portion of the electrode is approximately 3 to 5 cm proximal to the superior vena cava—right atrial junction.

If the electrode is to be placed in the coronary sinus, advance the lead into the right atrium and rotate the curved stylet to manipulate the tip over the tricuspid valve. Move the tip medially and posteriorly to the coronary sinus ostium and advance the lead into the coronary sinus. Continue advancing the lead through the coronary sinus to the desired position.

If the lead goes through the tricuspid valve opening, retract the lead with a gentle posterior rotation and then advance it toward the coronary sinus ostium.

The electrode for the TRANSVENE®-SVC must be as far as possible from other defibrillation electrodes. Also, the cardiac mass between the electrodes should be as large as possible. Insufficient separation between the electrodes may result in reduced defibrillation efficacy.

Proper positioning of the electrode is essential for defibrillation efficacy (Figure 7). Use fluoroscopy (P-A and lateral position) to ensure that the distal end of the electrode is properly positioned in the superior vena cava or is lodged in the coronary sinus with the proximal end of the electrode advanced beyond the coronary sinus ostium.

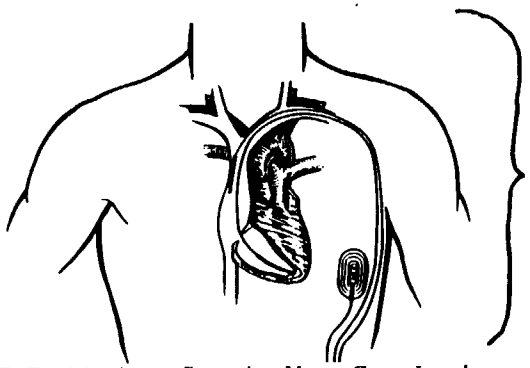

Figure 7. Positioning a Superior Vena Cava Lead

Bradycardia Pacemakers

Previously implanted bradycardia pacemakers, tachyarrhythmia devices and leads should be explanted. The output pulses of an implanted device may adversely affect the tachyarrhythmia detection capabilities of the PCD device. If leads must be abandoned rather than removed they should be capped to ensure they will not become a pathway for currents to or from the heart. If a patient requires a separate atrial or dual chamber pacemaker for hemodynamic reasons, either permanent or temporary, and allow adequate space between the pacing lead electrodes and the defibrillation lead electrodes.

Taking Electrical Measurements and Defibrillation Efficacy Measurements

Initial electrical measurements may deviate from the recommendations because of acute cellular trauma. If this occurs, wait five to fifteen minutes and repeat the testing procedure. Values may vary depending upon lead type, pulse generator settings, cardiac tissue condition, and drug interactions. If electrical measurements do not stabilize to acceptable levels, it may be necessary to reposition the lead and repeat the testing procedure.

To demonstrate reliable defibrillation efficacy with acute or chronic leads, it is recommended that VF be initiated and terminated either two consecutive times at a stored energy of 24 joules or less, or 3 out of 4 times at a stored energy of 24 joules or less. If more than one of the four VF inductions are not terminated by the ETCD and lead system, the decision to implant the PCD device should be re-evaluated.

In order to keep patient morbidity and mortality to a minimum, patients should be rescued promptly with an external device if the lead system and ETCD fails to terminate the VF episode and at least 5 minutes should elapse between VF inductions.

For more information on obtaining electrical measurements, consult the technical manual supplied with the testing device.

Recommended Pacing/Sensing Measurements at Implant
(when using a pacing system analyzer)

Measurements Required	Acute Lead System	Chronic Lead System
Capture threshold (at 0.5 ms pulse width)	≤ 1.0 V	≤ 3.0 V
Impedance	200 - 800 ohms	200 - 800 ohms
Filtered R-wave amplitude	≥ 5 mV (during sinus rhythm)	≥ 3 mV (during sinus rhythm)
Slew rate	≥ 0.75 V/s	≥ 0.45 V/s

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Anchoring the Lead

Do not secure the ligatures so tightly that they damage the vein, lead, or anchoring sleeve. Do not tie a ligature directly to the lead body (Figure 8). During anchoring, take care to avoid dislodging the lead tip.

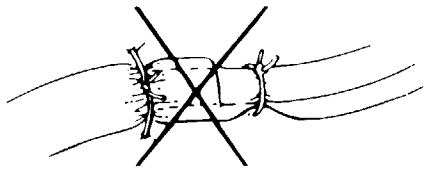


Figure 8. Do NOT secure the sutures too tightly and do NOT tie a suture to the lead body.

Use an anchoring sleeve to secure the lead from moving and to protect the lead insulation and conductor coil from damage caused by tight ligatures. A second anchoring sleeve should be placed in the tunnel entry site or in the pocket area for additional fixation.

Anchor the lead with nonabsorbable sutures.

The TRANSVENE®-SVC uses the triple groove anchoring sleeve illustrated in Figure 9. The triple groove anchoring sleeves are already situated at the connector end of the lead.

With a triple groove anchoring sleeve, all three grooves should be used with the following procedure (Figure 10).

- Partially insert the distal anchoring sleeve into the vein.
- **Use all three grooves to secure the anchoring sleeve (s) to the lead body.**
- Use the most distal suture groove to secure the anchoring sleeve to the vein.
- Use the middle groove to secure the anchoring sleeve to the fascia, vein, and lead body. First, create a base by looping a suture through the fascia underneath the middle groove and tying a knot. Continue by firmly wrapping the suture around the middle groove and tying a second knot.

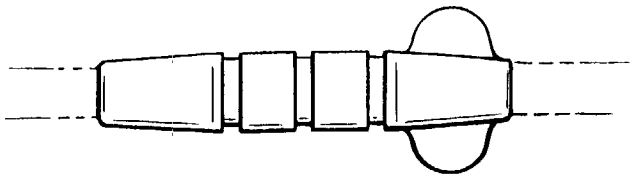


Figure 9. The triple groove anchoring sleeve.

CAUTION: Do not use the anchoring sleeve tabs for suturing.

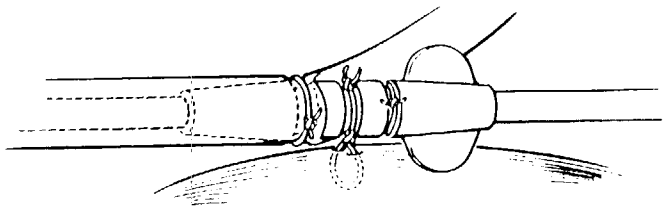


Figure 10. Triple groove anchoring sleeve secured to the lead and fascia using three grooves.

Tunneling the Lead

Before tunneling the lead connector, record each lead's serial number along with the function of the lead. Use of a chest tube is suggested in tunneling the lead connector to the pulse generator to prevent damage to the lead. Tunnel the lead subcutaneously to the pulse generator pocket.

CAUTION: Do not use surgical instruments to grasp the lead or connector pin when tunneling.

Connecting the Lead to a Tachyarrhythmia Device

Refer to Figures 11a and 11b for instructions and illustrations showing lead connections to the Medtronic® PCD® Tachyarrhythmia Control Device Model 7217B.

Insert the lead connector into the connector block. Refer to the PCD® Tachyarrhythmia Control Device technical manual for the use of setscrews and setscrew tools.

Before closing the pocket, verify sensing, pacing, and defibrillation efficacy.

CAUTION: Always remove the stylet before connecting the lead to the pulse generator. Failure to remove the stylet may result in lead failure.

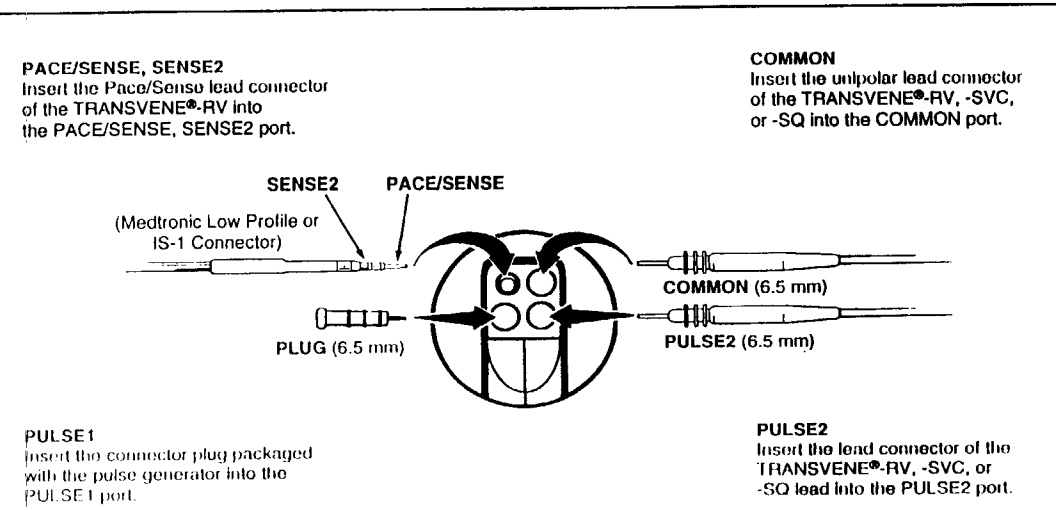
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillation Electrodes	Two-Electrode System Connection Diagram
Medtronic® Model 7217B PCD® Device	2	

Figure 11a. Connections for two-electrode system leads (single pulse) into the Medtronic® PCD® Tachyarrhythmia Control Device Model 7217B.

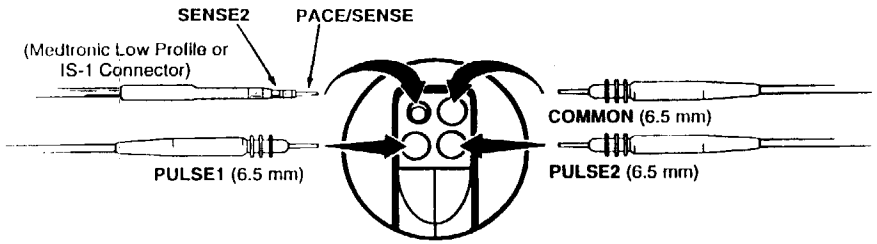
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillation Electrodes	Three-Electrode System Connection Diagram
Medtronic® Model 7217B PCD® Device	3	**PACE/SENSE, SENSE2** Insert the Pace/Sense lead connector of the TRANSVENE®-RV into the PACE/SENSE, SENSE2 port. **COMMON** Insert the unipolar lead connector of the TRANSVENE®-RV, -SVC, or -SQ into the COMMON port.  **PULSE1** Insert the lead connector of the TRANSVENE®-RV, -SVC, or -SQ lead into the PULSE1 port. **PULSE2** Insert the lead connector of the TRANSVENE®-RV, -SVC, or -SQ lead into the PULSE2 port.

Figure 11b Connections for three-electrode system leads (simultaneous or sequential pulse) into the Medtronic® PCD® Tachyarrhythmia Control Device Model 7217B.

Closing the Pocket

To prevent undesirable twisting of the lead body, wrap the excess lead length loosely under the pulse generator and place both into the subcutaneous pocket (Figure 12). Ensure that the leads do not leave the pulse generator at an acute angle. Sharp angles place undue stress on the lead conductor and insulation.

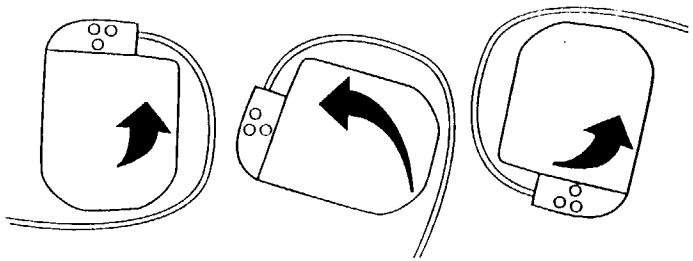


Figure 12. While rotating the pulse generator, loosely wrap the excess lead length and place it under the pulse generator.

To reduce the potential for abrasion on the lead body, it is recommended that the PCD be placed in a Parsonnet pouch.

When placing the pulse generator and leads into the subcutaneous pocket:

- Do NOT coil the lead. Coiling the lead can twist the lead body and may result in lead dislodgement (Figure 13).
- Do NOT grip the lead or pulse generator with surgical instruments.

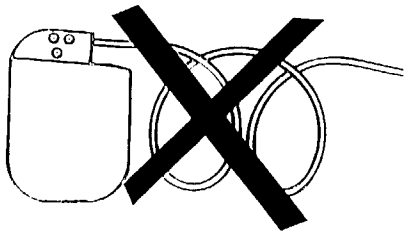


Figure 13. Do not coil or twist the lead body.

Post-Implant Evaluation

After implantation, monitor the patient's electrocardiogram continuously. If a lead dislodges, it usually occurs during the immediate postoperative period.

The patient should have X-rays and pacing/sensing thresholds taken every three months for the first year after implant and every six months thereafter to verify proper lead position and to check for conductor fractures.

In the event of a patient death, all implanted leads and devices should be explanted and returned to Medtronic with a completed PCD® Product Information Report. Any questions on product handling procedures can be addressed by calling 1-800-PCD-INFO.

SPECIFICATIONS (Nominal)

PARAMETER		MODEL 6963
Type		Unipolar
Position		Superior Vena Cava/ Coronary Sinus
Fixation		None. Tip lodges in the Superior Vena Cava or is placed in the Coronary Sinus
Length		110 cm
Connector		6.5 mm
Materials	Conductor:	Multifilar MP35N Composite
	Insulator:	Silicone
	Electrode:	Platinum Alloy

PARAMETER		MODEL 6963
Electrode Surface Area	Coil:	90 mm² (5 cm)
Diameters	Body:	1.7 mm
	Electrode:	2.3 mm
Unipolar Resistance		3.3 ohms
Lead Introducer (recommended size)		7.0 French

GENERAL WARNING

Medtronic® implantable leads are implanted in the extremely hostile environment of the human body. Leads are necessarily very small in diameter and must still be very flexible, which unavoidably reduces their potential performance or longevity. Leads may fail to function for a variety of causes, including, but not limited to: medical complications, body rejection phenomena, allergic reaction, fibrotic tissue, or failure of leads by breakage or by breach of their insulation covering. In addition, despite the exercise of all due care in design, component selection, manufacture, and testing prior to sale, leads may be easily damaged before, during, or after insertion by improper handling or other intervening acts. Consequently, no representation or warranty is made that failure or cessation of function of leads will not occur or that the body will not react adversely to the implantation of leads or that medical complications (including perforation of the heart) will not follow the implantation of leads or that the lead will, in all cases, restore adequate cardiac function.

For complete warranty information, see the accompanying card enclosed in the package.

SERVICE

Medtronic employs highly trained representatives and engineers located throughout the world to serve you and, upon request, to provide training to qualified hospital personnel in the use of Medtronic products. In addition, Medtronic maintains a professional staff of consultants to provide technical and medical consultation to product users. For supplemental information, contact your local Medtronic representative, or call or write Medtronic at the appropriate address or telephone number listed on the back cover.

Europe

Medtronic Europe
Immeuble Myron
6, avenue E. van Nieuwenhuyse
B-1160, Brussels
Belgium
Telephone: (32-2) 676 08 11
FAX: (32-2) 676 08 15

Asia-Pacific

Japan
Medtronic Asia-Pacific
Shuwa Kioi-cho Park Building, 5F
3-6 Kioi-cho, Chiyoda-ku
Tokyo 102, Japan
Telephone: (81-3) 3230-2701
FAX: (81-3) 3230-0446

Australia
Medtronic Australasia Pty. Ltd.
22 Clarke Street
Crows Nest, Sydney, N.S.W., 2065
Australia
Telephone: (61) 2 437-6066
FAX: (61) 2 437-6869

Asia
Medtronic International Ltd.
2002 C C Wu Building
308 Hennessey Road,
Wanchai
Hong Kong, B.C.C.
Telephone: (852-5) 891-4068
FAX: (852) 891-6830

Latin America

Medtronic, Inc.
450 Fairway Drive
Suite 103
Deerfield Beach, FL 33441
U.S.A.
Telephone: (305) 428-8556
FAX: (305) 428-8984

North America

Canada
Medtronic of Canada Ltd.
6733 Kitimat Road
Mississauga, Ontario L5N 1W3
Canada
Telephone: (905) 826–6020
FAX: (905) 826-6620
Toll-free: 1-800-268-5346
(24-hour consultation service)

United States
Medtronic, Inc.
7000 Central Avenue, NE
Minneapolis, MN 55432-3576
U.S.A.
Telephone: (612) 574-4000
FAX: (612) 574-4879
Toll-free: 1-800-328-2518
(24-hour consultation service)

Medtronic

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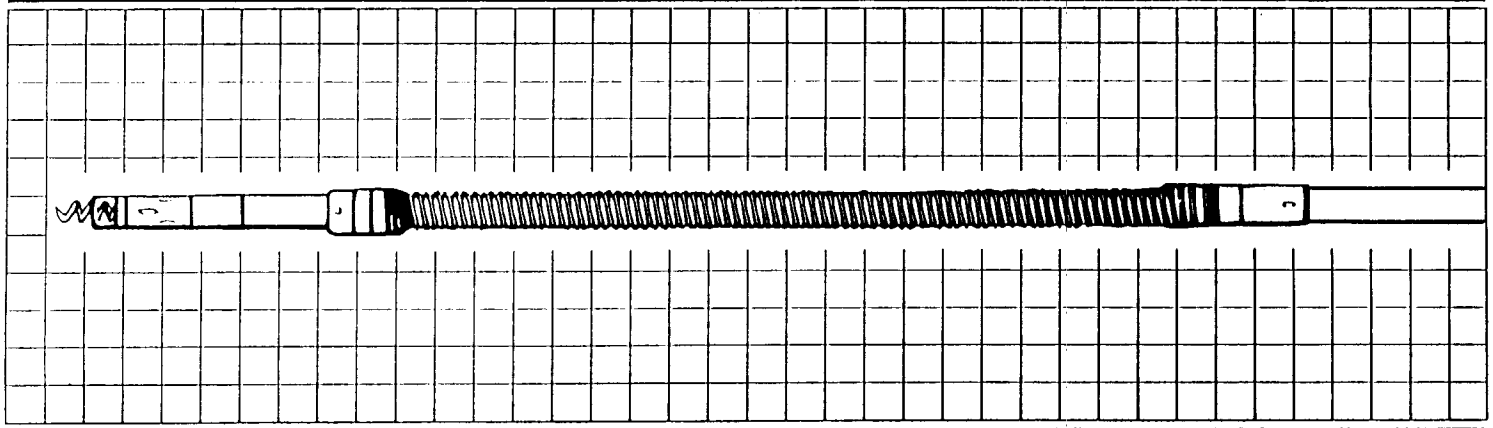
Medtronic

TRANSVENE®-RV 6966

Tripolar, Endocardial, Screw-in Ventricular Lead



Technical Manual

TECHNICAL MANUAL

TRANSVENE®-RV TRIPOLAR, ENDOCARDIAL, SCREW-IN LEAD FOR VENTRICULAR PACING, SENSING, CARDIOVERSION AND DEFIBRILLATION

MODEL 6966

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DESCRIPTION

The Medtronic® TRANSVENE®-RV Model 6966 Tripolar, Endocardial, Screw-In Ventricular Lead is designed for pacing, sensing, and delivering cardioversion and defibrillation therapies.

The Medtronic® TRANSVENE®-RV lead has a helical electrode made of platinum alloy that can be actively fixed in the endocardium. The helix can be extended or retracted by rotating the lead connector pin with a special fixation tool. Active fixation leads are particularly beneficial for patients who have smooth or hypertrophic hearts where lead dislodgement may be a potential problem.

The three electrodes of this lead are: coil, ring, and helix (Figure 1).

The defibrillating coil electrode is most proximal to the pulse generator and connects electrically to the connector PIN of the UNIPOLAR leg of the bifurcation. This UNIPOLAR leg will not accept a stylet.

The ring electrode is proximal to the helix and connects electrically to the connector RING of the BIPOLAR leg of the bifurcation.

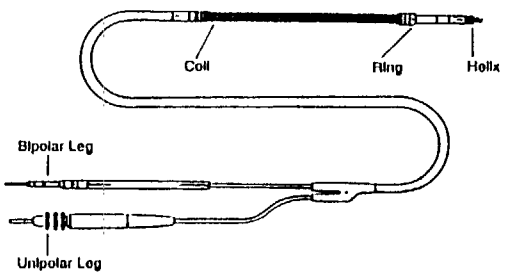

Figure 1. The three electrodes and two connector legs.

The helix tip electrode is most distal to the pulse generator and provides active fixation in the endocardium. It can be extended or retracted by rotating the lead connector PIN with a special fixation tool. The helix electrode connects electrically to the connector PIN of the BIPOLAR leg of the bifurcation. This BIPOLAR leg is the only one that will accept a stylet.

The lead's conductors are in a multifilar configuration and are insulated with polyurethane.

INDICATIONS FOR USE

The Medtronic® TRANSVENE®-RV Model 6966 is intended for single long-term use in the ventricle and is

The coil electrode is intended to be used for delivery of cardioversion and defibrillation pulses.

The helix tip electrode and the ring electrode may be used for bipolar pacing and sensing; however, when used with the standard bipolar PCD® pulse generators, pacing occurs between the tip electrode and the coil electrode.

designed to be used only with a compatible Medtronic implantable tachyarrhythmia control device along with at least one other Medtronic defibrillation lead.

The coil electrode is intended to be used for delivery of cardioversion and defibrillation pulses. The helix tip electrode and the ring electrode may be used for bipolar pacing and sensing; however, when used with the standard bipolar PCD® pulse generators, pacing occurs between the tip electrode and the coil electrode.

The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated. Current medical research indicates that such patients should:

- have survived at least one episode of a cardiac arrest, presumably due to a ventricular tachyarrhythmia as evidenced by resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; OR
- in the absence of a prior cardiac arrest, have poorly tolerated sustained VT and/or VF, which occurs spontaneously or can be induced despite the best antiarrhythmic drug therapy.

The natural history of patients with hemodynamically stable sustained VT is not well defined. While this patient population was included in the TRANSVENE® Lead clinical study, the study objectives did not include stratification of this specific patient group.

Prior to TRANSVENE® implant, it is strongly recommended that patients undergo a complete cardiac evaluation, which should include extensive electrophysiologic testing. Also, extensive electrophysiologic evaluation and testing of the safety and efficacy of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the TRANSVENE® system.

CONTENTS OF PACKAGE

The leads are supplied sterile. Each package contains:

- 1 TRANSVENE®-RV lead with two non-radiopaque anchoring sleeves, stylet, and stylet guide
- 2 fixation tools
- 1 vein lifter
- Extra stylets
- End Caps
- Product literature

CONTRAINDICATIONS

When tricuspid valvular disease or a mechanical heart valve is present, use of a ventricular endocardial lead is contraindicated.

The TRANSVENE® system is contraindicated for patients:

- with transient ventricular tachyarrhythmias due to reversible causes, e.g., drug intoxication, electrolyte imbalance, sepsis, or hypoxia.
- with transient ventricular tachyarrhythmias due to other factors, e.g., myocardial infarction and electrocution.

The TRANSVENE® system is contraindicated for the sole use of detection and treatment of atrial arrhythmias.

The TRANSVENE® lead system is contraindicated for use in any system other than a Medtronic implantable tachyarrhythmia control device system for which it has been tested. Refer to the appropriate Medtronic technical manual for the contraindications to the ICD system.

WARNINGS

Use only battery-powered equipment during lead implantation and testing to protect against fibrillation that may be caused by alternating currents. Line-powered equipment used in the vicinity of the patient must be properly grounded. Lead connector pins must be insulated from any leakage currents that may arise from line-powered equipment.

See also the section titled "General Warning."

PRECAUTIONS

Necessary Hospital Equipment

Defibrillation equipment should be kept nearby for immediate use during the acute lead system testing, implantation procedure, and whenever arrhythmias are possible or intentionally induced during post-implant testing.

Inspecting the Package

Carefully inspect the lead sterile package prior to opening; if the seal or package is damaged, contact your local Medtronic representative.

Handling the Lead

Leads should be handled with great care at all times. **Any severe bending, kinking, stretching, or handling with surgical instruments may cause permanent damage to the lead.**

new

Do not attempt to use the TRANSVENE® lead system with any device other than a Medtronic implantable tachyarrhythmia control device for which it has been tested. While there has been no testing of the TRANSVENE® leads with a non-Medtronic device, the potential adverse consequences of using such a combination may include, but are not limited to, undersensing cardiac activity and failure to deliver necessary therapy.

Two anchoring sleeves are provided with the lead. Both anchoring sleeves should be used as described in the section of this manual "Anchoring the Lead" to assure adequate fixation.

If patients do not meet the implant criteria (demonstration of a 10 Joule safety margin) for a transvenous lead system, physicians should consider implanting an epicardial cardioversion/defibrillation lead system. If an epicardial system is to be implanted after testing a transvenous system, consider performing the procedure at a later date. The Transvene® clinical study showed a 9.3% perioperative death rate for patients failing the implant criteria for a Transvene® system and receiving an epicardial system. This compares to 0.7% for those patients receiving a Transvene® system without the additional epicardial surgical procedure.

model 6966

New Warnings

Avoid placing the lead under extreme tension of angulation to prevent lead dislodgement and possible lead fracture. Do not grip the lead with surgical instruments.

Lead insulators attract small particles such as lint and dust. Therefore, protect the lead from materials shedding these substances. Handle the lead with sterile gloves that have been wiped with a sterile moist sponge or equivalent.

Do not immerse leads in mineral oil, silicone oil, or any other liquid.

The maximum number of revolutions of the electrode fixation tool needed to extend or retract the helix is 20. **Exceeding the maximum revolutions may damage the lead.**

Using an Anchoring Sleeve

Always use an anchoring sleeve with all leads to secure the lead from moving and to protect the lead insulation and conductor coil from damage. A second anchoring sleeve is provided for additional fixation.

Chronic Repositioning

Chronic repositioning or removal of screw-in leads may not be possible because of blood or fibrotic tissue development into the helix mechanism. Removal of the lead could result in avulsion of the endocardium, valve, or vein. In addition, the lead junctions may separate, leaving the lead tip and bare wire in the heart or vein. In most clinical situations, it is preferable to abandon unused leads in place.

However, if a lead must be removed or repositioned, proceed with extreme caution. If a helix does not disengage from the endocardium by rotating the connector pin, rotating the lead body counterclockwise may withdraw the helix and decrease the possibility of damage to the cardiovascular structures during removal.

If a lead is abandoned, it should be capped to avoid transmitting electrical signals from the pin to the heart. Return all removed or unused leads or portions thereof to Medtronic.

See additional cautions in the section "Suggested Implantation Procedure."

POTENTIAL ADVERSE EFFECTS

The potential adverse effects related to the use of endocardial leads include, but are not limited to, the following patient-related conditions: fibrillation or other arrhythmias, air embolism, cardiac perforation, heart wall rupture, cardiac tamponade, infection, endocarditis, constrictive pericarditis, pneumothorax, hemothorax, and tissue necrosis.

Resterilization
For resterilization use ethylene oxide only. Do not resterilize more than one time.

Rotating Helix
The maximum number of revolutions of the fixation tool needed to extend or retract the helix is 20. Exceeding the maximum number of revolutions may damage the lead.

Stylet Usage
To avoid damage to the lead or body tissue, do not use excessive force or surgical instruments to insert a stylet into the lead. When handling a stylet, avoid overbending, kinking, or blood contact.

Repeated insertions of a stylet increases the chance that blood or other fluids may accumulate on it, which may cause difficulty in passing the stylet through the lead and may cause damage to the lead.

To avoid damage to the stylet, do not use a sharp object to impart a curve to the distal end.

Always remove the stylet before connecting the lead to the pulse generator. Failure to remove the stylet may result in lead failure.

Insertion Site
Given the body diameter of transvenous defibrillation leads, insertion via a subclavian approach should be done as far lateral as possible to avoid clamping the lead body between the clavicle and the first rib. Clamping the lead can eventually cause the conductor to fracture, can cause damage to the insulation, or can cause other damage to the lead. This can result in complications such as loss of detection, loss of pacing therapies, or loss of cardioversion/defibrillation therapy. Certain anatomical abnormalities, such as thoracic outlet syndrome, can also precipitate pinching and subsequent fracture of the lead. If the subclavian approach is required, avoid techniques that can damage the lead. Specifically, do not force the lead if significant resistance is encountered. Do not use techniques such as adjusting the patient's posture (i.e. raising the arm or putting a towel behind the person's back) to facilitate the passage of the lead. If resistance is encountered, it is recommended that an alternate venous entry site be used, e.g. the cephalic vein.

Implant Technique
Avoid placing the lead under extreme tension or angulation to prevent dislodgement and possible lead fracture. Do not grip the lead with surgical instruments.

Do not use the anchoring sleeve for suturing.

Do not use surgical instruments to grasp the lead or connector pin when

Other potential adverse effects related to the lead system, but are not limited to the following: lead dislodgement, lead conductor or electrode fracture, insulation failure, and poor connection which may lead to loss of detection, cardioversion, defibrillation, or pacing therapies.

ENSURING PRODUCT INTEGRITY

Carefully inspect the sterile package before opening. It is not recommended that you use the product after its expiration date.

If the integrity of the sterile package has been compromised prior to the product expiration date, place the contents in a gas-permeable package and resterilize them with ethylene oxide as described below.

CAUTION: Use ethylene oxide only. Do not resterilize more than one time.

The process should not exceed temperatures of 55°C (130°F). Allow proper aeration of ethylene oxide residues prior to implantation. Use an acceptable method to determine sterilizer effectiveness, such as a biological indicator.

Due to the variability between sterilizers, precise sterilization instructions cannot be provided. Contact your sterilizer manufacturer for more information regarding sterilization procedures.

SUGGESTED IMPLANTATION PROCEDURE

The implantation procedure generally includes checking the mechanical functioning of the lead electrode before it is inserted; using a stylet guide, stylets, and vein lifter; selecting an insertion site; positioning the lead; securing the lead; taking electrical and defibrillation efficacy measurements; anchoring the lead; tunneling the lead; connecting the lead to the pulse generator; and closing the pocket.

Proper surgical procedures and sterile techniques are the responsibility of the medical professional. The implant procedures described in this manual are furnished for information only. Each physician must apply the information in these instructions according to professional medical training and experience.

modified

Opening the Package

Open the package according to the instructions. Inspect the lead. Remove the disc from the distal end of the lead. Verify that two anchoring sleeves are present.

Verifying the Mechanical Functioning of the Helix Electrode

Before implantation, verify the mechanical functioning of the electrode, as described below.

1. Within the sterile field, remove the lead and the accompanying stylets from the sterile packaging. The lead is packaged with a stylet guide attached and a stylet already inserted. The connector pin that accepts the stylet controls the helix mechanism.
2. To attach the fixation tool, first remove the stylet guide. Press both legs of the fixation tool together and place the most distal hole of the fixation tool on the connector pin that accepts the stylet (Figure 2).

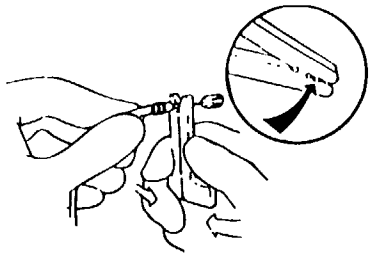

Figure 2. Attachment of the fixation tool to the connector pin.

3. Rotate the tool clockwise until the coiled electrode is completely exposed (Figure 3). Maximum electrode exposure reveals 2 coils.

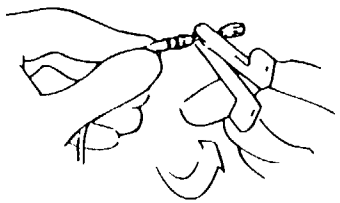

Figure 3. Rotating the fixation tool.

The maximum number of revolutions of the fixation tool needed to extend or retract the helix is 20.

CAUTION: Exceeding the maximum number of revolutions may damage the lead.

4. Disconnect the fixation tool from the connector pin and release the proximal end of the lead body. Allow several seconds for the lead and its conductor coil to unwind.
5. After allowing the lead and its conductor coil to unwind, reattach the fixation tool and turn it counterclockwise until the helix tip is retracted in the sheath.

Using the Stylet Guide and Stylets

The lead is packaged with a stylet guide attached and a stylet already inserted. The connector pin with the stylet in it controls the helix mechanism. Use of the stylet guide is optional. An attached stylet guide may be removed by gently pulling it off. To attach a stylet guide, gently push it as far as possible onto the connector pin that accepts the stylet (Figure 4).

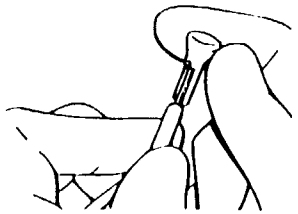

Figure 4. Stylet guide attachment.

A stylet provides additional stiffness and controlled flexibility for maneuvering the lead into position. Stylets vary in stiffness for different lead and stylet flexibility. Each stylet knob is etched with the stylet diameter and length.

If a slight curve is needed for the stylet, refer to instructions in the section titled "Positioning a Lead."

CAUTION: To avoid damage to the lead or body tissue, do not use excessive force or surgical instruments to insert a stylet into the lead. When handling a stylet, avoid overbending, kinking, or blood contact.

CAUTION: Repeated insertions of a stylet increases the chance that blood or other fluids may accumulate on it, which may cause difficulty in passing the stylet through the lead and may cause damage to the lead.

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Selecting an Insertion Site

The lead may be inserted by venotomy through several different venous routes, including the right or left cephalic vein or the external or internal jugular vein.

CAUTION: Given the body diameter of transvenous defibrillation leads, insertion via a subclavian approach should be done as far lateral as possible to avoid clamping the lead body between the clavicle and the first rib (Figure 5). Clamping the lead can eventually cause the conductor to fracture, can cause damage to the insulation, or can cause other damage to the lead. This can result in complications such as loss of detection, loss of pacing therapies, or loss of cardioversion/defibrillation therapy. Certain anatomical abnormalities, such as thoracic outlet syndrome, can also precipitate pinching and subsequent fracture of the lead. If the subclavian approach is required, avoid techniques that can damage the lead. Specifically, do not force the lead if significant resistance is encountered. Do not use techniques such as adjusting the patient's posture (i.e., raising the arm or putting a towel behind the person's back) to facilitate the passage of the lead. If resistance is encountered, it is recommended that an alternate venous entry site be used, e.g., the cephalic vein.

Use fluoroscopy to facilitate accurate lead placement.

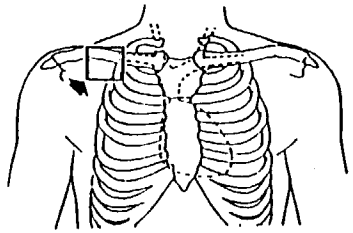

Figure 5. Insertion site.

Using the Vein Lifter

A vein lifter facilitates lead introduction. Insert its tapered end into the incised vein and gently push the lead tip underneath and into the vein (Figure 6).

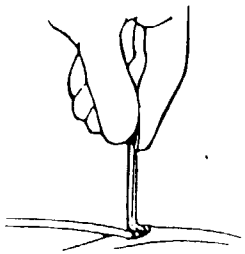

Figure 6. Using the vein lifter.

CAUTION: Avoid placing the lead under extreme tension or angulation to prevent lead dislodgement and possible lead fracture. **Do not grip the lead with surgical instruments.**

Positioning a Lead

Advance the lead into the right atrium. For added control in maneuvering the lead tip through the tricuspid valve, the distal end of the lead may be slightly curved by inserting a gently curved stylet (Figure 7). After the lead tip is passed into the ventricle, the curved stylet may be replaced with a straight stylet. The lead tip may then be advanced to the right ventricular apex while care is taken to avoid perforation of the ventricular wall.

CAUTION: To avoid damage to the stylet, do not use a sharp object to impart a curve to the distal end (Figure 7).

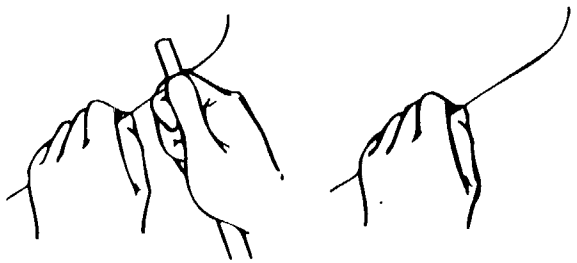

Figure 7. Imparting a curve to the stylet.

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Accurate positioning of the electrode is essential for stable endocardial pacing. A satisfactory position is usually achieved when the lead tip points straight toward the apex, or when the distal end dips or bends slightly (Figure 8).

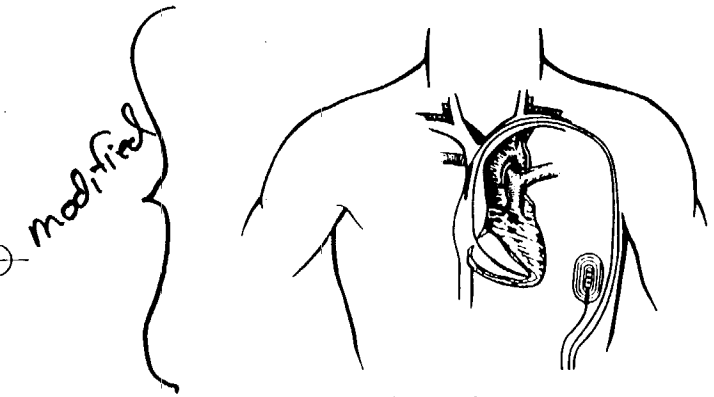


Figure 8. Positioning the Lead

Use fluoroscopy (lateral position) to ensure that the tip is not in a retrograde position or is not lodged in the coronary sinus.

After the stylet is inserted, gently remove the stylet guide so that it rests alongside the stylet knob.

Securing the Electrode into the Endocardium

The following procedure is recommended for electrode fixation:

1. Press both legs of the fixation tool together and place the most distal hole of the fixation tool on the connector pin that accepts the stylet (Figure 2).
2. Gently press the lead tip against the endocardium by pushing the stylet and the lead at the vein entry site. Then, rotate the tool clockwise until the coiled electrode is completely exposed (Figure 3). Maximum electrode exposure reveals 2 coils.

The maximum number of revolutions of the fixation tool needed to extend or retract the helix is 20.

CAUTION: Exceeding the maximum number of revolutions to extend or retract the helix may damage the lead.

3. Use fluoroscopy to verify helix electrode exposure. Closing of the space between the conductor (A) and the indicator ring (B) implies complete exposure of the helix electrode (Figure 9).

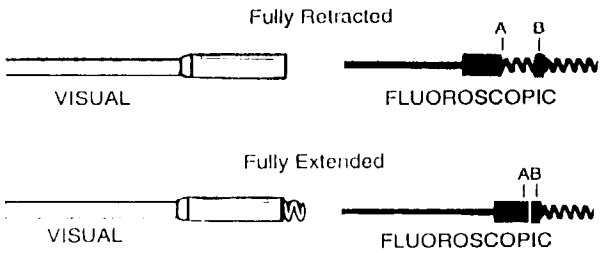


Figure 9. Possible views of the electrode.

4. Disconnect the fixation tool from the connector pin and release the proximal end of the lead body. Allow several seconds for the residual torque in the lead to be relieved.
5. After allowing the residual torque in the lead to be relieved, rotate the whole lead body clockwise approximately one revolution to ensure that the helical electrode is secured to the endocardium.
6. Carefully withdraw the stylet partially.
7. Obtain electrical measurements to verify satisfactory placement and electrode fixation. Refer to the following section, Taking Electrical and Defibrillation Efficacy Measurements, for recommended procedures and values.
8. Verify that the helix is affixed by gently pulling back on the lead and checking for resistance. A properly affixed helix will remain in position. If the helix is not properly affixed, the lead tip may become loose in the right ventricle.
9. If repositioning is required, reattach and rotate the fixation tool counterclockwise until the electrode is withdrawn. Use fluoroscopy to verify withdrawal. Repeat the procedure above.

CAUTION: When retracting the helix, do not rotate the fixation tool more than 20 revolutions. When the electrode is fully retracted, 2 coils of the helix will be visible between the indicator ring and the conductor.

10. Remove the stylet guide and stylet completely. When removing the stylet guide, grip the lead firmly just below the connector pin; this will help prevent possible lead dislodgement.

Bradycardia Pacemakers

Previously implanted bradycardia pacemakers, tachyarrhythmia devices and leads should be explanted. The output pulses of an implanted device may adversely affect the tachyarrhythmia detection capabilities of the PCD device. If leads must be abandoned rather than removed they should be capped to ensure they will not become a pathway for currents to or from the heart. If a patient requires a separate atrial or dual chamber pacemaker for hemodynamic reasons, either permanent or temporary, and allow adequate space between the pacing lead electrodes and the defibrillation lead electrodes.

Taking Electrical Measurements and Defibrillation Efficacy Measurements

Initial electrical measurements may deviate from the recommendations because of acute cellular trauma. If this occurs, wait five to fifteen minutes and repeat the testing procedure. Values may vary depending upon lead type, pulse generator settings, cardiac tissue condition, and drug interactions. If electrical measurements do not stabilize to acceptable levels, it may be necessary to reposition the lead and repeat the testing procedure.

To demonstrate reliable defibrillation efficacy with acute or chronic leads, it is recommended that VF be initiated and terminated either two consecutive times at a stored energy of 24 joules or less, or 3 out of 4 times at a stored energy of 24 joules or less. If more than one of the four VF inductions are not terminated by the ETCD and lead system, the decision to implant the PCD® device should be re-evaluated.

In order to keep patient morbidity and mortality to a minimum, patients should be rescued promptly with an external device if the lead system and ETCD falls to terminate the VF episode and at least 5 minutes should elapse between VF inductions.

For more information on obtaining electrical measurements, consult the technical manual supplied with the testing device.

Recommended Pacing/Sensing Measurements at Implant
(when using a pacing system analyzer)

Measurements Required	Acute Lead System	Chronic Lead System
Capture threshold		
(at 0.5 ms pulse width)	≤ 1.0 V	≤ 3.0 V
Impedance	200 - 800 ohms	200 - 800 ohms
Filtered R-wave amplitude	≥ 5 mV (during sinus rhythm)	≥ 3 mV (during sinus rhythm)
Slew rate	≥ 0.75 V/s	≥ 0.45 V/s

Anchoring the Lead

Do not secure the ligatures so tightly that they damage the vein, lead, or anchoring sleeve. Do not tie a ligature directly to the lead body (Figure 10). During anchoring, take care to avoid dislodging the lead tip.

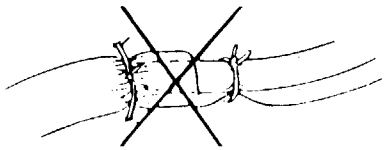


Figure 10. Do NOT secure the sutures too tightly and do NOT tie a suture to the lead body.

Use an anchoring sleeve to secure the lead from moving and to protect the lead insulation and conductor coil from damage caused by tight ligatures. A second anchoring sleeve should be placed in the tunnel entry site or in the pocket area for additional fixation.

Anchor the lead with nonabsorbable sutures.

TRANSVENE® RV uses a triple groove anchoring sleeve illustrated in Figure 11. The triple groove anchoring sleeves are situated at the connector end of the lead.

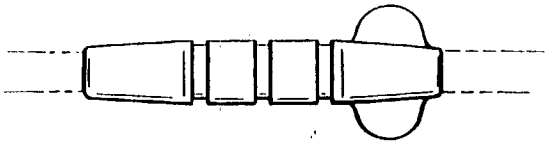


Figure 11. The triple groove anchoring sleeve.

With a triple groove anchoring sleeve, all three grooves should be used with the following procedure (Figure 12):

- Partially insert the distal anchoring sleeve into the vein.
- **Use all three grooves to secure the anchoring sleeve (s) to the lead body.**
- Use the most distal suture groove to secure the anchoring sleeve to the vein.
- Use the middle groove to secure the anchoring sleeve to the fascia, vein, and lead body. First, create a base

by looping a suture through the fascia underneath the middle groove and tying a knot. Continue by firmly wrapping the suture around the middle groove and tying a second knot.

CAUTION: Do not use the anchoring sleeve tabs for suturing.

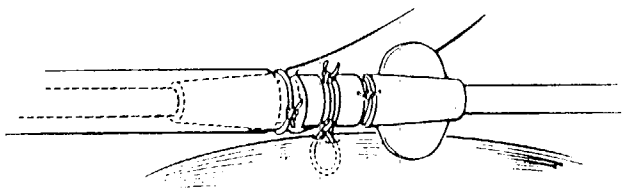


Figure 12. Triple groove anchoring sleeve secured to the lead and fascia using three grooves.

Tunneling the Lead

Before tunneling the lead connector, record each lead's serial number along with the function of the lead. Use of a chest tube is suggested in tunneling the lead connector to the pulse generator to prevent damage to the lead. Tunnel the lead subcutaneously to the pulse generator pocket.

CAUTION: Do not use surgical instruments to grasp the lead or connector pin when tunneling.

Connecting the Lead to a Tachyarrhythmia Device

Refer to Figures 13a and 13b for instructions and illustrations showing lead connections to the Medtronic® PCD® Tachyarrhythmia Control Device Model 7217B.

Insert the lead connector into the connector block. Refer to the PCD® Tachyarrhythmia Control Device technical manual for the use of setscrews and setscrew tools.

Before closing the pocket, verify sensing, pacing, and defibrillation efficacy.

CAUTION: Always remove the stylet before connecting the lead to the pulse generator. Failure to remove the stylet may result in lead failure.

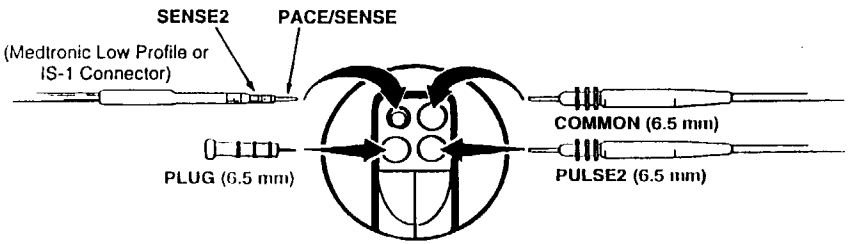
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillation Electrodes	Two-Electrode System Connection Diagram
Medtronic® Model 7217B PCD® Device	2	**PACE/SENSE, SENSE2** Insert the Pace/Sense lead connector of the TRANSVENE®-RV into the PACE/SENSE, SENSE2 port. **COMMON** Insert the unipolar lead connector of the TRANSVENE®-RV, -SVC, or -SQ into the COMMON port.  **PULSE1** Insert the connector plug packaged with the pulse generator into the PULSE1 port. **PULSE2** Insert the lead connector of the TRANSVENE®-RV, -SVC, or -SQ lead into the PULSE2 port.

Figure 13a. Connections for two-electrode system leads (single pulse) into the Medtronic® PCD® Tachyarrhythmia Control Device 7217B.

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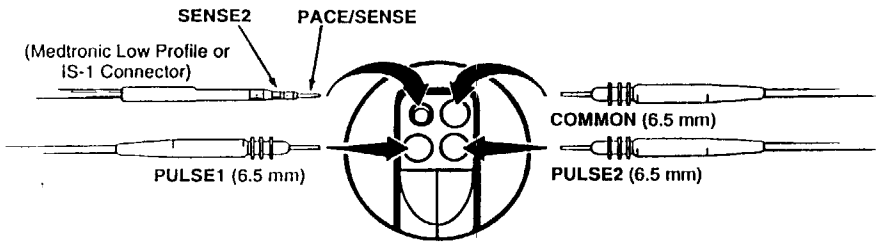
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillation Electrodes	Three-Electrode System Connection Diagram
Medtronic® Model 7217B PCD® Device	3	**PACE/SENSE, SENSE2** Insert the Pace/Sense lead connector of the TRANSVENE®-RV into the PACE/SENSE, SENSE2 port. **COMMON** Insert the unipolar lead connector of the TRANSVENE®-RV, -SVC, or -SQ into the COMMON port.  **PULSE1** Insert the lead connector of the TRANSVENE®-RV, -SVC, or -SQ lead into the PULSE1 port. **PULSE2** Insert the lead connector of the TRANSVENE®-RV, -SVC, or -SQ lead into the PULSE2 port.

Figure 13b. Connections for three-electrode system leads (simultaneous or sequential pulse) into the Medtronic® PCD® Tachyarrhythmia Control Device 7217B.

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Closing the Pocket

To prevent undesirable twisting of the lead body, wrap the excess lead length loosely under the pulse generator and place both into the subcutaneous pocket (Figure 14). Ensure that the leads do not leave the pulse generator at an acute angle. Sharp angles place undue stress on the lead conductor and insulation.

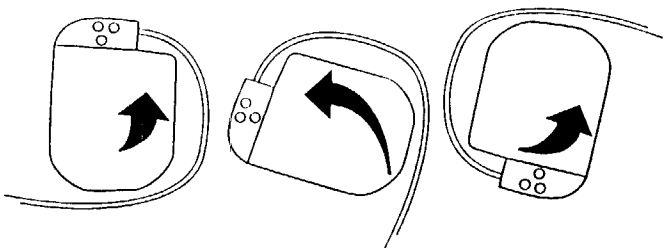

Figure 14. While rotating the pulse generator, loosely wrap the excess lead length and place it under the pulse generator.

To reduce the potential for abrasion on the lead body, it is recommended that the PCD be placed in a Parsonnet pouch.

When placing the pulse generator and leads into the subcutaneous pocket:

- Do NOT coil the lead. Coiling the lead can twist the lead body and may result in lead dislodgement (Figure 15).
- Do NOT grip the lead or pulse generator with surgical instruments.

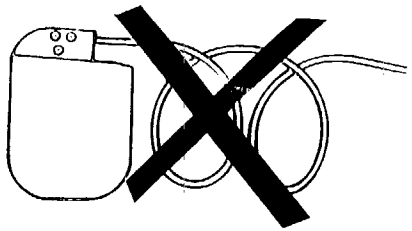

Figure 15. Do not coil or twist the lead body.

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Post-Implant Evaluation

After implantation, monitor the patient's electrocardiogram continuously. If a lead dislodges, it usually occurs during the immediate postoperative period.

The patient should have X-rays and pacing/sensing thresholds taken every three months for the first year after implant and every six months thereafter to verify proper lead position and to check for conductor fractures.

In the event of a patient death, all implanted leads and devices should be explanted and returned to Medtronic with a completed PCD® Product Information Report. Any questions on product handling procedures can be addressed by calling 1-800-PCD-INFO.

SPECIFICATIONS (Nominal)

PARAMETER		MODEL 6966
Type		Tripolar
Position		Ventricle
Fixation		Screw-In
Length		110 cm
Connectors	Unipolar:	6.5 mm
	Bipolar:	3.2 mm
Materials	Conductors:	Multifilar MP35N Composite
	Insulator:	Polyurethane
	Electrode:	Platinum Alloy
Electrode Surface Area	Helix:	10 mm^2
	Ring:	37 mm^2
	Coil:	426 mm^2 (5 cm length)

PARAMETER		MODEL 6966
Diameters	Body:	3.3 mm
	Helix:	1.6 mm
	Maximum Head:	3.5 mm
Helix Length (fully extended)		2 mm
Conductor Resistances	Pacing:	45 ohms (unipolar) 190 ohms (bipolar)
	Defibrillation:	3.5 ohms
Lead Introducer (recommended size)		11 French
Maximum Revolutions that can be used to extend or retract the helix when using a straight style		20

GENERAL WARNING

Medtronic® implantable leads are implanted in the extremely hostile environment of the human body. Leads are necessarily very small in diameter and must still be very flexible, which unavoidably reduces their potential performance or longevity. Leads may fail to function for a variety of causes, including, but not limited to: medical complications, body rejection phenomena, allergic reaction, fibrotic tissue, or failure of leads by breakage or by breach of their insulation covering. In addition, despite the exercise of all due care in design, component selection, manufacture, and testing prior to sale, leads may be easily damaged before, during, or after insertion by improper handling or other intervening acts. Consequently, no representation or warranty is made that failure or cessation of function of leads will not occur or that the body will not react adversely to the implantation of leads or that medical complications (including perforation of the heart) will not follow the implantation of leads or that the lead will, in all cases, restore adequate cardiac function.

For complete warranty information, see the accompanying card enclosed in the package.

SERVICE

Medtronic employs highly trained representatives and engineers located throughout the world to serve you and, upon request, to provide training to qualified hospital personnel in the use of Medtronic products. In addition, Medtronic maintains a professional staff of consultants to provide technical and medical consultation to product users. For supplemental information, contact your local Medtronic representative, or call or write Medtronic at the appropriate address or telephone number listed on the back cover.

Europe

Medtronic Europe
Immeuble Myron
6, avenue E. van Nieuwenhuyse
B-1160, Brussels
Belgium
Telephone: (32-2) 676 08 11
FAX: (32-2) 676 08 15

Asia-Pacific

Japan
Medtronic Asia-Pacific
Shuwa Kioi-cho Park Building, 5F
3-6 Kioi-cho, Chiyoda-ku
Tokyo 102, Japan
Telephone: (81-3) 3230-2701
FAX: (81-3) 3230-0446

Australia
Medtronic Australasia Pty. Ltd.
22 Clarke Street
Crows Nest, Sydney, N.S.W., 2065
Australia
Telephone: (61) 2 437-6066
FAX: (61) 2 437-6869

Asia
Medtronic International Ltd.
2002 C C Wu Building
308 Hennessey Road,
Wanchai
Hong Kong, B.C.C.
Telephone: (852-5) 891-4068
FAX: (852) 891-6830

Latin America

Medtronic, Inc.
450 Fairway Drive
Suite 103
Deerfield Beach, FL 33441
U.S.A.
Telephone: (305) 428-8556
FAX: (305) 428-8984

North America

Canada
Medtronic of Canada Ltd.
6733 Kitimat Road
Mississauga, Ontario L5N 1W3
Canada
Telephone: (905) 826–6020
FAX: (905) 826-6620
Toll-free: 1-800-268-5346
(24-hour consultation service)

United States
Medtronic, Inc.
7000 Central Avenue, NE
Minneapolis, MN 55432-3576
U.S.A.
Telephone: (612) 574-4000
FAX: (612) 574-4879
Toll-free: 1-800-328-2518
(24-hour consultation service)

Medtronic

October 1993
UC9002414cEN 195434-004

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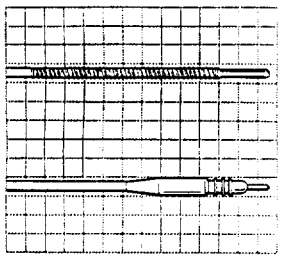
Medtronic

TRANSVENE®-SVC 6963

Unipolar Connector (6,5 mm)/Connecteur Unipolaire (6,5 mm)/Unipolarer Konnektor (6,5 mm)/Conector Monopolar (6,5 mm)/Connettore Monopolare (6,5 mm)



Serial Number Numéro de Série Seriennummer Número de Serie Numero di Serie	Use Before Utiliser Avant Zu implantieren vor dem Fecha de Caducidad Data di Scadenza
Lead Length Longueur de la Sonde Länge der Elektrode Longitud del Cable Lunghezza dell'Elettrocatetere	Sterilization Date Date de Stérilisation Sterilisationsdatum Fecha de Esterilización Data di Sterilizzazione

Contents: One lead with silicone insulation, accessories and product literature
Contenu: Une sonde avec isolant en silicone, accessoires et documentation relative au produit
Inhalt: Eine Elektrode mit Silikonisolation, Zubehör und Produktbeschreibung
Contenido: Un electrodo con aislante de silicona, accesorios y literatura del producto
Contenuto: Un elettrocatetere con isolante in silicone, accessori e letteratura del prodotto

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician
ATTENTION: La réglementation américaine (FDA) n'autorise la vente de ce produit que sur prescription médicale
ACHTUNG: Ein US-Bundesgesetz schränkt den Verkauf dieses Produkts auf Ärzte oder auf Anordnung durch einen Arzt ein
PRECAUCION: Las Leyes Federales (EE.UU.) restringen la venta de este dispositivo únicamente a médicos o por prescripción médica
ATTENZIONE: La Legge Federale (U.S.A.) limita la vendita di questo prodotto esclusivamente ai medici o su richiesta del medico

The contents (STERILE) of the inner package have been sterilized by ethylene-oxide gas
Le contenu (STERILE) du paquet interne a été stérilisé au gaz d'oxyde d'éthylène
Der Inhalt (STERIL) der inneren Verpackung ist in Äthylenoxydgas sterilisiert
El contenido (ESTERIL) del paquete interior ha sido esterilizado con gas óxido de etileno
Il contenuto (STERILE) della confezione interna è stato sottoposto a sterilizzazione con gas ossido di etilene

STORAGE: Store below 40° C/104° F
STOCKAGE: Au-dessous de 40° C/104° F
LAGERUNG: Unter 40° C/104° F
ALMACENAMIENTO: Por debajo de 40° C/104° F
IMMAGAZZINAGGIO: Al di sotto di 40° C/104° F

Recommended lead introducer size
Dimension recommandée de l'introducteur
Empfohlene Größe des Einführungsbestecks 7 French
Tamaño recomendado del introductor de cable
Dimensioni raccomandate dell'introduttore

A thoracotomy is not required
Une thoracotomie n'est pas nécessaire
Eine Thorakotomie ist nicht erforderlich
No es necesaria una toracotomía
Una toracotomia non è richiesta

DER GRÜNE PUNKT

CE 0123

Shelf Box Label

TRANSVENE®-SVC 6963

Unipolar, Endocardial, Coronary Sinus/SVC Lead for Cardioversion and Defibrillation
Unipolar Connector (6.5mm)

USE BEFORE

SERIAL NO.

End Label S.L.P.

Opening Instruction Label

INDIVIDUAL DATA SHEET
FICHE TECHNIQUE INDIVIDUELLE
INDIVIDUELLES TECHNISCHES DATENBLATT
HOJA DE DATOS
FOGLIO D'INFORMAZIONI SPECIFICO

MODEL-MODELE-MODELL-MODELO-MODELLO
6963

Use Before
Utiliser Avant
Zu implantieren vor dem
Fecha de Caducidad
Data di Scadenza

Sterilization Date
Date de Stérilisation
Sterilisationsdatum
Fecha de Esterilización
Data di Sterilizzazione

Serial Number
Numéro de Série
Seriennummer
Número de Serie
Numero di Serie

Sterilization
Stérilisation
Sterilisation
Esterilización
Sterilizzazione

For Your Records

Medtronic 6963 SERIAL NO.	Medtronic 6963 SERIAL NO.
Medtronic 6963 SERIAL NO.	Medtronic 6963 SERIAL NO.

Medtronic

TRANSVENE®-SVC 6963

Unipolar Connector (6,5 mm)/Connecteur Unipolaire (6,5 mm)/Unipolarer Konnektor (6,5 mm)/Conector Monopolar (6,5 mm)/Connettore Monopolare (6,5 mm)

Serial Number Numéro de Série Seriennummer Número de Serie Numero di Serie	Use Before Utiliser Avant Zu implantieren vor dem Fecha de Caducidad Data di Scadenza
Lead Length Longueur de la Sonde Länge der Elektrode Longitud del Cable Lunghezza dell'Elettrocatetere	Sterilization Date Date de Stérilisation Sterilisationsdatum Fecha de Esterilización Data di Sterilizzazione
Non Reusable Non Réutilisable Nicht wiederverwendbar Inferior Desechable Materiale Sterile Involucro Non Riutilizzabile	

Contents: One lead with silicone insulation and accessories
Contenu: Une sonde avec isolant en silicone et Accessoires
Inhalt: Eine Elektrode mit Silikonisolation und Zubehör
Contenido: Un electrodo con aislante de Silicona y Accesorios
Contenuto: Un elettrocatetere con isolante in silicone e accessori

Sterilization	Ethylene oxide gas
Stérilisation	Gaz d'oxyde d'éthylène
Sterilisation	Äthylenoxydgas
Esterilización	Gas óxido de etileno
Sterilizzazione	Gas ossido di etilene

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician
ATTENTION: La réglementation américaine (FDA) n'autorise la vente de ce produit que sur prescription médicale
ACHTUNG: Ein US-Bundesgesetz schränkt den Verkauf dieses Produkts auf Ärzte oder auf Anordnung durch einen Arzt ein
PRECAUCION: Las Leyes Federales (EE.UU.) restringen la venta de este dispositivo únicamente a médicos o por prescripción médica
ATTENZIONE: La Legge Federale (U.S.A.) limita la vendita di questo prodotto esclusivamente ai medici o su richiesta del medico

The contents of this package are STERILE	Recommended lead introducer size
Le contenu de cet emballage est STERILE	Dimension recommandée de l'introducteur
Der Inhalt dieser Packung ist STERIL	Empfohlene Größe des Einführungs-Einführungsbestecks 7 French
El contenido de este envoltorio está ESTERIL	Tamaño recomendado del introductor de cable
Il contenuto di questo imballaggio è STERILE	Dimensioni raccomandati dell'introduttore

If the package is damaged or opened see the Technical Manual for information
Si l'emballage est endommagé ou ouvert voir le Manuel Technique pour information
Im Falle einer beschädigten oder geöffneten Packung siehe Gebrauchsanweisung
Si el paquete ha sido dañado o abierto, ver el Manual Técnico para información
Se la confezione è danneggiata o aperta vedere il Manuale Tecnico per informazioni

CE 0123

Sterile Pak Label

Individual Data Sheet

For Your Records

Medtronic 6963 SERIAL NO.	Medtronic 6963 SERIAL NO.
Medtronic 6963 SERIAL NO.	Medtronic 6963 SERIAL NO.

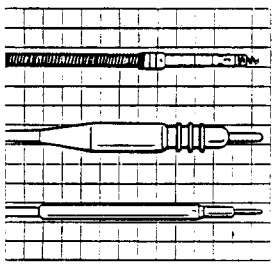
69

Medtronic

TRANSVENE®-RV 6966

HIGH VOLTAGE UNIPOLAR CONNECTOR (6.5 mm)
CONNECTEUR UNIPOLAIRE HAUTE TENSION (6.5 mm)
UNIPOLARER KONNEKTOR FUR HOCHSPANNUNG (6.5 mm)
CONECTOR MONOPOLAR PARA VOLTAJE ALTO (6.5 mm)
CONETTORE MONOPOLARE PER ALTA TENSIONE (6.5 mm)

PACE/SENSE BIPOLAR CONNECTOR (3.2 mm)
CONNECTEUR BIPOLAIRE PACE/SENSE (3.2 mm)
BIPOLARER KONNEKTOR FUR STIMULATION/WAHRNEHMUNG (3.2 mm)
CONECTOR BIPOLAR PACE/SENSE (3.2 mm)
CONNETTORE BIPOLARE PER STIMOLAZIONE/RIVELAMENTO (3.2 mm)



Serial Number
Numéro de Série
Seriennummer
Numero de Serie
Numero di Serie

Use Before
Utiliser Avant
Zu implantieren vor dem
Fecha de Caducidad
Data di Scadenza

Lead Length
Longueur de la Sonde
Länge der Elektrode
Longitud del Cable
Lunghezza dell'Elettrocatetere

Sterilization Date
Date de Stérilisation
Sterilisationsdatum
Fecha de Esterilización
Data di Sterilizzazione

Recommended lead introducer size
Dimension recommandée de l'introducteur
Empfohlene Größe des Elektroden-Einführungsbestecks 11 French
Tamaño recomendado del introductor de cable
Dimensioni raccomandate dell'introduttore

Contents: One lead with Polyurethane insulation, Accessories and Product Literature
Contenu: Une sonde avec isolation de Polyuréthane, Accessoires et Documentation
Inhalt: Eine Elektrode mit Polyurethan-Isolation, Zubehör und Dokumentation
Contenido: Un cable con Material Aislante de Poliuretano, Accesorios y Documentación
Contiene: Un catetere con Materiale Isolante in Poliuretano, Accessori e Documentazione

CAUTION: Federal Law (U.S.A.) restricts this device to sale by or on the order of a physician
ATTENTION: La réglementation américaine (FDA) n'autorise la vente de ce produit que sur prescription médicale
ACHTUNG: Ein US-Bundesgesetz schränkt den Verkauf dieses Produkts an Ärzte oder auf Anordnung durch einen Arzt ein
PRECAUCION: Las Leyes Federales (EE.UU) restringen la venta de este dispositivo únicamente a médicos o por prescripción médica.
ATTENZIONE: La legge Federale (U.S.A.) limita la vendita di questo prodotto esclusivamente ai medici o su richiesta del medico.

The contents (STERILE) of the inner package have been sterilized by ethylene oxide gas
Le contenu (STERILE) du paquet interne a été stérilisé au gaz d'oxyde d'éthylène
Der Inhalt (STERIL) der inneren Verpackung ist in Äthylenoxidgas sterilisiert
El contenido (ESTERILE) del paquete interior ha sido esterilizado con gas óxido de etileno
Il contenuto (STERILE) della confezione interna è stato sottoposto a sterilizzazione con gas ossido di etilene

STORAGE: Store below 40° C/104° F
STOCKAGE: Au-dessous de 40° C/104° F
LAGERUNG: Unter 40° C/104° F
ALMACENAMIENTO: Por debajo de 40° C/104° F
IMMAGAZZINAGGIO: Al di sotto di 40° C/104° F

A Thoracotomy is not required
Une thoracotomie n'est pas nécessaire
Eine Thorakotomie ist nicht erforderlich
No es necesaria una toracotomía
Una toracotomia non è richiesta

DER GRÜNE PUNKT

CE 0123

Sterile Pak Label

X Label

X Label

TRANSVENE®-RV 6966
Tripolar, Endocardial, Screw-In Lead
For Ventricular Pacing, Sensing, Cardioversion and Defibrillation
High Voltage Unipolar Connector (6.5 mm)
Pace/Sense Bipolar Connector (3.2 mm)

USE BEFORE

SERIAL NO

End Label S.L.P.

Opening Instruction Label

Medtronic

TRANSVENE®-RV 6966

Serial Number
Numéro de Série
Seriennummer
Numero de Serie
Numero di Serie

Use Before
Utiliser Avant
Zu implantieren vor dem
Fecha de Caducidad
Data di Scadenza

Lead Length
Longueur de la Sonde
Länge der Elektrode
Longitud del Cable
Lunghezza dell'Elettrocatetere

Sterilization Date
Date de Stérilisation
Sterilisationsdatum
Fecha de Esterilización
Data di Sterilizzazione

Non Reusable
Usage Unique
Nicht wiederverwendbar
Inhalt Nur Einmal Verwenden
Non Reusable

Contents: One lead with Polyurethane insulation
Contenu: Une sonde avec isolation de Polyuréthane
Inhalt: Eine Elektrode mit Polyurethan-Isolation
Contenido: Un cable con Material Aislante de Poliuretano
Contiene: Un catetere con Materiale Isolante in Poliuretano

Sterilization: Ethylene oxide gas
Stérilisation: Gaz d'oxyde d'éthylène
Sterilisation: Äthylenoxidgas
Esterilización: Gas óxido de etileno
Sterilizzazione: Gas ossido di etilene

CAUTION: Federal Law (U.S.A.) restricts this device to sale by or on the order of a physician
ATTENTION: La réglementation américaine (FDA) n'autorise la vente de ce produit que sur prescription médicale
ACHTUNG: Ein US-Bundesgesetz schränkt den Verkauf dieses Produkts an Ärzte oder auf Anordnung durch einen Arzt ein
PRECAUCION: Las Leyes Federales (EE.UU) restringen la venta de este dispositivo únicamente a médicos o por prescripción médica
ATTENZIONE: La legge Federale (U.S.A.) limita la vendita di questo prodotto esclusivamente ai medici o su richiesta del medico.

The contents of this package is STERILE.
Le contenu de ce paquet est STERILE.
Der Inhalt dieser Packung ist STERIL.
El contenido de este envoltorio esta ESTERIL.
Il contenuto di questa confezione è STERILE.

Recommended lead introducer size
Dimension recommandée de l'introducteur
Empfohlene Größe des Elektroden-Einführungsbestecks 11 French
Tamaño recomendado del introductor de cable
Dimensioni raccomandati dell'introduttore

If the package is damaged or opened see the Technical Manual for information
Si l'emballage est endommagé ou ouvert voir le manuel technique pour information
Im Falle einer beschädigten oder geöffneten Packung Gebrauchsanweisung beachten
Si el paquete ha sido danado o abierto, ver el Manual Técnico para información
Se la confezione è danneggiata o aperta vedere il Manuale Tecnico per le informazioni relative

CE 0123

Sterile Pak Label

INDIVIDUAL DATA SHEET
FICHE TECHNIQUE INDIVIDUELLE
INDIVIDUELLES TECHNISCHES DATENBLATT
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FOGLIO D'INFORMAZIONI SPECIFICO

MODEL/MODELE/MODELL/MODELO/MODELLO
6966

Serial Number
Numéro de Série
Seriennummer
Numero de Serie
Numero di Serie

Use Before
Utiliser Avant
Zu implantieren vor dem
Fecha de Caducidad
Data di Scadenza

Sterilization Date
Date de Stérilisation
Sterilisationsdatum
Fecha de Esterilización
Data di Sterilizzazione

Sterilization
Stérilisation
Sterilisation
Esterilización
Sterilizzazione

Medtronic 6966 SERIAL NO

Medtronic 6966 SERIAL NO

Medtronic 6966 SERIAL NO.

For Your Records

MFGR. #	MODEL	SERIAL NO.
013	6966	

Use with National Pacemaker Registry

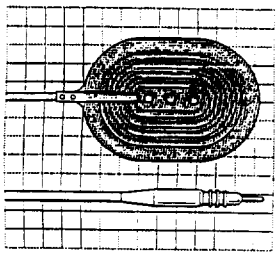
Serial Number Labels

Medtronic

TRANSVENE®-SQ 6999

Unipolar, Subcutaneous, Oval Patch Lead for Cardioversion and Defibrillation
Sonde patch unipolaire, sous-cutanée pour la cardioversion et la défibrillation
Unipolare, subkutane, ovale Flächenelektrode für Kardioversion und Defibrillation
Electrodo-Parche Monopolar subcutáneo oval para Cardioversión y Desfibrilación
Elettrocatetere monopolare sottocutaneo ovale per Cardioversione e Defibrillazione

Unipolar Connector (6.5 mm)/Connecteur Unipolaire (6,5 mm)/Unipolare Konnektor (6,5 mm)/Conector Monopolar (6,5 mm)/Connettore Monopolare (6,5 mm)



Serial Number
Numéro de Série
Seriennummer
Numero de Serie
Numero di Serie

Use Before
Utiliser Avant
Zu Implantieren vor dem
Fecha de Caducidad
Data di Scadenza

Lead Length
Longueur de la Sonde
Länge der Elektrode
Longitud del Cable
Lunghezza dell'Elettrocatetere

Sterilization Date
Date de Stérilisation
Sterilisationsdatum
Fecha de Esterilización
Data di Sterilizzazione

Contents: One lead with silicone insulation, accessory, and product literature. (Translations are pending)

CAUTION: Federal Law (U.S.A.) restricts this device to sale by or on the order of a physician.
ATTENTION: La réglementation américaine (FDA) n'autorise la vente de ce produit que sur prescription médicale.
ACHTUNG: Ein US-Bundesgesetz schränkt den Verkauf dieses Produkts an Ärzte oder auf Anordnung durch einen Arzt ein.
PRECAUCION: Las Leyes Federales (EE.UU) restringen la venta de este dispositivo únicamente a médicos o por prescripción médica.
ATTENZIONE: La legge Federale (U.S.A.) limita la vendita di questo prodotto esclusivamente ai medici o su richiesta d'un medico.

The contents (STERILE) of the inner package have been sterilized by ethylene oxide gas.
Le contenu (STERILE) du paquet intérieur a été stérilisé au gaz d'oxyde d'éthylène.
Der Inhalt (STERIL) der inneren Verpackung ist in Äthylenoxydgas sterilisiert.
El contenido (ESTERILE) del paquete interior ha sido esterilizado con gas óxido de etileno.
Il contenuto (STERILE) della confezione interna è stato sottoposto a sterilizzazione con gas ossido di etilene.

STORAGE: Store below 40° C/104° F
STOCKAGE: Au-dessous de 40° C/104° F
LAGERUNG: Unter 40° C/104° F
ALMACENAMIENTO: Por debajo de 40° C/104° F
IMMAGAZZINAGGIO: Al di sotto di 40° C/104° F

A Thoracotomy is not required
Une thoracotomie n'est pas nécessaire
Eine Thorakotomie ist nicht erforderlich
No es necesaria una toracotomía
Una toracotomía no è richiesta

Shell Box Label

X Label

X Label

TRANSVENE®-SQ 6999

Unipolar, Subcutaneous,
Oval Patch Lead For
Cardioversion and Defibrillation
Unipolar Connector (6.5 mm)

USE BEFORE

SERIAL NO

End Label S.L.P.

Opening Instruction Label

Medtronic

TRANSVENE®-SQ 6999

Unipolar, Subcutaneous, Oval Patch Lead for Cardioversion and Defibrillation
Sonde patch unipolaire, sous-cutanée pour la cardioversion et la défibrillation
Unipolare, subkutane, ovale Flächenelektrode für Kardioversion und Defibrillation
Electrodo-Parche Monopolar subcutáneo oval para Cardioversión y Desfibrilación
Elettrocatetere monopolare sottocutaneo ovale per Cardioversione e Defibrillazione

Unipolar Connector (6.5 mm)/Connecteur Unipolaire (6,5 mm)/Unipolare Konnektor (6,5 mm)/Conector Monopolar (6,5 mm)/Connettore Monopolare (6,5 mm)

Serial Number
Numéro de Série
Seriennummer
Numero de Serie
Numero di Serie

Use Before
Utiliser Avant
Zu Implantieren vor dem
Fecha de Caducidad
Data di Scadenza

Sterilization Date
Date de Stérilisation
Sterilisationsdatum
Fecha de Esterilización
Data di Sterilizzazione

Non Reusable
Usage Unique
Nicht wiederverwendbar
Interior Desechable
Non Riusabile

Lead Length
Longueur de la Sonde
Länge der Elektrode
Longitud del Electrodo
Lunghezza dell'Elettrocatetere

Sterilization: Ethylene oxide gas
Stérilisation: Gaz d'oxyde d'éthylène
Sterilisation: Äthylenoxydgas
Esterilización: Gas óxido de etileno
Sterilizzazione: Gas ossido di etilene

Contents: One lead with silicone insulation and accessory. (Translations pending)

CAUTION: Federal Law (U.S.A.) restricts this device to sale by or on the order of a physician.
ATTENTION: La réglementation américaine (FDA) n'autorise la vente de ce produit que sur prescription médicale.
ACHTUNG: Ein US-Bundesgesetz schränkt den Verkauf dieses Produkts an Ärzte oder auf Anordnung durch einen Arzt ein.
PRECAUCION: Las Leyes Federales (EE.UU) restringen la venta de este dispositivo únicamente a médicos o por prescripción médica.
ATTENZIONE: La legge Federale (U.S.A.) limita la vendita di questo prodotto esclusivamente ai medici o su richiesta d'un medico.

The contents of this package is STERILE.
Le contenu de ce paquet est STERILE.
Der Inhalt dieser Packung ist STERIL.
El contenido de este envoltorio está ESTERIL.
Il contenuto de questa confezione è STERILE.

If the package is damaged or opened see the Technical Manual for information.
Si l'emballage est endommagé ou ouvert voir le manuel technique pour information.
Im Falle einer beschädigten oder geöffneten Packung Gebrauchsanweisung beachten.
Si el paquete ha sido dañado o abierto, ver el Manual Técnico para información.
Se la confezione è danneggiata o aperta vedere il Manuale Tecnico per le informazione relative.

Stenle Pak Label

Individual Data Sheet

INDIVIDUAL DATA SHEET
FICHE TECHNIQUE INDIVIDUELLE
INDIVIDUELLES TECHNISCHES DATENBLATT
HOJA DE DATOS
FOGLIO DI INFORMAZIONI SPECIFICO

MODEL/MODELE/MODELL/MODELO/MODELLO
6999

Use Before
Utiliser Avant
Zu Implantieren vor dem
Fecha de Caducidad
Data di Scadenza

Sterilization Date
Date de Stérilisation
Sterilisationsdatum
Fecha de Esterilización
Data di Sterilizzazione

Serial Number
Numéro de Série
Seriennummer
Numero de Serie
Numero di Serie

Sterilization
Stérilisation
Sterilisation
Esterilización
Sterilizzazione

Serial Number Labels

Medtronic 6999 SERIAL NO.

Medtronic 6999 SERIAL NO.

For Your Records

Medtronic 6999 SERIAL NO.

MFGR. # 013 MODEL 6999 SERIAL NO.

Use with National Pacemaker Registry

THE PCD® TACHYARRHYTHMIA CONTROL DEVICE

MODEL 7217B TECHNICAL MANUAL

An Implantable Device for the Control of Ventricular Arrhythmias Through Pacing, Cardioversion, and Defibrillation

Medtronic

October 1993
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Printed in USA

7217B NTL TOC/MMC 10/5/93 7:14 PM Page ii

Before implanting a Model 7217B PCD device, it is strongly recommended that the physician do the following:

- Thoroughly read this manual, the systems applications manual for the programmer MemoryMod® cartridge, the External Tachyarrhythmia Control Device (ETCD™) technical manual, and the technical manuals for the leads used with the device.
- Provide a copy of the patient manual to the patient and discuss it with him or her and any other interested parties.
- Medtronic requires physicians to attend an education seminar on the complete PCD system. This includes the following topics:
  - Indications for use
  - Overview of the PCD system functions
  - Implant procedure
  - Patient management

Automatic defibrillation was invented and patented in 1953 by Dr. F. Zacouto, who designed an external device that delivered a defibrillation impulse to the heart upon detection of very rapid ECG activity in combination with the absence of arterial pulsations.

Certain antitachycardia pacing modes of this device, invented by Dr. Fred Zacouto of Paris, France, fall under one or more patent claims of U.S. Patents 3,857,399 and 4,052,991 and corresponding patents in other countries, which are licensed exclusively to Medtronic, Inc.

The primary reference for background information is Zacouto FI, Guize LJ. Fundamentals of Orthorhythmic Pacing. In: Luderitz B, ed. *Cardiac Pacing Diagnostic and Therapeutic Tools*. New York: Springer-Verlag; 1976: 212-218.

See these additional references for more background information:

1. Theisen K, Zacouto F, et al. Refraktarzeitmessung bei absoluter Arrhythmie mit orthorhythmischer Serienstimulation. *Klin. Wschr.* 1974; 52: 1082-1084.

2. Guize L, Zacouto F, et al. Stimulation endocardiaques orthorhythmiques. *La Nouvelle Presse medicale*. 1974; 3(33): 2083-2086.

3. Effert S. Automatische Uberwachungsgerate und Indikation zur Implantation von elektrischen Schrittmachern. *Thoraxchirurgie und Vaskulare Chirurgie*. 1963; 11: 158-165. This describes the automatic defibrillation equipment of Dr. F. Zacouto.

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GENERAL DESCRIPTION

The Medtronic Model 7217B PCD® (Pacer-Cardioverter-Defibrillator) Device is an implantable, multiprogrammable, automatic tachyarrhythmia control device. The PCD device is designed to automatically detect episodes of ventricular tachycardia (VT) or ventricular fibrillation (VF) and, upon detection, deliver the appropriate programmed pacing, cardioversion, or defibrillation therapies. The device has two independently programmable detection and therapy procedures, one for VT and a second for VF.

The VT Detection circuitry can use up to four separately programmable detection modes as it monitors the cardiac cycle length to identify the presence of a tachycardia. Upon detection, the PCD device delivers its first programmed VT therapy. If the VT episode persists and is again detected, up to three additional independently programmable VT therapies may be delivered to restore the patient's normal cardiac rhythm. This progression of four VT therapies can be tailored to each patient's needs. The therapies may be selected from two methods of overdrive pacing (Burst and Ramp) and synchronized Cardioversion.

The VF Detection circuitry uses three programmable parameters as it monitors the cardiac cycle length to identify a VF episode. Upon detection, VF therapy provides a programmable high-energy defibrillation shock. Up to a maximum of four VF therapies may be delivered for ongoing detected VF episodes. Each defibrillation therapy consists of a single shock or two simultaneous or sequential high-voltage pulses designed to restore the normal cardiac rhythm.

The PCD device provides bradycardia therapy via ventricular inhibited (VVI) pacing.

The PCD device requires an appropriate lead system, consisting of up to five electrodes. Cardioversion and defibrillation occur between the **PULSE1** and/or **PULSE2** and **COMMON** electrodes[1]. The optional **PULSE1** electrode and the **PULSE2** electrode serve as anodes for the cardioversion and defibrillation therapies. Pacing stimuli occur between the **PACE/SENSE** (pacing cathode) and **COMMON**. Sensing of cardiac activity occurs between the **PACE/SENSE** and **SENSE2** electrodes.

The PCD device is to be programmed with an appropriate Medtronic programmer (e.g., the Model 9710 or other equivalent unit). Instructions for programming the PCD device may be found in the Model 9788 MemoryMod® Software Cartridge Technical Manual (or equivalent). Programmers from other manufacturers are **NOT** compatible.

The physician may use the PCD device to conduct noninvasive electrophysiologic studies (EPS) via the Programmer and appropriate MemoryMod cartridge. The physician can also manually deliver various therapies via the Programmer to manage an induced or spontaneous tachyarrhythmia.

The PCD device will provide the physician with information, via the Programmer, about its present programmed parameters, status, and data on its operation accumulated between office visits. This information may be printed and retained in the patient's file.

1. See the Lead Technical Manuals for details on the lead system.

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PRESCRIBING THE MODEL 7217B PCD DEVICE

Intended Uses

The Model 7217B PCD device is intended for use in patients who are at high risk of sudden death due to ventricular tachyarrhythmia. Current medical research indicates that such patients should:

- have survived at least one episode of a cardiac arrest, presumably due to a ventricular tachyarrhythmia as evidenced by resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; OR
- in the absence of a prior cardiac arrest, have poorly tolerated sustained VT and/or VF, which occurs spontaneously or can be induced despite the best antiarrhythmic drug therapy.

modified

The natural history of patients with hemodynamically stable sustained VT is not well defined. While this patient population was included in PCD clinical studies the study objectives did not include stratification of this specific patient group.

The PCD device may be used as a replacement for a previously implanted, commercially-available Automatic Implantable Cardioverter Defibrillator. The PCD device is intended for use only with the defibrillation lead systems with which it has been tested, which are Medtronic epicardial patch leads and Cardiac Pacemakers, Inc., patch leads.

Prior to implant, it is strongly recommended that patients undergo a complete cardiac evaluation, which should include extensive electrophysiologic testing. Also, extensive electrophysiologic evaluation and testing of the safety and efficacy of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the Model 7217B PCD device.

Before permanently programming the PCD device to the automatic detection and delivery of the VT and/or VF therapies, the patient should have demonstrated a satisfactory response to the proposed therapy. For more information, see "Programming Considerations" and "Pre-Hospital Discharge" in "Post-Implant Information."

Contraindications

The Model 7217B PCD device is contraindicated for patients:

- with transient ventricular tachyarrhythmias due to reversible causes, e.g., drug intoxication, electrolyte imbalance, sepsis, or hypoxia.
- with transient ventricular tachyarrhythmias due to other factors, e.g., myocardial infarction and electrocution.

The Model 7217B PCD device is contraindicated for the sole use of detection and treatment of atrial arrhythmias.

Because of the potential for damage to the PCD device and/or induction of life-threatening arrhythmias, the use of the following techniques and/or therapies is contraindicated in patients who have an implanted Model 7217B PCD device:

- Magnetic Resonance Imaging (MRI) and
- Hydraulic Shock-wave Lithotripsy

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LONGEVITY EXPECTATIONS

The longevity of the Model 7217B PCD device depends upon several factors including programmed bradycardia pacing parameters, the percentage of paced to sensed events, the pacing load, and the frequency of high-voltage capacitor charging. The longevity projections found in Table 1 apply under the following conditions:

- 65 ppm pacing rate,
- 5.4 V pacing pulse amplitude,
- 0.49 ms pacing pulse width, and
- 500 ohm pacing load.

Table 1. Projected Longevity[1]

Pacing/Sensing	34-Joule Charging Frequency	Average Longevity
100% sensing	Quarterly	5.0 years
15% pacing	Monthly	4.2 years
100% pacing	Monthly	3.4 years

The longevity of the device decreases with the following:

- an increase in pacing rate,
- an increase in pacing amplitude,
- a decrease in pacing impedance,
- an increase in pacing pulse width,
- an increase in the percentage of bradycardia paced to sensed events, or
- an increase in the charging frequency.

Each 34-joule charging cycle will typically decrease the longevity of the device by approximately six days.

For information on when to replace the PCD device, see "Elective Replacement and Potential Loss of Function Indicators" in "Post-Implant Information."

1. These preliminary longevity projections are based upon accelerated battery discharge data and device modeling. They include an estimate of five months between time of manufacture of a PCD device and its implant. If a device was stored for the full twelve-month shelf life, the average longevity would be reduced an estimated 4.3 to 5.9 months, depending on device use. With the stated conditions, 100% pacing and monthly 34-joule charging cycles, the minimum longevity of the device will be 2.5 years. Average refers to the projected mean longevity of the modeled run of PCD devices at the stated conditions. Minimum longevity means that virtually all (i.e. 99.9%) of all modeled production runs of PCD devices will attain the value given.

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PRINCIPLES OF OPERATION

Overview

The Model 7217B PCD device is designed to detect two types of sustained ventricular tachyarrhythmia: ventricular tachycardia (VT) and ventricular fibrillation (VF). The sensing circuitry used for detection employs a bipolar electrode configuration (**PACE/SENSE** to **SENSE2**) to maximize rejection of myopotentials, far-field P-waves, and other electrical signals. Separately programmable detection criteria are designed to allow the PCD device to differentiate between VT and VF.

Once either VT or VF is detected, the PCD device will deliver the first programmed VT or VF therapy and up to three additional programmed therapies if the episode persists and is repeatedly detected. Three kinds of VT therapy are available: two different types of overdrive pacing therapy and a synchronized cardioversion therapy. VF therapy consists of high-energy defibrillation shocks; the stored energy level is separately programmable for all four VF therapies.

If required, the PCD device will provide bradycardia therapy with pacing (**PACE/SENSE** to **COMMON**) at the programmed lower rate in the VVI mode.

Figure 1 summarizes the detection and therapy features of the PCD device.

Complete details of these operations are found in the sections that follow:

- Features Used in Sensing and VT/VF Detection
- Ventricular Tachycardia (VT) Detection
- Ventricular Tachycardia (VT) Therapy
- Ventricular Fibrillation (VF) Detection
- Ventricular Fibrillation (VF) Therapy
- VVI Therapy

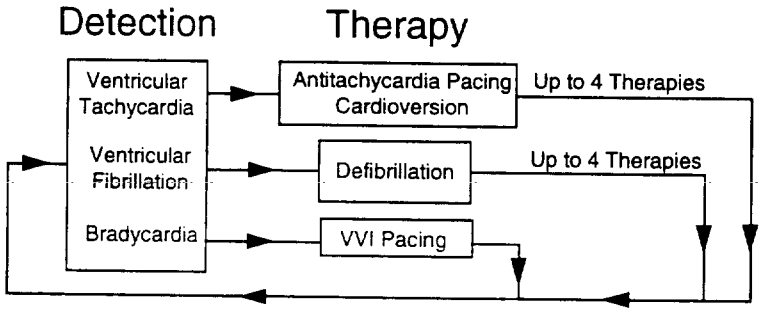

Figure 1. Detection and Therapy in the PCD Device

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Features Used In Sensing and VT/VF Detection

Proper sensing is essential for the safe and effective use of the PCD device. The device's sensing function should be regularly verified by means of Marker Channel™ telemetry (see "Telemetry Reports" and Figure 26). If sensing or detection are inappropriate, VT and VF Detection should be programmed OFF until verification studies are performed.

Auto-Adjusting Sensitivity Threshold

The Model 7217B PCD device automatically adjusts its sensitivity following signal detection on the bipolar electrogram (between the **PACE/SENSE** and **SENSE2** electrodes). This feature is designed to prevent the sensing of T-waves when very low sensing threshold levels are used. When the amplitude of the sensed event exceeds the programmed setting, the PCD device notes that a sensed event has occurred. The sensing level is raised to about 75% of the electrogram peak (or about 6 times the programmed setting, whichever is less) and gradually returns to the programmed value with a 560 ms exponential decay time constant. Figure 2 illustrates how the sensing level is changed by increasing or decreasing the Auto-Adjusting Threshold.

NOTE: The Auto-Adjusting Sensitivity level is not increased by pacing, VT therapy, or VF therapy outputs. The physician should be aware that the programmed sensitivity setting and the associated blanking periods are also used to detect a VT or VF episode and, therefore, Auto-Adjusting Sensitivity is active during VT and VF detection.

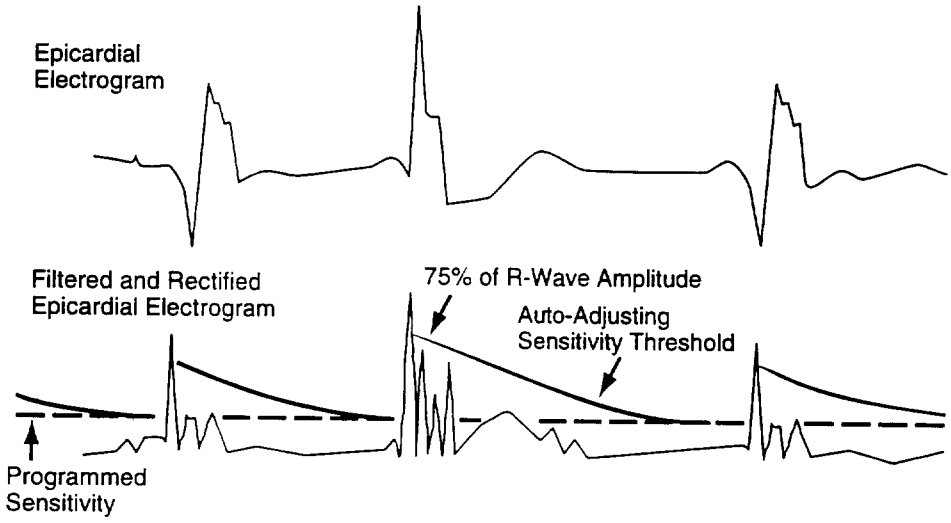

Figure 2. Auto-Adjusting Sensitivity Threshold

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Blanking Periods

Nonprogrammable blanking periods follow paced and sensed events, capacitor charging periods, and therapy deliveries. These blanking periods prevent the sensing of device outputs or multiple sensing of the same event. Signals on the sensing electrodes during a blanking period are not used by the PCD device. The blanking period following a pacing output is longer than that following a sensed event. This feature is designed to avoid sensing the polarization signal on the electrodes. There are four blanking periods:

- 120 ms after a sensed event,
- 320 ms after a paced event (i.e., either VVI bradycardia pacing or VT pacing level Burst or Ramp stimuli),
- 300 ms after a cardioversion or defibrillation charging period and also after delivery of a cardioversion or defibrillation therapy, and
- During a charging period.

Refractory Periods

Refractory periods follow some events. The PCD device assumes that signals detected on the sensing electrodes during a refractory period are caused by noise, lead polarization, the trailing edge of an R-wave, or a T-wave. There are five refractory periods:

- 400 ms after a cardioversion or defibrillation charging period,
- 200 ms following sensed events in the automatic cardioversion synchronization period,
- 520 ms following the delivery of any VT or VF therapy,
- 320 to 520 ms after a therapy is aborted, and
- 320 to 480 ms (programmable) after paced events (Refractory After Pace).

No additional refractory period extends beyond the blanking period after sensed events. During VVI operation, **the PCD device will not revert to asynchronous operation in the presence of noise.**

Both the VT and VF detection criteria ignore an event sensed within a refractory period. An event sensed in the refractory period will not inhibit a pacing output. Such an event, however, does restart the sensed event blanking period of 120 ms.

Programming the Refractory After Pace to more than 320 ms may impair the PCD device's ability to detect VT or VF. Events sensed within the refractory period restart a 120 ms blanking period but are ignored by both VT and VF detection criteria and for bradycardia pacing inhibition. Therefore, a short bradycardia escape interval (i.e., a pacing rate greater than 50 ppm) combined with a long Refractory After Pace (360 ms or longer) may prevent a VT event from inhibiting a pacing output. **In such circumstances, the VT could remain undetected.**

To avoid this possibility when the Refractory After Pace is programmed to 360 ms or longer, ensure that at least one of the following is true: (1) the difference between the bradycardia escape interval and the effective refractory period should be greater than the

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Tachycardia Detection Interval (TDI); or (2) the bradycardia escape interval must be greater than twice (2X) the effective refractory period. (The effective refractory period for a programmed refractory of 360 ms or longer is the programmed value plus 120 ms.) The following example and table show how programmed refractory periods of 360 ms and greater affect VT detection at various pacing rates above 50 ppm.

For example, if the Refractory After Pace equals 360 ms, then the effective refractory period could be 480 ms. If the escape interval equals 670 ms (90 ppm), then intrinsic rhythms with 190–480 ms intervals may not be detected if the rhythm initiates during VVI pacing.

Programmed Refractory After Pace	VT or VF Interval Lengths That Could Remain Undetected –At 70 ppm (860 ms)	–At 90 ppm (670 ms)
360 ms	380 - 480 ms	190 - 480 ms
400 ms	340 - 520 ms	150 - 520 ms
440 ms	300 - 560 ms	110 - 560 ms
480 ms	260 - 600 ms	70 - 600 ms

In order for the programmed refractory period to have **any** effect on VT detection, the VT episode must initiate during VVI pacing at rates **over** 50 ppm and with the Refractory After Pace **greater** than 320 ms.

Measurement of Intervals

The PCD device measures cardiac cycle lengths in multiples of 10 ms. Intervals are rounded down to the nearest 10 ms multiple (e.g., 457 ms becomes 450 ms). The PCD device uses this rounded interval value when applying the programmed criteria and calculating interval averages.

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Ventricular Tachycardia (VT) Detection

Overview of VT Detection

With VT Detection enabled, the PCD device monitors the cardiac cycle length for the fulfillment of the programmed VT detection criteria. When the programmed criteria are fulfilled, the PCD device detects a VT episode and delivers the first programmed VT therapy. If this therapy is ineffective and the VT is again detected, the next programmed VT therapy is delivered. This progression continues until the PCD device confirms VT termination or delivers all programmed VT therapies. VT Detection is suspended if all programmed therapies are ineffective in terminating the arrhythmia. VT Detection is re-enabled when VT termination is confirmed or if VT Detection is manually reprogrammed ON.

All programmed VT detection criteria must be fulfilled for a rhythm to be detected as a VT episode. Whenever VT Detection is enabled (ON) there are three available criteria: the **Interval Criterion** is automatically enabled, the **Interval Stability Criterion** and the **Onset Criterion** are optionally programmable. The number of detected episodes is stored in the device's memory. The data for previously detected VT episodes may be accessed with the programmer.

NOTE: VF Detection must be programmed ON before VT Detection can be programmed ON.

VT and VF Detection may be programmed ON to permit the PCD device to function solely as a tachyarrhythmia monitor with all tachyarrhythmia therapies programmed OFF.

VT Detection Criteria

Interval Criterion

The Interval Criterion is designed to detect a sustained high ventricular rate by measuring each cardiac cycle length and comparing it to the **Tachycardia Detection Interval (TDI)**. If an interval is less than the TDI, then that cycle is potentially a count toward the fulfillment of the **Number of Intervals to Detect (VT NID)**. The Interval Criterion is activated when VT Detection is enabled and, therefore, requires programming both the TDI and VT NID parameters.

The Interval Criterion requires that the measured cardiac cycle length be less than the programmed TDI value and greater than or equal to the programmed Fibrillation Detection Interval (FDI). The VT event counter counts the number of intervals that meet the Interval Criterion. The VT event counter is reset to zero if an interval is greater than or equal to the TDI. The count is not increased nor reset if an interval is less than the FDI. When the cumulative VT event count is equal to the VT NID, the Interval Criterion for VT detection is fulfilled.

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Thus, fulfillment of VT Detection when only the Interval Criterion is enabled requires both of the following:

- Measured cardiac cycle lengths be **less than** the programmed Tachycardia Detection Interval (**TDI**), and **greater than or equal** to the programmed Fibrillation Detection Interval (**FDI**), and
- The cumulative number of these intervals be **equal to** the programmed Number of Intervals to Detect (**VT NID**).

Counting is reset to zero when an interval is greater than the programmed TDI and is interrupted when the interval is less than the FDI.

The Relationship Between the TDI and FDI

Figure 3 illustrates how the relationships between the blanking period (120 ms) after a sensed event, FDI, TDI, and bradycardia escape interval determine whether a sensed event is a VF event (B), a VT event (C), or a normal sensed event (D). In addition, all these events inhibit the bradycardia output pulse.

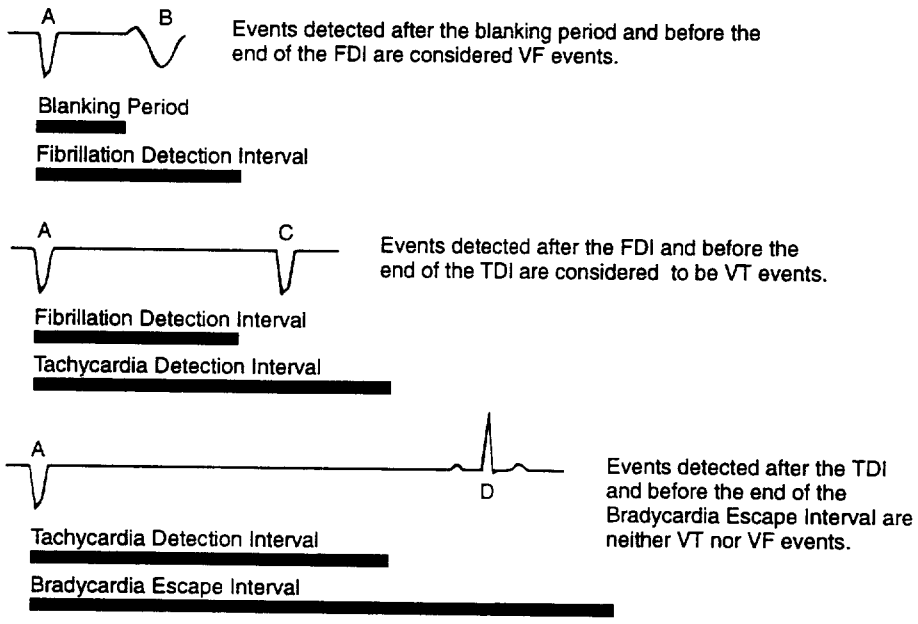

Figure 3. The Relationship of the TDI and FDI

NOTE: Programming the FDI to a value greater than or equal to the TDI effectively disables VT Detection. **When programming these two values, the physician should keep the TDI at least 40 ms longer than the FDI to allow for variability of the clinical VT cycle length.**

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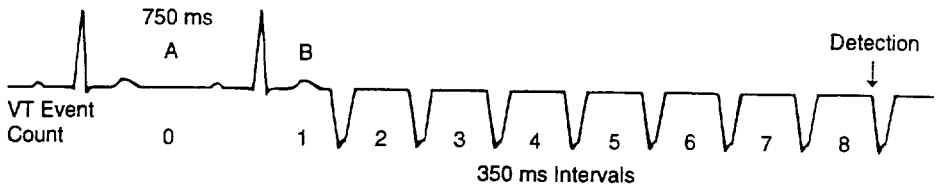

Programmed to: TDI = 400 ms; FDI = 250 ms; VT NID = 8

In this example, Interval "B " and the intervals following B increment the VT event counter.

Figure 4. Interval Criterion (Example)

Figure 4 illustrates how the PCD device could use the Interval Criterion to detect a tachycardia. The interval at "B" is 350 ms, i.e., 50 ms less than the programmed TDI value of 400 ms. Because it is less than the TDI and greater than the FDI and since no other VT Detection Criteria are programmed, the VT event count, in this example, begins. When the VT event count reaches 8, VT detection occurs.

NOTE: Some of the timing diagrams provided in this manual depict representative surface ECGs and are illustrative of the operation being discussed. The PCD device actually uses epicardial or intracardiac electrograms (EGMs) for measurement and analysis of the cardiac cycle lengths. Detection and delivery of therapies are based on EGMs, not on surface ECGs.

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Interval Stability Criterion

The Interval Stability Criterion is a programmable option that provides an additional restriction to the Interval Criterion. It is intended, for example, to prevent VT detection when rapid ventricular rhythms with irregular intervals due to conduction of atrial fibrillation or flutter would otherwise fulfill the Interval Criterion.

When enabled, this criterion analyzes only those measured cardiac cycle lengths that fulfill the Interval Criterion. A measured cardiac cycle length is considered unstable when the difference between the current measured cycle length and any of the three previous cycle lengths is greater than the programmable Interval Stability value (in milliseconds). Note that the VT event count must be at least "3" before the PCD device can apply the Interval Stability Criterion. If the current cardiac cycle length varies more than the programmed Interval Stability value, then the VT event count is reset to zero. The measurement and counting of cardiac cycle lengths then begins anew.

Thus, with Interval Stability and Interval Criteria enabled, VT Detection requires all of the following:

- Measured cardiac cycle lengths be **less than** the programmed Tachycardia Detection Interval (**TDI**) and **greater than or equal to** the programmed Fibrillation Detection Interval (**FDI**),
- **Each of these measured cardiac cycle lengths** vary from each of the three previous cycles by a value **less than or equal to** the programmed Interval Stability value, and
- The cumulative number of these intervals be **equal to** the programmed Number of Intervals to Detect (**VT NID**).

Counting is reset to zero when an interval is greater than the programmed TDI or is considered "unstable." The count is suspended when the interval is less than the FDI. When this criterion is enabled and a VT therapy is unsuccessful in treating a detected VT, Interval Stability must be fulfilled before the episode can be redetected.

NOTES: Choosing a small Interval Stability value may not allow for normal variation in a VT cycle length.

Decreasing the programmed interval stability increases the specificity of the Interval Stability Criterion to detect the targeted stable tachycardia, but may also decrease the sensitivity of the detection algorithm.

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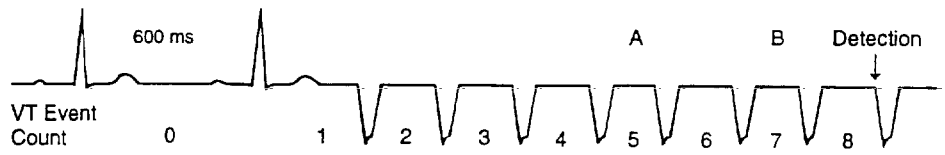
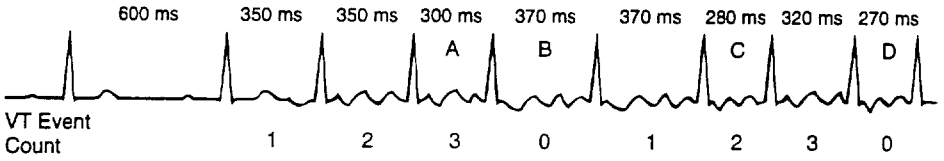


All VT intervals above are 350 ms, except "A" and "B", which are 300 ms.

Programmed to: TDI = 400 ms; FDI = 250 ms;
VT NID = 8; and Stability = 60 ms

Figure 5. Interval Stability Criterion Fulfilled (Example)

Figure 5 illustrates how the Interval Stability Criterion may be fulfilled. Interval "A" is a "stable" interval, i.e., only 50 ms shorter than the three previous intervals and less than the programmed Stability of 60 ms. Interval "B" similarly qualifies as a stable interval, because it is equal to one of the three previous intervals and is 50 ms shorter than the other two. VT detection occurs when the VT event count reaches the programmed VT NID value (8).



Programmed to: TDI = 400 ms; FDI = 250 ms;
VT NID = 8; and Stability = 60 ms

Figure 6. Interval Stability Criterion Not Fulfilled (Example)

Figure 6 illustrates how an "unstable" interval is identified. Interval "B" is 70 ms longer than "A" and therefore exceeds the programmed Stability value by 10 ms. As a result, the VT event count is reset to zero. Interval "C", though 90 ms less than the previous interval and greater than the programmed Stability of 60 ms, does not reset the VT event count, because the counter has not yet reached "3". Interval "D", however, is an unstable interval; it occurs after the event count reaches "3", and thus also resets the VT event count to zero.

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Onset Criterion

The Onset Criterion, a programmable option, monitors the cardiac cycle length for a sudden onset of a high ventricular rate. It is intended to avoid VT detection of an episode of sinus tachycardia with gradually increasing (e.g., exercise-induced) high ventricular rates.

This criterion, when enabled, **must first be satisfied** before the device begins counting VT events that otherwise satisfy the Interval Criterion and, if programmed, the Interval Stability Criterion. When the Onset Criterion is enabled, the PCD device evaluates each cardiac cycle for a decrease in cycle length from previous intervals. The Onset Criterion is fulfilled when both of the following conditions are met:

- If the current interval is **less than** a programmed percentage of the average of the previous four intervals, and
- Either the second and/or third interval preceding the current interval is **equal to or greater than** the programmed TDI.

If two consecutive intervals after the Onset Criterion is satisfied are greater than or equal to the TDI, the Onset Criterion is reset and must again be satisfied before a VT can again begin to be detected. When a VT is detected, however, the Onset Criterion is not required again for redetection until the PCD device confirms VT episode termination.

NOTES: If the Onset Criterion is ON and not met at the beginning of a ventricular tachycardia, the VT episode could remain "undetected", such as with an exercise-induced VT. For example, if VT Detection uses the Onset Criterion and is enabled after the start of a VT, the VT may not be detected.

A low programmed onset percentage value will increase the specificity of the Onset Criterion to detect the targeted tachycardia, but may also decrease the sensitivity of the detection algorithm.

Intervals that are shorter than the programmed FDI may also fulfill the Onset Criterion, even though they are not VT events. Such an interval does not increase nor reset the VT event counter.

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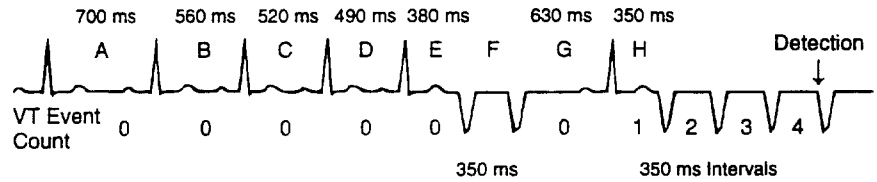
Programmed Values: TDI = 400 ms; FDI = 250 ms; VT NID = 4; and Onset = 81%

Figure 7. Onset Criterion Fulfilled (Example)

Figure 7 illustrates how the PCD device uses the Onset Criterion to identify a VT episode. Interval "E" meets the programmed Onset Criterion because it is less than 81% of the average of intervals A through D and because B (and/or C) is greater than the TDI. The VT event count begins with the next interval because it is less than the programmed TDI.



Programmed Values: TDI = 400 ms; FDI = 250 ms; VT NID = 4; and Onset = 81%

Figure 8. Onset Criterion Fulfilled (Example)

In Figure 8, interval E satisfies the Onset Criterion, i.e., it is less than the programmed 81% of the average of intervals A through D, with interval B (and/or C) greater than the TDI. Interval G by itself, though longer than the TDI, does not reset the Onset Criterion, since two such consecutive intervals are required for a reset of the Onset Criterion. Interval G, however, does reset the VT event count; thus, the event count begins at F, resets to zero at G, and then begins again at H.

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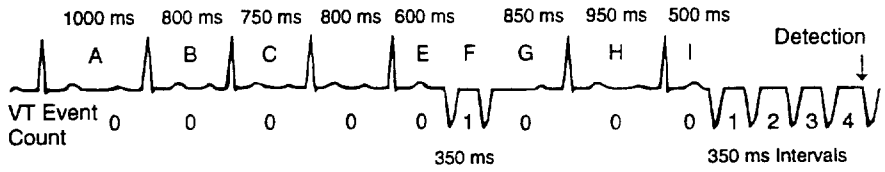

Figure 9. Onset Criterion Reset and Fulfilled (Example)

In Figure 9, a situation occurs that resets the Onset Criterion, which is first satisfied by Interval E. Two intervals (G and H), longer than the TDI, reset both the Onset Criterion and the VT event count. Thus, a second interval (I) must fulfill the Onset Criterion before the VT event count can begin counting toward VT detection.

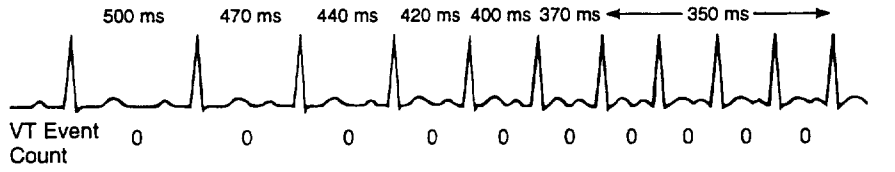

Figure 10. Onset Criterion Not Fulfilled (Example)

Figure 10 illustrates a sinus rhythm with a gradually accelerating rate. No interval is less than 81% of the average of the four previous intervals. Thus, this rhythm would not be detected by the PCD device as a VT. This example demonstrates how the Onset Criterion may be used to help differentiate between a sinus tachycardia (possibly exercise-induced) and a pathological VT.

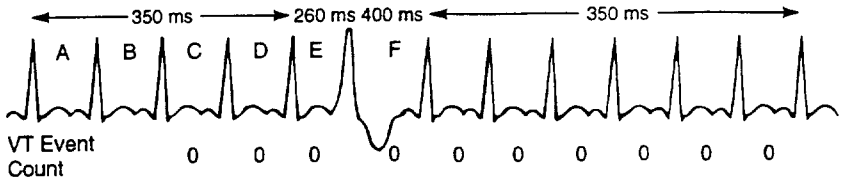

Figure 11. Onset Criterion Not Fulfilled (Example)

In Figure 11, all intervals, except "E" and "F", are 350 ms. Interval E, which is 260 ms, appears to satisfy the Onset Criterion. Although Interval E is indeed less than 81% of the average of Intervals A through D, neither Interval B or C is greater than the TDI. Both requirements must be satisfied to fulfill the Onset Criterion.

Subsequent Reconfirmation/Redetection of an Ongoing VT Episode

After initially detecting a VT episode and delivering the first programmed therapy, the PCD device monitors the cardiac cycle length for the continued fulfillment of the programmed detection criteria. Reconfirmation, i.e., redetection, is required before the next programmed therapy is delivered. **The Onset Criterion is only used for the initial detection of a VT episode and is not used for redetection of the same VT episode.**

VT detection begins immediately with the first cardiac cycle after VT therapy delivery. However, the first event detected may have a longer cycle than the programmed TDI due to the 520 ms refractory period following VT therapy.

NOTE: Programming high VT NID counts will result in correspondingly longer delays between VT therapies (when the previous therapy is ineffective in terminating the VT episode), due to the need to reconfirm the VT episode between therapies. The physician should understand that the programmed VT NID count applies to both initial detection and redetection of an ongoing episode after therapy delivery.

VT Episode Termination and Determination of Therapy Efficacy

The PCD device defines a VT episode as **terminated** when **eight consecutive** cardiac cycles (paced or sensed) all have intervals **greater than or equal to** the TDI.

The PCD device defines a VT therapy "effective" if VT termination occurs prior to any further VT detection. The PCD device is considered "ineffective" if, after **all** programmed therapies, VT detection occurs before VT termination. Once the PCD device detects a VT, it considers the episode as ongoing until a termination occurs. After episode termination, a subsequent VT detection marks the start of a new VT episode. See "Device Reporting Features" in "General Device Information" for information about how effectiveness is reported.

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NOTE: A rhythm following a therapy that does not satisfy the VT termination definition is considered part of an ongoing episode. However, the next VT therapy will not be delivered unless the programmed VT detection criteria are again fulfilled.

If all programmed therapies prove ineffective in terminating the arrhythmia, **only a later VT termination (either spontaneous or via a programmer-activated therapy) or manually programming VT Detection ON will restart** the programmed VT detection criteria and automatic therapy delivery.

Suspending and Disabling VT Detection

When the PCD device is "suspended," its detection functions are temporarily inactivated. "Disabled" is a permanently programmed state in which detection and/or therapies are not available (OFF condition). These functions can only be re-enabled via a programming sequence.

The programmed VT Detection criteria are temporarily **suspended** during

- Magnet application (unless a "Cancel Magnet" is programmed),
- Delivery of high rate pacing,
- Capacitor charging, in preparation for the delivery of a cardioversion or defibrillation shock or during a programmed charge period,
- Delivery of VT therapies,
- The period after all programmed VT therapies have proved ineffective (i.e., until VT episode termination is confirmed or VT Detection is again programmed ON),
- Delivery of VF therapies,
- The first 64 ventricular events (pace, sense, and therapy) after VF detection, and
- The period following VT and VF therapies that are manually initiated via the programmer, e.g., following programmed emergency or manual therapies (removing the programming head enables VT Detection).

The programmed VT Detection criteria are **disabled** whenever

- Three consecutive 35-second charge intervals have failed to reach the programmed energy level and the "Charge Circuit Inactive" condition occurs,
- Nominal or VVI option under Emergency VVI is programmed, and
- Power-on reset (an electrical reset) or a detected memory error occurs.

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Ventricular Tachycardia (VT) Therapy

The PCD device has three programmable VT therapy types: **Burst, Ramp, and Cardioversion.** Up to four separate therapies may be programmed **in any combination** of the three types. Here are four examples (read across):

Example	Therapy One	Therapy Two	Therapy Three	Therapy Four
No. 1	Ramp	Burst	Cardioversion	Cardioversion
No. 2	Ramp	Ramp	Burst	OFF
No. 3	Cardioversion	Cardioversion	Cardioversion	Cardioversion
No. 4	Cardioversion	OFF	OFF	OFF

NOTES: Programming a therapy OFF disables all subsequent therapies. For example, if the PCD device is programmed to Therapy #1 OFF, Therapy #2 Ramp, Therapy #3 Burst, and Therapy #4 Cardioversion, none of the VT therapies is enabled, and none will be delivered.

The PCD device cannot be programmed to deliver automatic VT therapies without VF detection and therapies programmed ON.

The physician may elect not to program any VT therapy. If VT Detection alone is enabled, the PCD device will only monitor the cardiac rhythm and record the number of detected VT episodes for subsequent interrogation via the programmer.

Burst Therapy[1]

A Burst sequence consists of a **rate-adaptive**, equal-interval set of pulses. A single Burst Therapy consists of one to 15 burst sequences. The physician programs the following: number of S1 pulses, adaptive percentage, number of sequences, millisecond decrement per sequence, and minimum pulse interval.

Burst Therapy is rate-adaptive. The PCD device determines the pulse interval of the first burst sequence as a programmable percentage of the tachycardia cycle length. The cycle length is determined by calculating the average of the last four intervals preceding VT detection.

The first pulse of the Burst sequence is delivered at the calculated "percentage", and is timed from the sensed event at which the VT event count equaled the programmed VT NID. Subsequent pulses in the same sequence are delivered at the same interval.

If a Burst sequence is ineffective in terminating the VT, and VT detection is reconfirmed, the pulse interval for the next sequence will be determined by calculating a percentage of the newly measured tachycardia cycle length and shortening that interval by a programmable value.

1. Certain antitachycardia pacing modes of this device, invented by Dr. Fred Zacouto of Paris, France, fall under one or more patent claims of U.S. Patents 3,857,399 and 4,052,991 and corresponding patents in other countries, which are licensed exclusively to Medtronic, Inc.

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The calculated pulse interval can never be less than a programmed "minimum" interval.[1] If the calculated interval is shorter than the programmed minimum, then the pulses will be delivered at the programmed minimum interval.

If the last programmed sequence of a Burst Therapy is ineffective in terminating the VT and the VT is again detected, the PCD device initiates the next therapy (if programmed).

During Burst Therapy, the PCD device operates in the VVI mode, although the programmable Refractory After Pace may affect this operation. R-waves, sensed outside the Refractory After Pace, are counted as individual pulses of the burst train (even though they are not output pulses). Whenever a sensed R-wave inhibits the scheduled pulse, the next pulse is scheduled at the calculated or minimum interval from the time of the sensed event.

A Burst sequence has the following characteristics:

- The pulse width and amplitude for an individual Burst pulse are the same as those programmed for bradycardia pacing output pulses.
- Burst sequences can be programmed as to the number of pulses, from one to 15 (in steps of one).
- The average of the last four intervals leading to VT detection and the resultant rate-adapted burst interval are both rounded to the nearest 10 ms (e.g., 387 ms is rounded to 390 ms).
- Following a Burst sequence, a 300 ms blanking period, a 520 ms refractory period, and a bradycardia escape interval of 1000 ms begin. The circuitry resumes monitoring the cardiac cycle for detection of a new/old VT episode, a VF episode, or bradycardia.

1. The "minimum" pulse interval is the same for all Burst and Ramp therapies.

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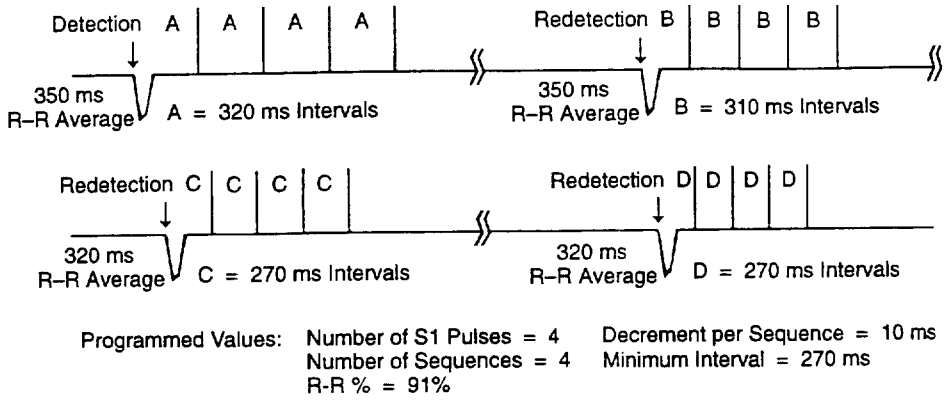

Figure 12. Burst Therapy (Example)

In the example in Figure 12, a VT episode is detected in which the R–R average interval is 350 ms. Note the programmed settings for the example.

The PCD device determines that the calculated pulse interval for the **first Burst sequence (A)** should be 320 ms, i.e., the R–R average interval of 350 ms X 91% (rounded). The first pulse is delivered at 320 ms from the R-wave that fulfilled the programmed VT NID. All subsequent pulses of this sequence are separated by 320 ms intervals.

Assuming the VT is redetected and that the R–R average interval remains at 350 ms, the calculated pulse interval for the **second Burst sequence (B)** is 310 ms (320 ms minus the 10 ms programmed decrement).

Before the **third Burst sequence (C)**, the average R-R interval shortens to 320 ms. Thus, the calculated pulse interval is 270 ms, i.e., (320 X 91%) – 20 ms = 290 – 20 ms = 270 ms (rounded).

The R-R average for the detected VT prior to the **fourth and final Burst sequence (D)** remains at 320 ms. The calculated pulse interval (with a decrement of 30 ms) would have been 260 ms; but, by definition, it cannot be shorter than 270 ms (the programmed minimum interval). Therefore, the pulse interval is 270 ms.

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Ramp Therapy

A Ramp sequence consists of a rate-adaptive, set of pulses delivered at decreasing intervals. A single Ramp Therapy consists of from 1 to 15 Ramp sequences.

Ramp Therapy is **rate-adaptive**. The PCD device calculates the interval for the first pulse of the Ramp sequence as a programmable percentage of the average cycle length of the last four cycles prior to VT detection. **Each subsequent interval in the Ramp sequence is shortened from the preceding interval by a programmable value.**

The number of pulses in the first ramp sequence is programmable (up to 15). If additional sequences are programmed and the VT is redetected, the PCD device **automatically increases the number of pulses by one in each successive sequence (to a maximum of 29 in the fifteenth sequence, if programmed to 15 pulses for the first sequence and to the maximum 15 sequences)**.

If a Ramp sequence is ineffective in terminating the VT and the VT is again detected, the first interval of the next sequence will be a programmed percentage of the newly measured tachycardia cycle length. As described above, each subsequent interval is shortened from the preceding interval by a programmable value. After each VT detection that initiates a Ramp sequence, the initial interval of the sequence is recalculated.

NOTE: If the tachycardia cycle length has not changed, the first interval of the next programmed sequence will be the same as the previous sequence. This is in contrast to Burst Therapy, in which the intervals of each sequence are shortened by a programmed value, even when the tachycardia cycle length is unchanged.

If the last programmed Ramp sequence proves ineffective in terminating the VT and the VT is redetected, the PCD device will deliver the next therapy (if programmed).

During Ramp Therapy, the PCD device operates in the inhibited mode, although the programmable Refractory After Pace may affect this operation. This means that R-waves, sensed outside the Refractory After Pace, are counted as individual pulses of the ramp sequence (even though they are not output pulses). Whenever a sensed R-wave inhibits the scheduled pulse, the next pulse is scheduled at the calculated or minimum interval from the time of the sensed event i.e., the interval is shortened (if possible) as if the sensed R-wave was an output pulse. A Ramp Therapy has the following characteristics:

- Each Ramp Therapy can be programmed from 1 to 15 pulses (in steps of one) for the initial sequence. Each successive sequence adds one pulse.
- The pulse width and amplitude for an individual Ramp pulse are the same as those programmed for the pacing output pulses.
- The average of the last four detected intervals and the resultant rate-adapted Ramp interval are both rounded to the nearest 10 ms (e.g., 387 ms is rounded to 390 ms).
- The calculated pulse interval during any Ramp sequence can never be less than the programmed "minimum" interval. If the calculated interval is shorter than the

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programmed "minimum", the pulses will be delivered at the programmed "minimum" interval.

- The PCD device operates in the VVI mode during Ramp Therapy. This means that sensed R-waves are counted as individual pulses of the Ramp sequence (even though they are not output pulses). A sensed R-wave inhibits the scheduled pulse, and the next pulse is scheduled at the calculated or minimum interval from the time of the sensed event.
- Following a Ramp sequence, a 300 ms blanking period, a 520 ms refractory period, and a bradycardia escape interval of 1000 ms begin. The circuitry resumes monitoring the cardiac cycle for detection of a new/old VT episode, a VF episode, or bradycardia.

Figure 13 shows a detected tachycardia episode with an R–R interval of 350 ms.

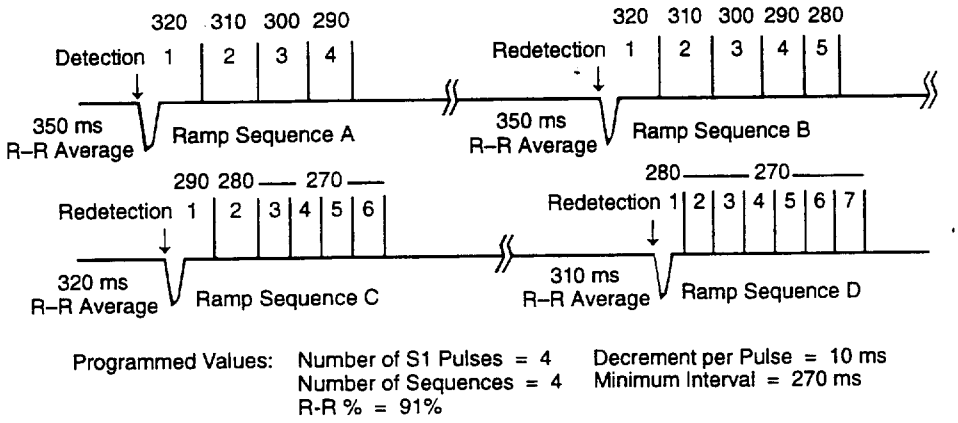

Figure 13. Ramp Therapy (Example)

The PCD device determines that the calculated pulse interval for the **first Ramp sequence (A)** should be 320 ms (i.e., 350 ms X 91% rounded). The first pulse is delivered at 320 ms from the R-wave that fulfilled the programmed VT NID, with each interval thereafter shortened by 10 ms so that the fourth interval equals 290 ms.

Assuming that the VT is redetected and the R–R average interval remains at 350 ms, the calculated initial pulse interval for the **second Ramp sequence (B)** is again 320 ms. Subsequent intervals are shortened as described above. In this sequence, however, a fifth pulse is delivered at 280 ms.

Before the **third Ramp sequence (C)**, the average R-R interval shortens to 320 ms. Thus, the initial interval is 290 ms (320 ms X 91% rounded); due to the 10 ms decrement, intervals three, four, five, and the additional sixth are all delivered at the programmed minimum of 270 ms.

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The R–R interval shortens to 310 ms prior to the **fourth Ramp sequence (D)**. In this case, the initial interval is 280 ms. All subsequent intervals (including the additional seventh) are delivered at 270 ms, since this is the programmed minimum value.

VT Acceleration During a Burst or Ramp Therapy

If, after the delivery of a Burst or Ramp sequence, the average cycle length for the four intervals preceding redetection has decreased by a value equal to or greater than 60 ms compared to the average cycle length for the initial VT detection of the episode, the PCD device determines that the VT has accelerated. Subsequent sequences (of a Burst or Ramp therapy) will not be delivered.

For example, assume the programmed therapies were Burst (with multiple sequences), Ramp (with multiple sequences), Cardioversion, and Cardioversion. If the VT were to accelerate after the first sequence of the Burst therapy, the PCD device would cancel the remaining sequences and initiate the programmed Ramp therapy. Similarly, if the VT was still considered accelerated after the initial sequence within the Ramp therapy, the PCD device would go immediately to the next programmed therapy, Cardioversion.

NOTE: This progression to the next therapy applies only when two or more sequences are programmed for a Burst or Ramp therapy. If at any time the detected rhythm satisfies the programmed VF criteria, the PCD device will deliver the first (or next) programmed VF therapy.

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Cardioversion Therapy

Overview

Cardioversion therapy may be programmed as any one of the four VT therapies. The pathway for the Cardioversion pulse(s) may be separately programmed for each of the four therapies as:

- a **SINGLE** pulse delivered over one pathway, i.e., from the PULSE2 anode to the COMMON cathode;
- two **SIMULTANEOUS** pulses delivered over two pathways, i.e., one from the PULSE1 anode and the other from the PULSE2 anode, with both flowing to the COMMON cathode;
- two **SEQUENTIAL** pulses, separated by a very short period and delivered over the same two pathways as the **SIMULTANEOUS** pulses.

In all three pathway options, the Cardioversion pulse(s) must be synchronized to a ventricular sensed event.

The physician also separately programs the stored energy[1] and pulse width of the pulse(s) for each of the programmed cardioversion therapies.

When a VT is detected and Cardioversion is the next programmed therapy, the PCD device will initiate a **Charging Period**. During this period, the device charges the high voltage capacitors to the programmed stored energy.

NOTE: The Cardioversion pulse may be programmed to the same range of stored energies as a defibrillation shock used in VF therapy.

Following the completion of charging, the device initiates a **Synchronization Sequence**. During this period the device attempts to confirm the continued presence of the VT (by ensuring that the first interval is less than the TDI) and to synchronize the delivery of the Cardioversion pulse(s) to an R-wave.[2]

1. The Programmer displays stored energy in "Joules" as the programmable value. The cardioversion/defibrillation output capacitors are charged in the PCD device to a corresponding voltage value. See Table 4 for the conversion of stored energy to volts. The physician should be aware that the delivered energy for both cardioversion and VF therapies depends on the total impedance (of the system and cardiac interface) and the programmed pulse width.
2. Since the Model 7217B cardioversion pulses are synchronized to events sensed on the PACE/SENSE to SENSE2 electrodes, monitoring by surface ECGs will exhibit morphologies and timing that do not necessarily coincide exactly with those taking place at the electrode sites.

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The differences between cardioversion and defibrillation in the PCD device are:

- A cardioversion pulse is delivered in response to VT detection, whereas a defibrillation shock is delivered only when VF detection criteria are fulfilled.
- Following the VT charging period, the PCD device reconfirms that the rhythm still has an interval defined as VT. After the VF charging period, no such reconfirmation is attempted.
- Cardioversion requires synchronization to a sensed R-wave for delivery to occur. In VF therapy, the PCD device attempts to deliver the defibrillation shock in synchrony with a sensed event, but does not require such synchronization.
- Current pathways are separately programmable for each programmed cardioversion therapy. All VF therapies must be programmed to the same current pathway.

Charging Period

After a VT detection that is to be followed by cardioversion therapy, there is a Charging Period during which the high-voltage capacitors in the PCD device are charged to the programmed stored energy (leading edge voltage).

Several points should be noted about the Charging Period:

- Electrogram sensing does not occur during this time.
- Bradycardia therapy does not take place.
- Marker Channel and electrogram telemetry are not available.
- Programming is disabled during this period. However, if a magnet is placed over the PCD device and is kept in position until the end of the charging period, the device will recognize the presence of the magnet and the Cardioversion therapy will not be delivered.

The capacitor charging period usually varies from less than one second to ten (10) seconds at beginning-of-life power source status, depending on the programmed stored energy. This time will lengthen as the power source is depleted or as time increases from the last charging period. **If the Charging Period reaches a maximum duration of 35 seconds, charging is terminated**, the cardioversion therapy attempt is aborted, and the device returns to its programmed mode. This situation presents a potential loss of device function (see "Potential Loss of Function Indicators").

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Synchronization Sequence

The Synchronization Sequence is designed to ensure the continued presence of the VT after completion of the Charging Period and to synchronize the delivery of the cardioversion pulse(s) to an R-wave, sensed on the implanted electrodes. To do this, the PCD device monitors the cardiac cycle for a sensed R-wave within the timing requirements described below. When these timing requirements are met, the VT is confirmed and the delivery of the cardioversion shock is synchronized to the sensed event.

Following completion of the Charging Period, the Synchronization Sequence requires that the interval from the first non-refractory sensed event to the next sensed event be (1) less than the programmed TDI plus 60 ms and (2) greater than 200 ms.[1]

VT detection is not confirmed and the cardioversion therapy is aborted under the following conditions:

- The timing requirements are not met,
- The initial three events after the Charging Period are sensed during refractory periods, or
- No sensed event occurs within a synchronization period following completion of capacitor charging.

If, after an aborted cardioversion therapy, there is a subsequent VT detection within the same VT episode, the PCD device will again attempt to deliver the same therapy.

If some energy remains on the capacitors after a therapy or because a therapy was aborted, the capacitors are discharged internally when VT episode termination is identified unless they were charged by a programmer-initiated charge command or a VF episode is ongoing.

Timing Periods After Non-Confirmation of VT

If no R-wave is sensed during a synchronization period, the PCD device returns to the programmed settings after a single cycle with a 300 ms blanking period, a 520 ms refractory period, and a 1000 ms escape interval.

If the Synchronization Sequence is terminated by three consecutive refractory sensed events, the PCD device returns to the programmed settings after a single cycle. The single cycle has a 320 ms blanking period, a programmed Refractory After Pace, and the programmed pacing escape interval.

1. When cardioversion is manually initiated via the programmer, the Synchronization Sequence timing requirement simply requires the period from the first non-refractory sensed event to the next sensed event to be less than the programmed bradycardia escape interval.

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Cardioversion Timing

Figures 14 through 17 are timing diagrams that illustrate what may occur during the Synchronization Sequence.

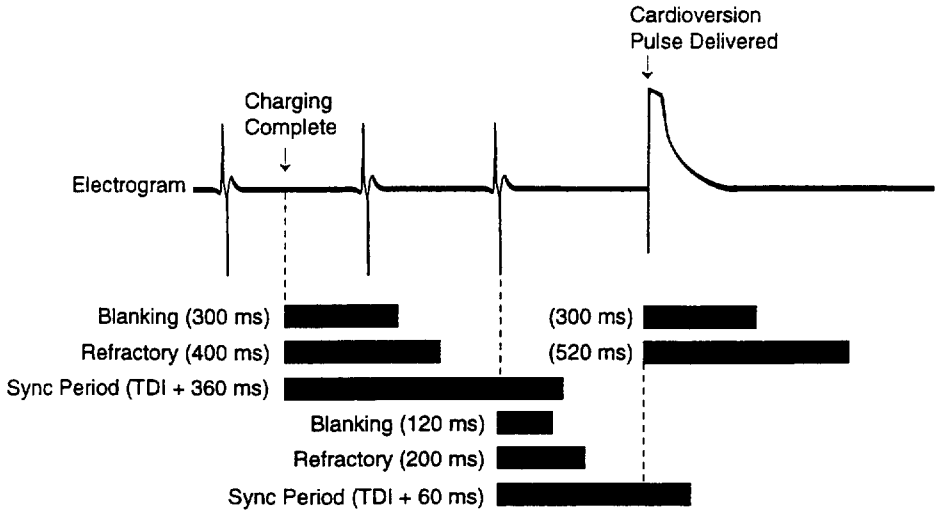

Figure 14. Cardioversion (Scenario "A")

Figure 14 depicts the simplest scenario in which the PCD device delivers the programmed cardioversion pulse(s) at the time of the second non-refractory sensed ventricular event following the Charging Period. The Synchronization Sequence consists of both sets of blanking, refractory, and synchronization periods. During the Synchronization Sequence, the PCD device confirms the continued presence of the tachycardia and identifies the R-wave to which it synchronizes delivery of the programmed cardioversion pulse(s).

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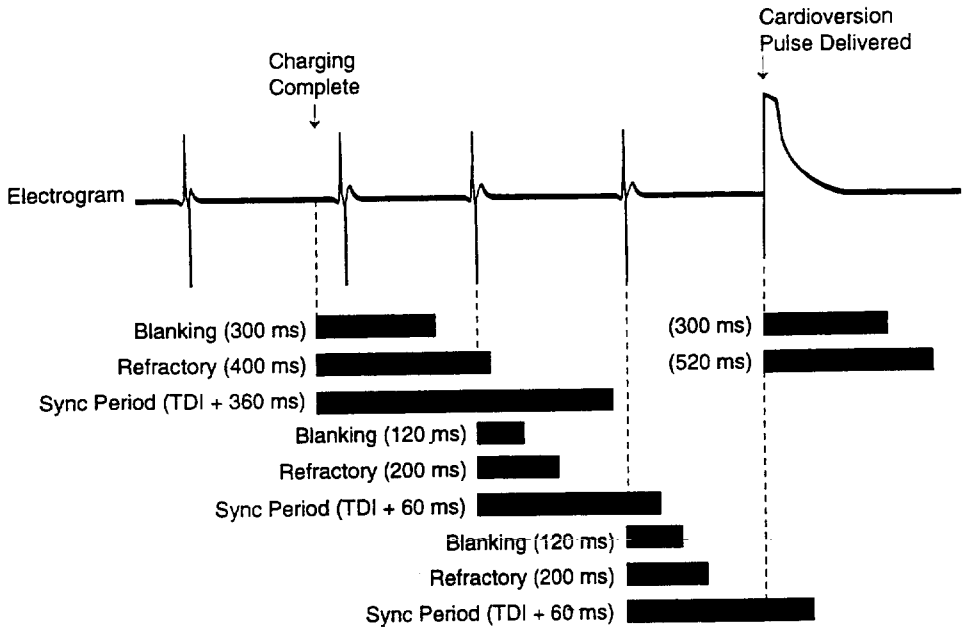

Figure 15. Cardioversion (Scenario "B")

In Figure 15, the first ventricular event after the end of the first blanking period is a refractory sensed event. As a result, the PCD device initiates a second set of periods in an attempt to identify an initial event outside the refractory period. Such an event is sensed and the resulting operation is the same as that in Figure 14. In this case, all three sets of periods comprise the Synchronization Sequence.

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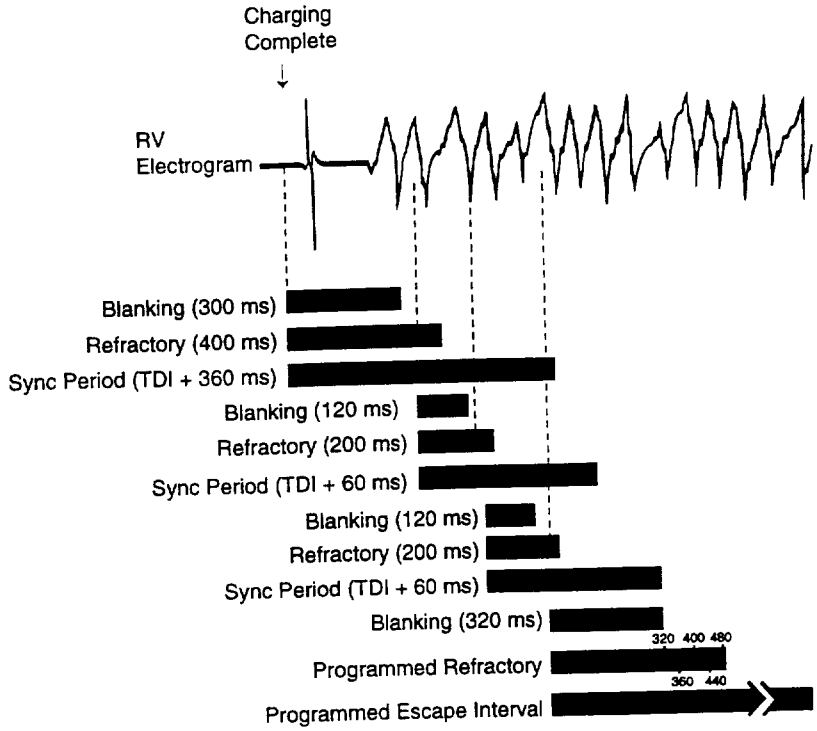

Figure 16. Cardioversion (Scenario "C")

In Figure 16, the PCD device fails to sense any ventricular events outside of a refractory period and, therefore, the VT cannot be confirmed. Thus, the cardioversion cannot be synchronized to a known R-wave. The therapy is aborted. After the third refractory sensed event, a pacing escape interval starts.

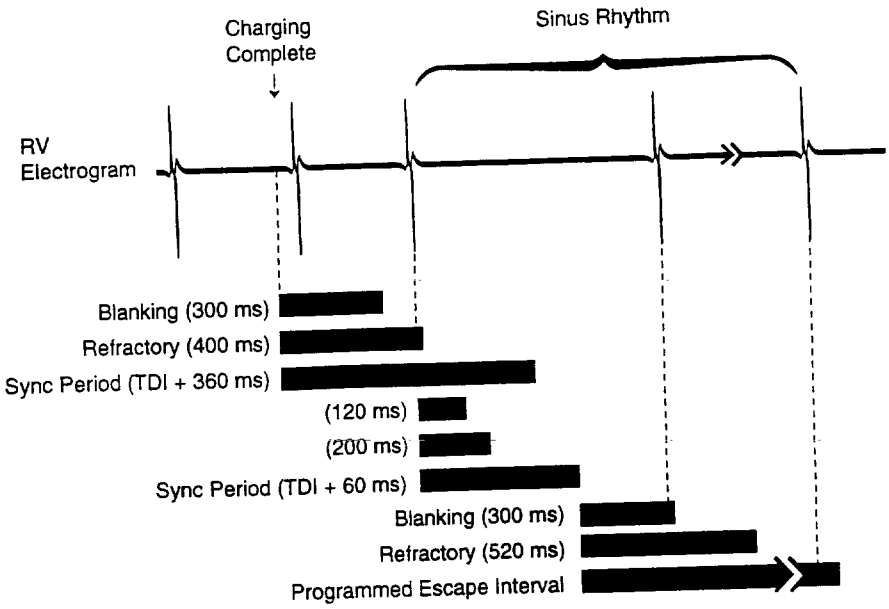

Figure 17. Cardioversion (Scenario "D")

Figure 17 depicts a situation in which the tachycardia terminates spontaneously sometime between VT Detection and completion of the Charging Period. Since the PCD device could not identify two non-refractory sensed ventricular events during the synchronization sequence, it aborted the VT therapy and initiated a bradycardia escape sequence. A sensed R-wave inhibits the bradycardia output.

Delivery of the Cardioversion Pulse

Delivery of the programmed cardioversion pulse(s) is synchronized to the second non-refractory sensed event following completion of charging. The current pathways for the cardioversion therapy are programmable, i.e., single, simultaneous, or sequential.

Following the cardioversion pulse, a 300 ms blanking period, a 520 ms refractory period, and a bradycardia escape interval of 1000 ms begin. The circuitry resumes monitoring the cardiac cycle for detection of a new VT episode, a VF episode, or bradycardia.

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Ventricular Fibrillation (VF) Detection

Overview

The PCD device detects ventricular fibrillation using three programmable parameters: Sensitivity of the ventricular sensing circuit, the Fibrillation Detection Interval (FDI), and the Number of Intervals to Detect (VF NID) that must be attained by the VF event counter. Up to four Defibrillation Therapies may be delivered in an attempt to terminate a single VF episode. If the first therapy is ineffective in terminating the arrhythmia and VF is detected again, a second defibrillation shock is delivered. Similarly, a third and fourth shock will be delivered if VF continues to be detected. If all the programmed VF therapies are ineffective, additional VF therapies will not be delivered until the PCD device identifies termination of the VF episode, or if VF detection is manually programmed ON.

NOTE: VT detection must be programmed OFF before VF detection can be programmed OFF.

VF Detection

The VF Detection Criterion is designed to detect a very fast ventricular rate. This criterion requires that 75% or more of the previous intervals are shorter than the programmed FDI. This is done to ensure detection for two reasons: (1) the signal amplitude of events within a VF episode may vary and (2) some intervals may be longer than others.

The Detection Criterion for VF requires that a programmed number of cardiac cycle lengths are less than the programmed FDI. This required number is called the Number of Intervals to Detect (VF NID). The PCD device continuously monitors a number of previous intervals equal to 133% of the programmed VF NID. It analyzes each cycle length to determine if it is shorter than the FDI. If the number of intervals shorter than the FDI equals the number required for VF detection (the VF NID), VF detection occurs.

VF NID	VF Detection Window
6	8
12	16
18	24
24	32
30	40

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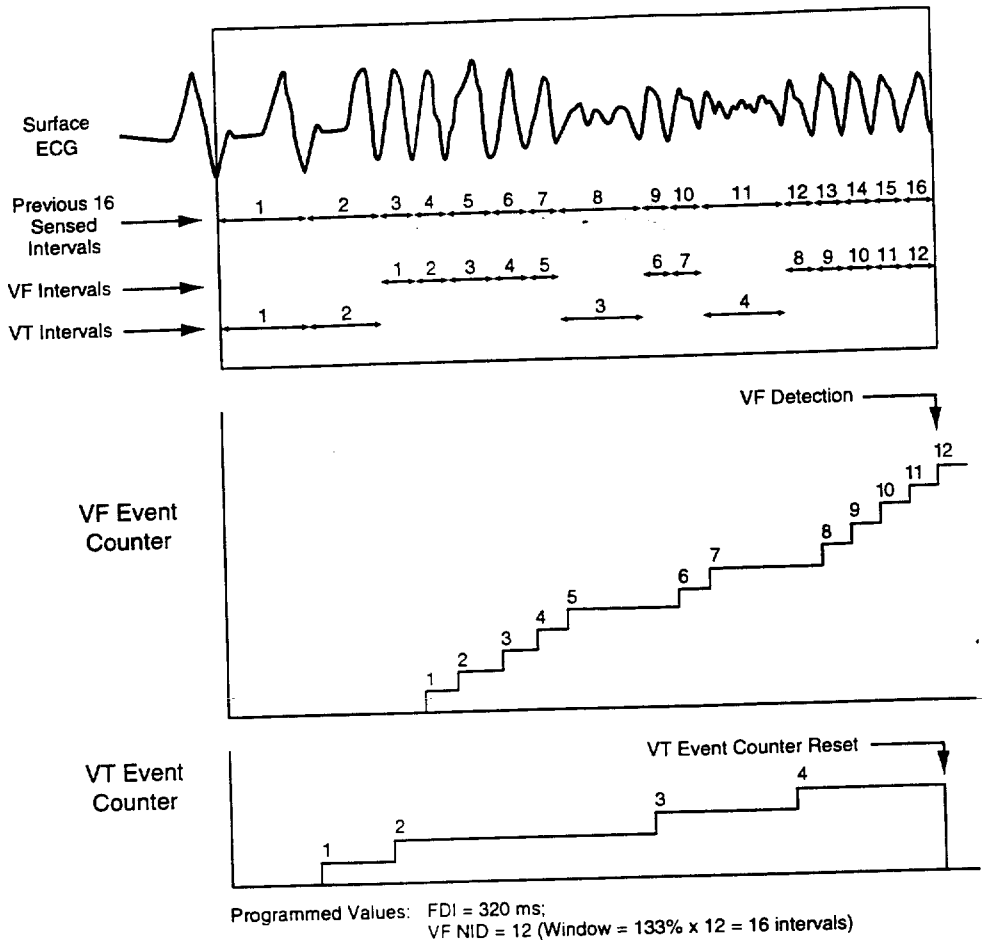

Figure 18. VF Detection (Example)

Figure 18 illustrates how VF Detection may be fulfilled. The PCD device is programmed to a VF NID of 12, which means it will evaluate the 16 intervals preceding the current interval (133% of 12). Since 12 of the intervals within the 16-interval "window" of detection are shorter than the FDI, VF detection occurs.

Relationship of VT and VF Detection

The PCD device separately processes the measured cardiac cycle lengths against the programmed VT and VF Detection Criteria. It is possible that, while a detected VT episode is in progress, a VF episode begins (i.e., to have both an active VT and an active VF episode). In such cases, when VF detection occurs, the PCD device will deliver the next programmed VF therapy.

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When VT detection occurs, the fibrillation event count is not reset and interval data that occurred prior to the VT therapy will be used. However, when VF is detected, the VT event count is reset.

VF Episode Termination and Efficacy Determination

The PCD device defines a VF episode as **terminated** when eight consecutive cardiac cycles (sensed or paced) have intervals **greater than or equal to** the FDI.

The PCD device defines a VF therapy "effective" if VF termination occurs prior to any further VF detection. The PCD device is considered "ineffective" if after delivery of the last programmed VF therapy, VF detection occurs before VF termination is detected. See "Device Reporting Features" in "General Device Information" for information about how effectiveness is reported.

NOTE: A rhythm following a therapy that does not satisfy the VF termination definition is considered part of an ongoing episode. However, additional VF therapies will not be delivered unless the VF Detection Criterion is again fulfilled.

If all programmed therapies proved ineffective in terminating the arrhythmia, **only a later VF termination (either spontaneous, or via a programmer-activated therapy or transthoracic defibrillation) or manually programming VF Detection ON** will restart VF detection and automatic therapy delivery.

Suspending and Disabling VF Detection

When the PCD device is "suspended," its detection functions are temporarily inactivated.

"Disabled" is a permanently programmed state in which detection and/or therapies are not available (OFF condition). These functions can only be re-enabled via a programming sequence.

The VF Detection Criterion is temporarily **suspended** during

- Magnet application (unless a "Cancel Magnet" is programmed),
- Capacitor charging (i.e., in preparation for the automatic delivery of a cardioversion or defibrillation shock or during a programmed charge period),
- Delivery of high-rate pacing,
- Delivery of VT therapies,
- Delivery of VF therapies,
- The period after all programmed VF therapies are proved ineffective (i.e., until VF termination is confirmed or VF Detection is programmed ON), and
- The period following VT and VF therapies that are manually initiated via the programmer, e.g., following programmed emergency or manual therapies (removing the programming head enables VT and VF Detection).

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The VF Detection Criterion is **disabled** whenever

- Three consecutive 35-second charge intervals have failed to reach the programmed energy level and the "Charge Circuit Inactive" condition occurs,
- Nominal or VVI option under Emergency VVI is programmed, and
- Power-on reset (an electrical reset) or a detected memory error occurs.

Ventricular Fibrillation (VF) Therapy

Overview

For each detected VF episode, the PCD device can deliver up to four defibrillation therapies. Each therapy consists of a high-energy defibrillation shock separately programmable as to stored energy and pulse width. The current pathway (i.e., single, simultaneous, or sequential) is programmable but must be the same for all VF therapies.

NOTES: A therapy programmed OFF disables all subsequent therapies. For example, if the first VF therapy is programmed OFF, all therapies are effectively disabled.

VF therapy cannot be programmed OFF if the PCD device is programmed to deliver automatic VT therapies.

After detection of a VF episode, the PCD device initiates a charging period for the first programmed therapy. During this period the device charges the high voltage capacitors to the programmed stored energy level. After completion of the charging, the device initiates the Synchronization Sequence. During this sequence, the device attempts to synchronize the defibrillation shock to the leading edge of a sensed event. If synchronization is not possible, an asynchronous shock will be delivered. Defibrillation Therapy, unlike Cardioversion, is "committed", i.e., once the charging cycle has begun, a shock will be delivered[1].

If the first and/or subsequent VF therapies prove ineffective and the VF arrhythmia is again detected after each therapy, the PCD device repeats the above operation up to a total of four times.

NOTE: It is recommended that the physician program the second, third, and fourth VF therapy to the maximum stored energy of 34 joules.

Charging Period

After a VF detection, the high-voltage capacitors are charged to the programmed stored energy (leading edge voltage) level for the next VF therapy. This period has the same function and range of durations as the cardioversion charging period.

1. See the section titled "Cardioversion and Defibrillation Charging Periods" under "Programming Considerations" for a complete description of charging periods.

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NOTE: If a cardioversion shock is programmed to a stored energy level higher than that for VF therapy and cardioversion is aborted, leaving the energy stored on the capacitors, the delivered energy of a subsequent VF shock could be higher than the programmed value, if VF is detected prior to the end of the VT episode.

The capacitor charging period usually varies from less than one second to ten (10) seconds at beginning-of-life power source status, depending on the programmed stored energy and the elapsed time since the previous charging cycle. This time will lengthen as the power source is depleted or as time increases from the last charging period. **If the charging period reaches a maximum duration of 35 seconds, charging is terminated,** the VF therapy attempt is aborted, and the device returns to its programmed mode. This situation presents a potential loss of device function (see "Potential Loss of Function Indicators").

Synchronization Sequence

Upon completion of the capacitor charging period, the Synchronization Sequence follows during which the device attempts to synchronize the defibrillation shock to a sensed cardiac event. The defibrillation shock is delivered at the time of the first non-refractory sensed event following completion of the charging period. If there is no non-refractory sensed event within the Synchronization Sequence, then the defibrillation shock is delivered at the end of the Synchronization Sequence.

In Figure 19, a non-refractory event is sensed during the first synchronization period. As a result, the PCD device synchronizes the delivery of the VF therapy to this event.

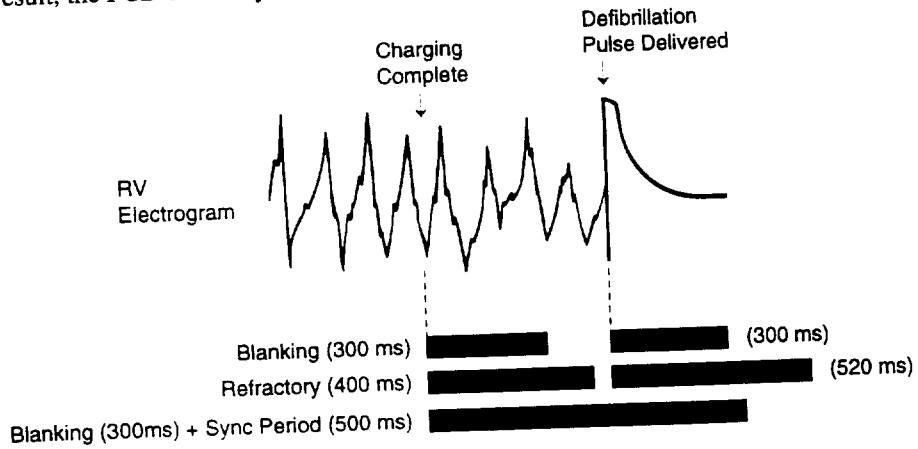

Figure 19. Defibrillation (Scenario "A")

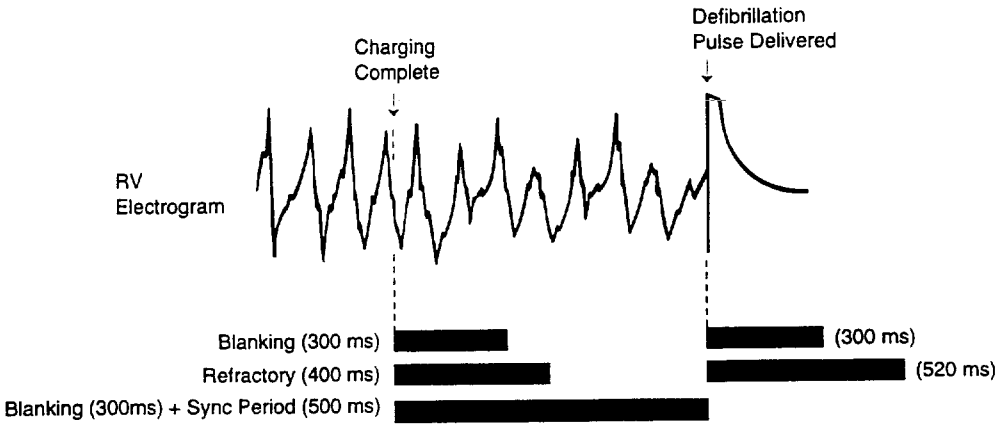

Figure 20. Defibrillation (Scenario "B")

Figure 20 illustrates an absence of sensed events during the synchronization period. As a result, the PCD device delivers the VF therapy at the end of the synchronization period.

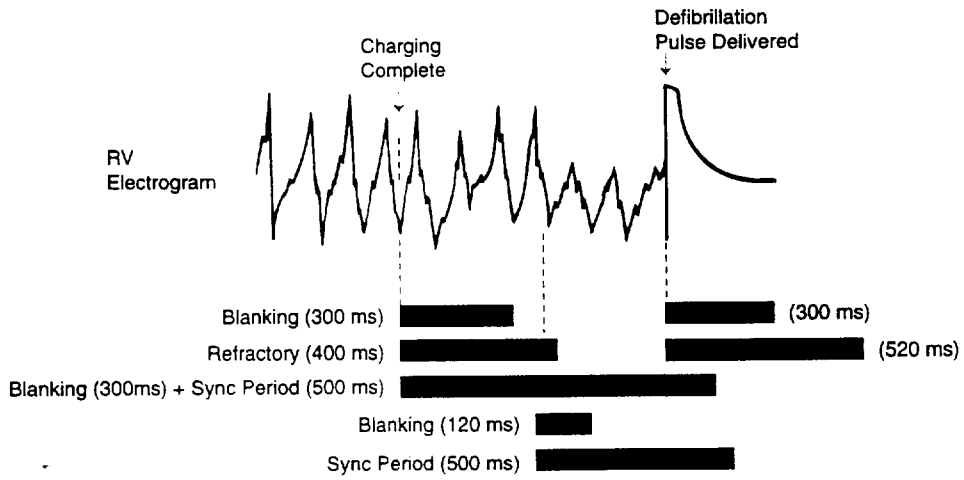

Figure 21. Defibrillation (Scenario "C")

Figure 21 shows how the PCD device might synchronize the delivery of a VF therapy to the second of two sensed events, the first of which is a refractory sensed event. Note the Synchronization Sequence that starts after the charging period. The refractory sensed event starts a second synchronization period as the PCD device attempts to synchronize the VF therapy to a non-refractory sensed event.

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Programmable Current Pathways

All four VF therapies must have the same pathway, programmable between:

- a SINGLE pulse delivered over one pathway, i.e., from the PULSE2 anode to the COMMON cathode;
- two SIMULTANEOUS pulses delivered over two pathways, i.e., one from the PULSE1 anode and the other from the PULSE2 anode, with both flowing to the COMMON cathode; or
- two SEQUENTIAL pulses, separated by a very short period and delivered over the same two pathways as the SIMULTANEOUS pulses.

The PCD device delivers sequential and simultaneous pulses with three cardioversion/ defibrillation electrodes. Single pulses can be delivered with two or three electrodes.

The physician also programs the stored energy and pulse width of the pulse(s) for each of the four VF therapies (or as many as are programmed ON).

Operation Following VF Therapy

After a VF therapy, there is a 300 ms blanking period, a 520 ms refractory period, and an escape interval of 1000 ms for one cycle. The device returns to the programmed settings and, if enabled, automatically begins to evaluate the cardiac cycle for the possible detection of VF or bradycardia.

VT detection is automatically suspended[1] for 64 events (including paced events, sensed events, and therapy, except during a Charging Period) after each VF detection that initiates a VF therapy. This operation is designed to avoid detection of a transient VT which may follow such a VF therapy. After 64 events have occurred, the VT detection process is re-enabled and, if the Onset Criterion is programmed ON, then this criterion is considered fulfilled.

If some energy remains on the capacitors after a therapy, the capacitors are internally discharged when VF episode termination is detected, unless they were charged by a programmer-initiated command or a VT episode is ongoing.

1. During the 64 events following an automatic defibrillation therapy, the algorithm for detecting VT episode termination is also suspended.

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VVI Therapy

The Model 7217B PCD device provides backup bradycardia therapy, i.e., pacing in the ventricular inhibited (VVI) mode. Thus, unless a sensed event occurs and resets the pacing interval (the bradycardia escape interval), the PCD device will pace at the programmed rate.

These parameters are programmable:

- **Rate:** rates from 30 to 90 ppm for backup bradycardia pacing.
- **Pulse width:** keep in mind that this programmed setting also applies to VT Burst and Ramp therapies. When programming this parameter, ensure an adequate safety margin above the stimulation threshold.
- **Pulse Amplitude:** choose one of two settings that ensures an adequate safety margin above the stimulation threshold. The setting selected also applies to VT Burst and Ramp therapies.
- **Sensitivity:** this programmed setting will also be used to detect VT or VF. Therefore, program a setting that will sense R-wave and VF wave amplitudes, but not sense P- or T-waves or electromagnetic interference. Sensitivity should be programmed to 0.3 mV to maximize the probability that VF will be detected. A value greater than 1.2 mV may be too insensitive for VF detection. Values less sensitive than 1.2 mV are not recommended except for testing and troubleshooting. If undersensing is observed in normal sinus rhythm, verify that VF sensing and detection are appropriate. Repositioning the lead or implanting a new pacing/sensing lead may be necessary.
- **Refractory period:** the PCD device has a blanking period and Refractory After Pace after a paced event, and only a blanking period after a sensed event. (See "Refractory Periods.") The Refractory After Pace is usually the same duration as the 320 ms blanking period but may be programmed to a longer duration. Events sensed after the 320 ms blanking period are noted on Marker Channel telemetry as refractory sensed events. There is a 120 ms blanking period (nonprogrammable) after sensed events.

Events sensed within the programmed refractory period do not inhibit the pacing output. The PCD device does not revert to asynchronous operation (VOO) in the presence of continuous electrical "noise." Also, placing a magnet over the device does not inhibit VVI therapy.

A combination of wide pacing pulse width, high pacing amplitude, and high sensitivity (low sensing threshold) may cause inappropriate sensing after pacing. Programming a narrower pulse width, a lower amplitude pulse, a longer refractory period after pace, or a higher sense threshold may eliminate this inappropriate sensing. If sensitivity is reprogrammed to eliminate inappropriate sensing, VF should be reinduced and the PCD device should be allowed to automatically detect and treat the arrhythmia to ensure proper sensing and detection.

A long refractory period, coupled with a high programmed pacing rate, may impair the PCD device's ability to detect VT or VF and may cause asynchronous pacing.

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IMPLANTING THE PCD DEVICE

Handling and Storage

Dropping the PCD device onto a hard surface (e.g., dropped from a height of 12 inches (30 cm) or more onto a concrete floor) could damage the device. Should this occur, the unit should not be implanted.

Environmental temperature limits for transportation and storage are:

Maximum: +52° C (125° F)
Minimum: –18° C (0° F).

Resterilization

Medtronic has sterilized the PCD device with ethylene oxide prior to shipment. The sterile package is designed to maintain the device in a sterile condition. If the device was not used, it may be resterilized in ethylene oxide.

DO NOT AUTOCLAVE OR STERILIZE THE PCD DEVICE BY GAMMA IRRADIATION. DO NOT ATTEMPT TO CLEAN THE DEVICE IN ULTRA-SONIC CLEANERS.

Avoid the application of certain organic cleaning agents (e.g., alcohol and acetone) prior to resterilization, because they may have a detrimental effect on the device's connector assembly.

When resterilizing, place the device in an ethylene oxide permeable package. Due to the variability between sterilizers, precise resterilization instructions must come from the sterilizer manufacturer. However, the process should not exceed temperatures of 55° C (130° F) nor 15 psi. Use some acceptable method for determining sterility, such as biological indicators.

Prior to implantation of the PCD device, aerate the packaged device to ensure that ethylene oxide residues are no longer present.

Resterilization of a PCD device does not change the "use before" date established at the time of manufacture.

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Implantation Procedure

Overview

Patients should undergo the following procedures before implant of the PCD device to help determine if they are appropriate candidates for a PCD system:

- Electrophysiologic evaluation to determine the patient's ventricular arrhythmia and how it responds to different therapies,
- Exercise stress test to determine the patient's maximum sinus rate, and
- Cardiac catheterization to determine if there is a need for concomitant surgery.

modified

If patients do not meet the implant criteria (demonstration of a 10 Joule safety margin) for a transvenous lead system, physicians should consider implanting an epicardial cardioversion/defibrillation lead system. If an epicardial system is to be implanted after testing a transvenous system, consider performing the procedure at a later date. The Transvene® clinical study showed a 9.3% perioperative death rate for patients failing the implant criteria for a Transvene® system and receiving an epicardial system. This compares to 0.7% for those patients receiving a Transvene® system without the additional epicardial surgical procedure.

Implanting the PCD device and corresponding lead system involves seven main steps:

- Operative Set-Up
- Lead System Implantation and Evaluation
- Defibrillation Efficacy Testing
- Connecting the Leads to the PCD Device
- Placing the PCD Device
- PCD System Evaluation
- Closing

During implantation, the PCD system requires an appropriate Medtronic programmer and MemoryMod cartridge and the Medtronic External Tachyarrhythmia Control Device (ETCD) to evaluate and monitor the implanted lead system and therapy efficacy.

Each of the above steps is explained in the following sections. At the end of this chapter, instructions for replacing a PCD device and implanting a PCD device with a chronically implanted lead system are also given.

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Operative Set-Up

The preparation and procedures before implanting the lead system are grouped into four main steps: assembling the necessary equipment, setting up the equipment, pre-programming and testing the PCD device, and pre-programming and testing the ETCD and auxiliary equipment.

Necessary Equipment

The equipment listed below should be available for each implant. Duplicates of sterile items should also be on hand.

- Model 7217B PCD device
- External Tachyarrhythmia Control Device (ETCD)
- Appropriate Medtronic programmer and printer
- Appropriate MemoryMod software cartridge
- Cardioversion/defibrillation and pacing/sensing leads
- Appropriate adaptors
- External defibrillator
- Pacing system analyzer (PSA)
- Patient cable for connecting lead system to the ETCD
- EGM cable to connect the programmer to the ETCD
- Cable (and connector pins if necessary) to connect a pacing system analyzer to the ETCD or a surgical cable to connect the PSA directly to the leads
- Test load for discharging high-voltage shocks from the ETCD
- Cables for connecting the EGM output of the ETCD and Marker Channel output of the programmer to a hospital monitor/recorder
- Appropriate batteries for the pacing system analyzer and ETCD
- Extra printer paper for the pacing system analyzer and programmer/printer
- Sterile bag to place over programming head and cable
- Implant documentation forms

Some optional equipment includes an external fibrillation source or stimulator, tape or multi-channel recorder, dual-channel oscilloscope, and appropriate cables.

Equipment Set-Up

Set up the ETCD/programmer with the appropriate MemoryMod cartridge, an external defibrillator, and auxiliary equipment such as monitors, recorders, a fibrillator, and their related cabling. Also, connect the test load to the ETCD.

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Pre-Programming and Testing the PCD Device

Check the "use before" date printed on the package. It is recommended that you do not use the product after its expiration date.

Prepare the PCD device for implant by doing the following:

1. Interrogate the device while it is still in its sterile package and print out a full report.
2. Review the battery status. Devices with an initial battery voltage less than 6.1 volts before charging should not be implanted. If the device is charged without obtaining the initial voltage, it should be implanted only if the battery voltage reaches 6.1 volts or more within thirty minutes after charging.
3. Test the charge circuit by charging the capacitors to the maximum output. The charge time must meet the following requirements:
   - If the charge time is less than or equal to 10 seconds, implant the device. If it is greater than 10 seconds, wait 5 minutes, discharge (dump) the capacitors, and then perform a second charge.
   - If the second charge time is less than or equal to 10 seconds, implant the device. If it is greater than 10 seconds, do not implant the device.
4. While still in the sterile package set the device parameters for implant as appropriate for the patient.
5. Ensure that VT and VF Detection are programmed OFF.

Pre-Programming and Testing the ETCD & Auxiliary Equipment

To prepare for lead system evaluation and defibrillation efficacy testing, do the following:

1. Verify that the ETCD's battery status is acceptable.
2. While recording the ETCD's output signals and the Marker Channel output from the printer, calibrate the hospital's monitoring/recording equipment.
3. Test the ETCD's high-energy output capability using the test load.

Lead System Implantation and Evaluation

The PCD lead system uses electrodes designed to carry high current for cardioversion or defibrillation. The cardioversion/defibrillation electrodes (PULSE1, PULSE2, and COMMON) must be specifically suited for this purpose and have a large electrode surface area to reduce cardioversion/defibrillation thresholds and minimize tissue damage possibly caused by the high cardioversion/defibrillation currents.

While the PCD is connected to the leads, no metal portion of any electrode should contact the metal of any other electrode. If the electrodes are in contact during a cardioversion or defibrillation therapy, the current will bypass the heart and may also damage the PCD device.

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Pacing occurs between a pacing/sensing lead and one of the cardioversion/defibrillation leads (COMMON). Sensing is accomplished through two pacing/sensing electrodes. Either epicardial or endocardial leads may be used. To reduce the effects of electromagnetic interference (EMI), the PACE/SENSE and SENSE2 electrodes should be positioned adjacent to each other, and where separate leads are used, the lead wires should be routed together with several loose twists.

Depending on what kind of operative approach is used to implant the leads, the PCD Device can use two different kinds of lead systems: an epicardial lead system or a Transvene® lead system. Each system is described briefly below. See the appropriate Lead Technical Manual for more details.

The physician chooses the lead system that best meets the patient's needs. Patient factors that affect the decision include the following:

- Overall size of the patient's heart,
- Size and location of previous infarcts, aneurysms, or bypass grafts, and
- Surgical approach.

The epicardial lead system uses two or three epicardial patch leads for cardioversion/defibrillation. Three patch sizes allow the physician the flexibility to meet the varying patient conditions. Clinical experience has shown that approximately half of all patients receive a three-patch system; the other half receives two patches. Three patches may be required initially if the physician expects difficulty in meeting defibrillation implant criteria. Adding a third patch to a two-patch system may be required if the implant criteria cannot be met with the two-patch system.

The Transvene® non-thoracotomy lead system can use two or three leads in four different areas:

- A tripolar lead in the right ventricle (RV).
- A unipolar lead in the coronary sinus (CS) and/or superior vena cava (SVC).
- A subcutaneous (SQ) patch lead.

addition

Clinical experience with the Transvene® lead system has shown that most patients (65.6%) received an RV-SVC-SQ system; an additional 29.3% received an RV-CS-SQ system, and the remaining 5.1% recieved an RV-CS-SVC system. The majority of patients were programmed to Sequential Pulse (75.3%), 23.4% were programmed to the Simultaneous Pulse, and 1.3% were programmed to Single Pulse.

Cardioversion/defibrillation occurs between the COMMON electrode (cathode) and one or two anodes. These electrodes can be any of the following: the CS lead, the SVC lead, the RV coil, or the SQ patch. Sensing occurs between the tip and ring of the tripolar RV lead. Pacing occurs between the tip of the RV lead and the COMMON electrode.

addition

The RV electrode was COMMON in the majority (75.3%) of the clinical implants, the SQ patch in 13.9%, the CS in 7.6%, and the SVC electrode in 2.4% of the clinical implants. The overall efficacy in terminating spontaneous episodes of VF was approximately 98% for all pathways, pulsing techniques and choice of cathode.

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Lead system implantation and evaluation consists of placing the lead system, connecting the leads for pacing and sensing measurements, performing pacing and sensing measurements, and verifying lead connections. Each step is explained in the following sections. See the appropriate lead technical manual for more details.

Placing the Lead Systems

Placing the Epicardial Lead System

Depending on the physician's preference, a variety of surgical approaches can be used to implant the lead system, such as a limited thoracotomy or median sternotomy.

Placing Pacing/Sensing Leads:
The pacing/sensing leads should be placed close to the ventricular apex to avoid sensing P-waves. Approximately 1 cm should separate the electrodes from each other.

Placing Epicardial Patch Leads:
Suture two or three patch leads to the epicardium or pericardium in locations that produce optimal defibrillation, pacing, and sensing. In all locations, place the leads so that they encompasses the maximum amount of cardiac mass and they have approximately equal amounts of mass between them.

For a two-patch system, a typical approach is to use an anterior right ventricular patch as COMMON and a posterolateral left ventricular patch as PULSE2. For a three-patch system, a typical approach is to use a posterior ventricular septal patch as COMMON, an anterior right ventricular patch as PULSE1, and an anterolateral left ventricular patch as PULSE2. The PULSE1 and PULSE2 patches should be the same size.

Placing Transvene Leads

CAUTION: Given the body diameter of transvenous defibrillation leads, insertion via a subclavian approach should be done as far lateral as possible to avoid clamping the lead body between the clavicle and the first rib. Clamping the lead can eventually cause the conductor to fracture, can cause damage to the insulation, or can cause other damage to the lead. This can result in complications such as loss of detection, loss of pacing therapies, or loss of cardioversion defibrillation therapy. Certain anatomical abnormalities, such as thoracic outlet syndrome, can also precipitate pinching and subsequent fracture of the lead. If the subclavian approach is required, avoid techniques that can damage the lead. Specifically, do not force the lead if significant resistance is encountered. Do not use techniques such as adjusting the patient's posture (i.e., raising the arm or putting a towel behind the person's back) to facilitate the passage of the lead. If resistance is encountered, it is recommended that an alternate venous entry site be used, e.g. the cephalic vein.

There are several possible lead systems that can be evaluated depending on the desired pathway and physician placement preference.

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Two Lead System

- Right ventricle, coronary sinus.
- Right ventricle, superior vena cava.
- Right ventricle, subcutaneous patch.

Figure 23 shows a flowchart for lead system evaluation that begins with the two lead system and adds an additional lead if the implant criteria is not met with the two lead system. The decision to evaluate a two lead system is based on the desire to achieve the simplist transvenous defibrillation system.

modified

Three Lead System:

- Right ventricle, superior vena cava, and subcutaneous patch.
- Right ventricle, coronary sinus, and subcutaneous patch.
- Right ventricle, coronary sinus, and superior vena cava.

Clinical results do not indicate superiority of any pulsing technique, lead system, or choice of cathode for transvenous defibrillation. The choice of lead system for initial evaluation can therefore be based on other factors including simplicity (SVC vs CS lead placement) and physician preference.

The RV, CS, and SVC lead should be implanted using standard transvenous implant techniques. Follow the general guidelines below for initial positioning of the Transvene lead system (the final positions will be determined by defibrillation threshold tests):

- Position the RV lead tip in the right ventricular apex.
- Advance the CS lead tip to just under the left atrial appendage, if possible.
- Place the SVC lead tip approximately 5 cm proximal to the right atrium and SVC junction.
- Place the SQ patch lead along the left midaxillary with the center over the fourth-to-fifth intercostal space.

Other positioning recommendations to consider:

- The CS lead position should be considered unacceptable if the proximal end of the CS defibrillation coil is at or outside the CS ostium.
- A cutaneous patch electrode may also be used during acute testing to minimize invasive procedures. Once defibrillation efficacy has been demonstrated, a permanent subcutaneous can be implanted.
- The subcutaneous patch may be placed subcutaneously, submuscularly, or directly on the periosteum of the ribs. The patch may be repositioned on the left lateral chest wall, if necessary, to meet the implant defibrillation efficacy criteria.
- If the Transvene lead system implant criteria cannot be met, an epicardial lead system may be evaluated, as described in this section.
- If the CS lead is proving difficult to position, a temporary pacing catheter can be positioned in the coronary sinus ostium. This can be used as a guide to cannulate the coronary sinus with the permanent lead.

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Connecting the Leads for Pacing and Sensing Measurements

Depending on the physician's preference, two approaches can be used to connect a pacing system analyzer (PSA) to the implanted leads: passing through the ETCD or by direct connection. See the appropriate ETCD or PSA technical manual for connecting instructions.

Performing Pacing and Sensing Measurements

For a Transvene lead system, the pacing connections should be the RV tip electrode as cathode (-) and the defibrillation COMMON electrode as anode (+). Sensing measurements should be made between the RV tip and RV ring electrodes.

For an epicardial lead system, the PACE/SENSE electrode serves as the cathode (-) for pacing and the COMMON patch electrode serves as the anode (+). Measure between this patch electrode and each pacing/sensing electrode to obtain the best pacing threshold. Designate the best pacing/sensing electrode as PACE/SENSE. The other electrode should be SENSE2.

Listed below are the acceptable PCD system implant values for acute and chronically implanted lead systems.

	Acceptable Implant Values	
Measurements Required	**Acute Lead System**	**Chronic Lead System**
Capture threshold (at 0.5 ms pulse width)	≤ 1.5 V - epicardial ≤ 1.0 - endocardial	≤ 3.0 V - epicardial ≤ 3.0 V - endocardial
Impedance	200 - 800 ohms	200 - 800 ohms
Filtered R-wave amplitude	≥ 5 mV (during sinus rhythm)	≥ 3 mV (during sinus rhythm)
Slew rate	≥ 0.75 V/s	≥ 0.45 V/s

Also, check that P- and T-wave oversensing are not occurring by pacing at the maximum output (5.4 V, 1.59 ms) and sensing at the maximum sensitivity (0.3 mV).

Defibrillation Efficacy Testing

Verifying Lead Connections

After connecting all of the leads to the ETCD, confirm that the sensing leads are connected properly by observing sensed events on the Marker Channel telemetry. Verify the cardioversion/defibrillation lead connections to the ETCD by delivering a low-energy shock (0.6 joules) synchronously into sinus rhythm.

The path resistance should be approximately 20 to 100 ohms for epicardial leads, or 40 to 150 ohms for Transvene leads.

If the path resistance measurements (ohms) do not fall within these ranges, check the lead connections and lead placements and tighten or reposition if necessary.

CAUTION: Implanting the PCD device when the path resistance is less than 20 ohms may damage the device.

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Performing Defibrillation Efficacy Testing

After checking the lead connections, test defibrillation efficacy to show the ability to properly treat ventricular fibrillation. Before testing defibrillation efficacy, ensure an external defibrillator is charged for a rescue shock. Use the ETCD to perform the following:

1. Program the ETCD to properly detect VF with an adequate safety margin (sensitivity = 1.2 mV, VF NID = 18, FDI = 320 ms).
2. Program the VF therapy parameters (energy, pathway, and pulse width) to the desired settings. See Table 5 in "General Device Information" for information on choosing optimal pulse widths.
3. Induce VF using AC stimulation or the fibrillation induction feature present in the ETCD. See the appropriate programmer manual for specific instructions on inducing VF with the ETCD.
4. Convert the arrhythmia using the ETCD and lead system.

To demonstrate reliable defibrillation efficacy with acute or chronic leads, it is recommended that VF be initiated and terminated three out of four times at a stored output energy of 24 joules or less. The protocol shown in Figures 22 and 23 are suggested. If more than one of the four VF inductions are not terminated by the ETCD and lead system, the decision to implant the PCD device should be re-evaluated.

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In order to keep patient morbidity and mortality to a minimum, patients should be rescued promptly with an external device if the lead system and ETCD fails to terminate the VF episode and at least 5 minutes should elapse between VF inductions.

At their option, physicians may also test for ventricular tachycardia therapy efficacy after testing for defibrillation efficacy.

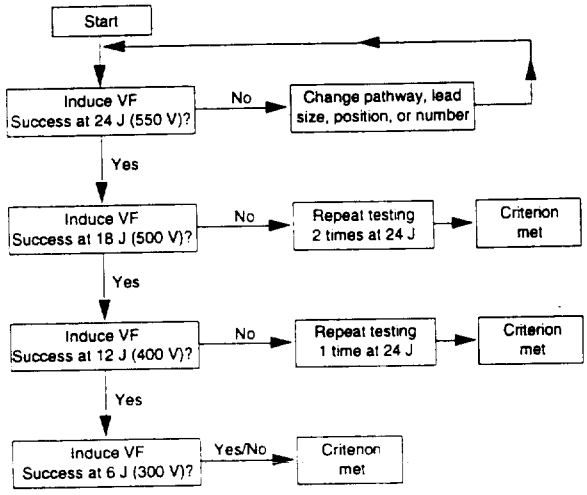

Figure 22. Defibrillation Efficacy Protocol Flowchart

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Evaluating VF Sensing

While testing for defibrillation efficacy, evaluate VF sensing by reviewing the Marker Channel symbols and electrograms and checking for post-shock T-wave sensing. If VF sensing is not appropriate, it may be necessary to reposition the leads and repeat the VF inductions.

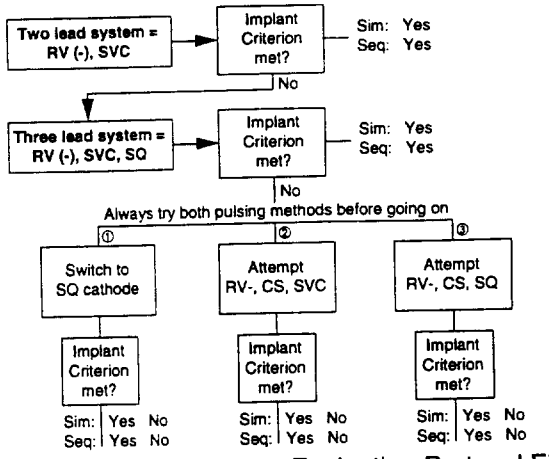

Figure 23. Transvene Lead System Evaluation Protocol Flowchart

CAUTION: Use of a chest tube is suggested in tunneling the lead connector to the pulse generator to prevent damage to the lead. DO NOT use surgical instruments to grasp the lead or connector pin when tunneling.

Connecting the Leads to the PCD Device

The Model 7217B PCD device is connected to a lead system consisting of either two or three cardioversion/defibrillation electrodes. Figures 24 and 25 illustrate these two connection configurations. Both the PULSE2 and COMMON electrodes are used in either configuration. The PULSE1 electrode is required in a lead system that uses the sequential or simultaneous therapy current pathway, but it is not required when the single pulse therapy is used. When the PULSE1 electrode is not used, the 6.5 mm plug provided with the PCD device must be positioned in the lower left port of the connector block.

The COMMON, PULSE2 and PULSE1 lead connectors must be of the 6.5 mm style. If the lead connector is not the correct size, an adaptor designed for use in a 6.5 mm port must be positioned on the lead connector.

In either configuration shown in Figures 24 and 25, both a PACE/SENSE and a SENSE2 electrode are required. The PACE/SENSE and SENSE2 lead connector must be either the Medtronic low-profile bipolar or the IS-1[1] bipolar style. The PACE/SENSE electrode must be on the pin of the lead connector and the SENSE2 electrode must be on the ring of the lead connector. If two unipolar myocardial leads are used for pacing and sensing, insert their connectors into an appropriate adaptor that will fit into the PCD device's bipolar pacing/sensing port. See the appropriate lead technical manual for more details.

1. IS-1 refers to the International Connector Standard (ISO 5841-3: 1992) whereby generators and leads so designated are assured of a basic mechanical fit.

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CAUTION: For questions about lead—pulse generator compatibility, consult your Medtronic representative or call Medtronic Technical Services at our 24-hour toll-free number, 1-800-328-2518.

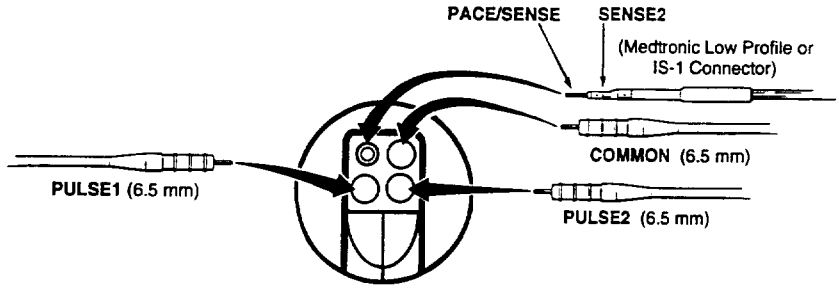

Figure 24. The Three Cardioversion/Defibrillation Electrode System

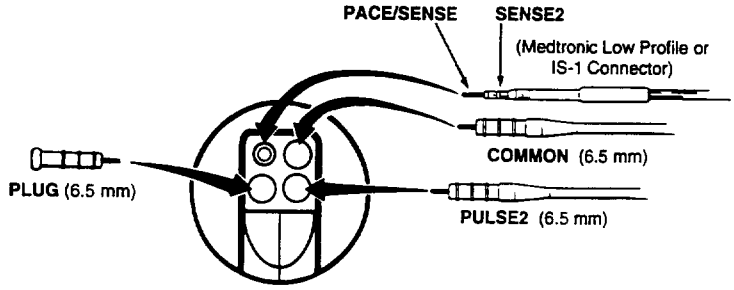

Figure 25. The Two Cardioversion/Defibrillation Electrode System

It should be noted that the insertion depth of an IS-1 lead pin is less than the insertion depth of a low-profile lead pin. The insertion mark for the IS-1 lead connector on the connector module (Figure 26) indicates that the IS-1 lead pin may not be inserted any further than the bar. Since the pin cavity is longer than the IS-1 requirement, the front part of the pin cavity will be empty when using an IS-1 lead.

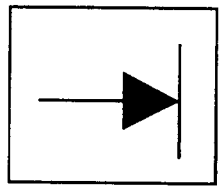

Figure 26

To connect each of the leads and plug, if required, to the PCD device:

1. Place a lead or plug into the appropriate port as shown in Figure 24 or 25.
2. Ensure full insertion of the connector pin by observing it protrude into the pin viewing area (i.e., beyond the metal block of the connector).

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3. Pass the hex wrench through the associated grommet and tighten the setscrew securely by turning clockwise until tight. For the PACE/SENSE and SENSE2 connector, tighten both setscrews.

If there is difficulty with lead insertion due to the setscrew obstructing the port, turn the setscrew counterclockwise—but only until the port becomes clear.

CAUTION: Counterclockwise rotation beyond this point may disengage the setscrew from the connector block.

The setscrews must be tightened securely using the hex wrenches provided with the PCD device. The hex wrenches are designed to yield at the handle when overtorqued, thus preventing damage to the socket of the setscrew. **Do not use Medtronic blue handled, right angle, or allen-type wrenches** since they possess torque capabilities far greater than intended for this device.

PCD System Evaluation

After connecting the leads to the PCD device, test the defibrillation efficacy of the PCD system. Before testing defibrillation efficacy, ensure an external defibrillator is charged for a rescue shock. Perform the following:

1. Program the PCD device to appropriately detect and treat the VF episode.
2. If using external fibrillation equipment, place the PCD device in magnet mode (VT and VF Detection are suspended).
3. Induce VF using external fibrillation equipment or the fibrillation feature present in the PCD device. If using external fibrillation equipment, apply the signal between the PACE/SENSE terminal of the PCD and an indifferent electrode attached to body tissue. The SENSE2 terminal may be used instead of the PACE/SENSE terminal with an indifferent electrode. See the appropriate programmer manual for specific instructions on inducing VF with the PCD device.

   CAUTION: When using external fibrillation equipment, make only one connection to the PCD lead system. This connection should be disconnected immediately after VF is induced.

   CAUTION: DO NOT MOVE THE PROGRAMMING HEAD from the beginning of detection through delivery of the shock. If the head is moved, remove it from the PCD device to allow the device to operate automatically. Replacing the head during the sequence may suspend VF Detection or abort the therapy.

4. After verifying sustained VF, press the CANCEL MAGNET key and then the PROGRAM key to allow automatic VF detection and therapy delivery to convert the arrhythmia.[1]

1. When using the fibrillation feature present in the PCD device, pressing the CANCEL MAGNET key and then the PROGRAM key prior to induction of VF will cause VF Detection to be enabled immediately after the end of the fibrillation sequence.

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5. Observe the ECG signal and Marker Channel symbols for proper detection and therapy. Proper sensing following therapy delivery must be observed. Wait ten seconds after VF has been terminated before interrogating the device and printing a partial summary report of the data.
6. Program VT and VF Detection OFF before closing.

Placing the PCD Device

To ensure telemetry and programming function post-implant, the Model 7217B PCD device must be placed within 5 cm of the skin and with the engraved side facing toward the skin.

The Model 7217B PCD device has two suture holes located in the connector assembly. Use of these suture holes may help secure the device in the subcutaneous pocket, thus minimizing rotation and/or migration of the device post-implant. Penetration of the holes can be achieved with normally available surgical needles.

Closing

At closing perform or verify the following:

- All leads are sutured or positioned for chronic implant.
- All leads are fully inserted into the PCD device connector and all setscrews are tight.
- Place the PCD device in the pocket within 5 cm of the skin and with the **engraved side toward the skin**.
- Ensure that there are no kinks in the leads.
- Close the pocket.
- Program VF Detection and Therapies ON.
- Interrogate the device and print a full summary to document the post-operative programmed status of the PCD device.

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Replacing a PCD Device

To replace a Model 7217B PCD device:

1. Program VT and VF Detection OFF.
2. Carefully dissect the leads and the PCD device free from the surrounding tissues in the pocket. Be especially careful not to nick or breach the lead insulation inadvertently during the process of exposing the PCD system.
3. Insert the proper hex wrench through the slits in the rubber grommet and loosen the setscrew by turning counterclockwise.
4. Gently retract the lead connectors from the connector ports.
5. If any lead pin shows signs of pitting or corrosion, the entire lead should be evaluated and tested to assure the integrity of the system.
6. Take pacing, sensing, and defibrillation efficacy measurements.
7. Connect the leads to the replacement device.
8. Evaluate the defibrillation efficacy of the PCD system.
9. Place the PCD device and close.
10. Interrogate the device and print a full summary to verify and document that the programmed status of the device is as desired.
11. Return the explanted device after cleaning/gas sterilizing to your Medtronic representative for device evaluation.

Implanting a PCD Device With a Chronic Lead System

When implanting a PCD device that connects to a chronically implanted lead system, evaluate the following to ensure the device will detect and treat ventricular arrhythmias appropriately:

1. Integrity of the chronic patch leads. Evaluate by chest X Ray, inspection, or test shock.
2. Chronic pacing and sensing measurements (see "Performing Pacing and Sensing Measurements" in "Implantation Procedure"). Repositioning the chronic leads or implanting new pacing/sensing or patch leads may be necessary.
3. Defibrillation efficacy (see "Defibrillation Efficacy Testing" in "Implantation Procedure"). Repositioning the chronic leads or positioning a third patch lead may be necessary to meet the defibrillation efficacy protocol (Figure 22).
4. VF sensing (see "Evaluating VF Sensing" in "Defibrillation Efficacy Testing"). Repositioning the chronic leads or implanting new pacing and sensing leads may be required.
5. Fit of the connectors in the PCD device (see "Connecting the Leads to the PCD Device" in "Implantation Procedure"). The leads must be properly inserted into the connector block for the device to function properly.

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POST-IMPLANT INFORMATION

Programming Considerations

The following suggestions have been developed to assist the physician in programming the Model 7217B PCD device. These suggestions should be used to help program the proper detection and therapy parameters for the patient's clinical arrhythmias. They are **only** considerations based on the review of the clinical experience and are not the result of unanticipated adverse results or complications. The programming choices will also depend on the patient's specific clinical arrhythmia and the results of pre- and post-implant electrophysiologic testing.

NOTE: Always interrogate the device at the beginning and end of each follow-up session and print a full summary to verify and document that the programmed status of the PCD device is as desired.

The suggestions are divided into six main areas: VT Detection, VT Therapy, VF Detection, VF Therapy, VVI Therapy, and General.

VT Detection

The PCD device uses two primary parameters to detect ventricular tachycardia: the Tachycardia Detection Interval (TDI) and the Number of Intervals to Detect (VT NID). The two optional detection methods are the Onset and Stability Criteria. Keep in mind the following when programming VT Detection:

Tachycardia Detection Interval (TDI)

The choice of the TDI is based on the cycle length of the patient's clinical ventricular tachycardia. To provide a safety margin that allows the VT cycle length to vary somewhat and still be appropriately detected, the TDI should be programmed at least 40 ms longer than the clinical VT cycle length (since a single cycle length greater than or equal to the TDI resets the VT event counter to zero). However, it must also be short enough to avoid inappropriate detection of sinus tachycardia and atrial fibrillation or flutter with rapid ventricular response.

Programming the FDI to a value greater than or equal to the TDI effectively disables VT Detection. **When programming these two values, the physician should keep the TDI at least 40 ms longer than the FDI to allow for variability of the clinical VT cycle length.**

Number of Intervals to Detect (VT NID)

The choice of the VT NID is based on the hemodynamic consequences of the clinical VT. Smaller VT NIDs will allow rapid detection of hemodynamically unstable VT. Larger VT NIDs may be indicated in patients with a history of non-sustained but well-tolerated VT. For patients other than these, programming an initial VT NID of 16 is appropriate.

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Programming larger VT NID counts will result in correspondingly longer delays between VT therapies (when the previous therapy is ineffective in terminating the VT episode), due to the need to redetect the VT episode after each unsuccessful VT therapy.

The physician should understand that the programmed VT NID applies to both initial detection and redetection of an ongoing episode after each therapy is delivered.

Onset Criterion

Onset Criterion is indicated only if inappropriate detection of sinus tachycardia resulting in inappropriate VT therapy delivery has occurred. Treadmill testing, beginning at 81% Onset, is suggested to evaluate the appropriate function of this algorithm.

This algorithm was used safely in 8.5% of 434 patients in the clinical study. Its use has demonstrated its safety and effectiveness.

If the Onset Criterion is ON and is not met at the beginning of a spontaneous ventricular tachycardia, the VT episode could remain "undetected", such as with an exercise-induced VT. If VT Detection uses the Onset Criterion and detection is enabled after the start of a VT, the VT may not be detected.

A low programmed onset percentage value will increase the specificity of the Onset Criterion to detect the targeted tachycardia, but will also decrease the sensitivity of the overall VT detection algorithm.

Stability Criterion

Stability Criterion is indicated if atrial fibrillation or atrial flutter with a rapid ventricular response has caused inappropriate detection and therapy delivery. A stability value of 60 ms is suggested initially.

This algorithm was used safely in 17.9% of 434 patients in the clinical study. Its use has demonstrated its safety and effectiveness.

Decreasing the programmed interval stability value increases the specificity of the Interval Stability Criterion to detect the targeted stable tachycardia, but may also decrease the sensitivity of the detection algorithm.

Programming VT Detection ON

VT Detection can be programmed ON only after VF Detection has been programmed ON.

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VT Therapy

VT Therapy consists of four independently programmable therapies that can be delivered to restore the patient's normal cardiac rhythm. The physician can tailor these four therapies to each patient's needs by choosing from two methods of overdrive pacing (Ramp and Burst) and synchronized Cardioversion. Since the actual programmed parameters used will be patient dependent, the suggestions below may help in programming them appropriately.

The physician should be aware that even when there has been a satisfactory response to VT therapies (i.e., Burst, Ramp, or Cardioversion) during clinically conducted EP studies, underlying or accompanying disease may over time alter the heart's electrophysiologic characteristics. Thus, over time, the programmed automatic therapies may not only be ineffective but also deleterious to the patient (e.g., initiate an atrial tachyarrhythmia or accelerate a ventricular tachycardia to flutter or fibrillation).

Ramp and Burst Therapy

Clinical experience has shown that the most commonly programmed values for Ramp Therapy are the following:

Initial # of S Pulses:	5
First R-S Interval	91%
Per Pulse Decrement	10 ms
# of Sequences	5
Minimum Interval	250 ms

Clinical experience has shown that the most commonly programmed values for Burst Therapy are the following:

# of S1 Pulses:	6
First S1-S1 Interval	84%
Per Sequence Decrement	10 ms
# of Sequences	5
Minimum Interval	250 ms

The values selected for Ramp and Burst Therapies will depend on the patient's clinical VT cycle length, electrophysiologic testing results, and antiarrhythmic drug therapy.

Evaluating VT Therapies

For evaluation of VT therapies, the exact number of inductions and successful terminations that should be completed is primarily dependent on a patient's hemodynamic response to their ventricular tachycardia. In patients with poorly-tolerated VT, it is recommended that at least **ONE** episode of VT be induced and successfully terminated using any of the VT therapies selected. For patients with well-tolerated VT, it is recommended that at least **FOUR** episodes of VT be induced and successfully terminated. This testing should be conducted whenever the following are performed:

- Initial selection of VT therapies,
- Permanent reprogramming of VT therapies, and
- Modification of antiarrhythmic drug therapy.

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Detecting VF as VT

In cases where VF may be detected as VT, consider using one pacing sequence and three high-energy cardioversion shocks for the VT therapies.

VT Therapy #4

The last VT therapy should be high-energy cardioversion.

Programming VT Therapies ON and OFF

VT Therapy cannot be programmed ON unless VF Therapy is also programmed ON. Also, programming one of the four VT therapies OFF will disable all subsequent VT therapies. For example, if VT Therapy #1 is programmed OFF, all VT therapies are effectively disabled.

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VF Detection

The PCD device detects ventricular fibrillation using three programmable parameters: the Sensitivity of the ventricular sensing circuit, the Fibrillation Detection Interval (FDI), and the Number of Intervals to Detect (VF NID) that must be attained by the VF event counter. The programming suggestions for VF Detection are the following:

Sensitivity

Sensitivity should be programmed to 0.3 mV to maximize the probability that VF will be detected. Values of 0.6 or 0.9 mV should be used **only** if oversensing (such as P- and T-waves) would cause inappropriate shocks or inhibit pacing therapies. If sensitivity is reprogrammed to eliminate inappropriate sensing, VF should be reinduced and appropriately treated to ensure proper sensing and detection. Repositioning or implanting new pacing/sensing leads may be necessary. Use of values less sensitive (higher threshold) than 1.2 mV are not recommended except for testing and troubleshooting.

In the event of post-pace oversensing, consider increasing the Refractory After Pace if it does not interfere with VT Detection or reducing the pacing pulse width or amplitude if it does not affect proper pacing capture. See "Refractory Periods" in "Principles of Operation" for more information on programming the Refractory After Pace.

Fibrillation Detection Interval (FDI)

FDI should generally be programmed to **at least** 320 ms. If VT therapies are required for faster VTs, then a shorter FDI should be programmed **only** if repeated inductions of true VF are detected as VF at the shorter FDI. Using the Last Episode Detection Sequence memory, the FDI should be lengthened if 3 or more of the intervals from the start of VF detection are greater than or equal to the programmed FDI. Some drugs, such as Amiodarone, may slow the VF intervals to greater than 320 ms, which would require the FDI to be increased.

Number of Intervals to Detect (VF NID)

For most patients a programmed VF NID of 18 should be used. VF NIDs greater than 18 may be indicated for some patients, for example, those with non-sustained rapid tachyarrhythmias. However, in general, VF NIDs greater than 18 should be avoided to prevent prolonged detection and redetection times.

Programming VF Detection OFF

VT Detection must be programmed OFF before VF Detection can be programmed OFF.

VF Therapy

VF Therapy delivers up to four high-energy defibrillation shocks to treat ongoing detected VF episodes. The stored energy and pulse width for each therapy is separately programmable (see Table 5 in "General Device Information" for information on how to program the optimal pulse width); the electric current pathway is also programmable but must be the same for all VF therapies.

Current Pathways

The multiple pathway options the PCD device offers (sequential, simultaneous, and single) allow the physician to provide an adequate defibrillation efficacy safety margin for most patients. For example, the simultaneous pathway may be indicated for patients who have difficulty meeting the defibrillation implant criteria with a different pathway.

Stored Energy

modified

Although the Transvene clinical study provided evidence that defibrillation thresholds remain stable in the study population, individual patients may experience threshold changes relative to changes in their underlying disease state. Therefore, VF therapy number 1 should be programmed to at least twice the lowest energy of defibrillation or 34 Joules.

The second, third, and fourth VF therapies should be programmed to the maximum stored energy of 34 joules.

Programming VF Therapies OFF

VF Therapy cannot be programmed OFF unless VT Therapy is programmed OFF. Also, programming one of the four defibrillation therapies OFF will disable all subsequent defibrillation therapies. For example, if VF Therapy #1 is programmed OFF, all defibrillation therapies are effectively disabled.

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VVI Therapy

Pacing Parameters

Rate: VVI pacing may be required for underlying conduction disease and after delivery of cardioversion/defibrillation therapy. Program the rate for appropriate bradycardia support, but allow for contribution of the patient's intrinsic rate.

Pulse Width: keep in mind that this programmed setting also applies to VT Burst and Ramp therapies. When programming this parameter, ensure an adequate safety margin above the stimulation threshold.

Pulse Amplitude: choose from two settings. The setting selected also applies to VT Burst and Ramp therapies; the value selected should ensure an adequate safety margin above the stimulation threshold.

Sensitivity: this programmed setting will also be used to detect VT or VF. Therefore, sensitivity should be programmed to 0.3 mV to maximize the probability that VF will be detected. A threshold greater than 1.2 mV may be too insensitive for VF detection. Values less sensitive than 1.2 mV are not recommended except for testing and troubleshooting. If undersensing is observed in normal sinus rhythm, verify that VF sensing and detection are appropriate. Repositioning or implanting new pacing/sensing leads may be necessary. See also the programming considerations for VF Detection above.

A combination of wide pacing pulse width, high pacing amplitude, and high sensitivity (low sensing threshold) may cause inappropriate sensing after pacing. Programming a narrower pulse width, a lower amplitude pulse, a longer refractory period after pace, or a higher sense threshold may eliminate this inappropriate sensing. If sensitivity is reprogrammed to eliminate inappropriate sensing, VF should be reinduced and the PCD device should be allowed to automatically detect and treat the arrhythmia to ensure proper sensing and detection.

Long Refractory After Pace

A long refractory period (more than 320 ms), coupled with a high programmed pacing rate, may impair the PCD device's ability to detect VT or VF and may cause asynchronous pacing. Events sensed within the refractory period restart a 120 ms blanking period but are ignored by both VT and VF detection criteria and for bradycardia pacing inhibition. Therefore, a short bradycardia escape interval (i.e., a pacing rate greater than 50 ppm) combined with a long Refractory After Pace (360 ms or longer) may prevent a VT event from inhibiting a pacing output. **In such circumstances, the VT could remain undetected**.

To avoid this possibility when the Refractory After Pace is programmed to 360 ms or longer, ensure that at least one of the following is true: (1) the difference between the bradycardia escape interval and the effective refractory period should be greater than the Tachycardia Detection Interval (TDI); or (2) the bradycardia escape interval must be greater than twice (2X) the effective refractory period. (The effective refractory period

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for a programmed refractory of 360 ms or longer is the programmed value plus 120 ms.) See "Refractory Periods" in "Principles of Operation" for more information.

General

Estimates of Time to Device Therapy

The time to device therapy depends on several factors including programmed detection parameters, the PCD device's remaining battery life, and the time since the last charge of the device capacitors. For all therapies, the time to device therapy increases with higher programmed NIDs. For cardioversion and defibrillation therapies, the time also increases as the device's battery voltage decreases and as the time since the last charge of the capacitors increases.

The time to device therapy projections found in Table 2 apply under the following conditions:

- The episode interval lengths to be detected are all less than the programmed TDI for VT episodes or FDI for VF episodes,
- A programmed TDI of 400 ms and VT NID of 16,
- A programmed FDI of 320 ms and VF NID of 18
- A beginning-of-life charge time to 34 J of 6.00 seconds,
- A cardioversion or defibrillation therapy of 34 J.

Table 2. Estimated Time to Device Therapy from Onset of Episode

Therapy	Time to Therapy
Ramp or Burst	6.4 seconds
Cardioversion	12.4 seconds
Defibrillation	11.8 seconds

Cardioversion and Defibrillation Charging Periods

The PCD device cannot be programmed during the cardioversion or defibrillation charging periods or during delivery of VT and VF therapies. Positioning (i.e., applying or removing) the programming head during a charging period has no immediate effect on the operation of the PCD device. However, if such positioning changes between the time the charging period begins and ends, the PCD device will abort the scheduled cardioversion or VF therapy.[1]

If the capacitors are not fully charged after three consecutive 35-second charging periods, the PCD device disables all VT and VF detection parameters and charging cycles and all VT pacing therapies.

1. VF therapy is aborted only if a refractory event is sensed at the end of charging.

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Permanent Telemetry Enable

This feature, which appears on the 9710 Programmer, is designed for future applications. At that time, it may be used to provide continuous telemetry (after removal of the programming head) for a programmable number of hours, or continuously. **This feature is normally programmed OFF.**

Conditioning the PCD Device Output Capacitors

The cardioversion/defibrillation output capacitors function more efficiently if they periodically receive an electrical charge. The charge conditions and helps maintain the efficiency of the capacitor function. The electrical charge should be used to condition the capacitors at every PCD follow-up visit. See the appropriate MemoryMod cartridge technical manual for charging instructions.

Elective Replacement and Potential Loss of Function Indicators

See Table 3 on the next page for a summary of voltage and charge time requirements at implant, elective replacement, and potential loss of function.

Elective Replacement Indicators

Replacement of the Model 7217B PCD device is recommended when any of the following occur:

- The telemetered voltage for the battery is 4.97 V or less, or
- The capacitor charging time is greater than or equal to 11.00 seconds.

These are elective replacement indicators only. They do not indicate that the PCD device has altered its operation in any way.

Potential Loss of Function Indicators

Whenever any of the following are observed an **immediate replacement** of the PCD device is recommended:

- The potential for altered or loss of function is present when the telemetered voltage for the **Battery** is 4.74 V or less.

  When the telemetered battery voltage is less than this value, the PCD device may be unable to successfully complete a charging cycle to the programmed energy. That is, a charging period may terminate prematurely and result in the "Reset Parameter Value" (see Table 4).

- As the battery depletes, the charging time will generally increase (typically less than 25 seconds), but a single charging period should not exceed 35 seconds. If the output capacitors have not reached their full programmed charge in this time, the charge circuit "times out." (This data is available via telemetry.) After such a timeout, the PCD device will again attempt to confirm VT/VF detection before resuming with an

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additional 35-second charging period. If after three successive charging periods the capacitors do not reach their programmed level, the PCD device identifies a "Charge Circuit Inactive" state. (This data is also available via telemetry.) In this state, the PCD device disables the following:

All automatic VT and VF detection and therapies
Programmer-initiated therapies (except emergency Burst Pacing)
Programmer-initiated charging periods

Table 3. Voltage and Charge Time Requirements

	Requirements		
Event	**Voltage**		**Charge Time**
Implant	≥ 6.10 V	and	≤ 10.00 seconds
Elective Replacement	≤ 4.97 V	or	≥ 11.00 seconds
Potential Loss of Function	≤ 4.74 V		*

*Not applicable

Time from Elective Replacement Indicator to Potential Loss of Function

The time from the Elective Replacement Indicator to potential loss of function should be used to determine the frequency of follow-up and the schedule for replacement of the unit.

The time from the Elective Replacement Indicator to potential loss of function is four months (minimum)[1], based on the following conditions:

- 100% pacing at 65 ppm,
- 5.4 V pulse amplitude,
- 0.49 ms pulse width,
- 500 ohm pacing load, and
- two 34-joule high-voltage capacitor charging cycles per month.

This time may be shorter with increased pacing rates, increased pacing pulse widths, lower pacing impedances, or an increase in high-voltage capacitor charging frequency. Potential loss of function means the PCD device may be unable to successfully complete a charging cycle to the programmed energy.

1. The preliminary projection of the time from Elective Replacement to potential loss of function is based on accelerated battery data and device modeling. Minimum projection means that virtually all (i.e. 99.9%) of the modeled production run of PCD devices will attain the values given at the stated conditions.

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Pre-Hospital Discharge

Monitor the patient appropriately post-implant and take X rays as soon as possible to document and assess the location of the leads.

While the patient is in the hospital, interrogate the device after each spontaneous episode to assess the appropriateness of the detection and delivered therapy. Depending on the physician's judgment, the clinical tachyarrhythmia should be induced and terminated if no spontaneous episodes have occurred to confirm the appropriateness of the programmed values. Induction can be performed using the noninvasive electrophysiologic study (EPS) features present in the PCD device. See the appropriate MemoryMod cartridge technical manual for instructions.

Pacing and sensing values should also be tested and adjusted if necessary.

CAUTION: The physician should be aware that even when there has been a satisfactory response to VT therapies (i.e., Burst, Ramp, or Cardioversion) during clinically conducted EP studies, underlying or accompanying disease may over time alter the heart's electrophysiologic characteristics. Thus, over time, the programmed automatic therapies may not only be ineffective but also deleterious to the patient (e.g., initiate an atrial tachyarrhythmia or accelerate a ventricular tachycardia to flutter or fibrillation).

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Patient Follow-Up

Regular patient follow-up testing should be scheduled every three months post-implant to confirm that the programmed parameter values are appropriate and to monitor the condition of the implanted system and of the device's battery. After the battery voltage falls below 5.25 volts, patient follow-up should be scheduled every month.

Perform the following during each follow-up visit:

- Evaluate the patient's clinical status.
- Interrogate the device at the beginning and end of each follow-up session and print a full summary to verify and document that the programmed status of the PCD device is as desired.
- Observe the battery voltage before charging the device's capacitors.
- Review device experience and status.
- Evaluate pacing and sensing performance.
- Perform a programmer-initiated 34-joule charge of the capacitors and interrogate for the charge time[1]. Do not "dump" the energy from the capacitors so as to allow them to reform.

If the charge time is greater than or equal to 11.00 seconds, wait five minutes before dumping the energy on the capacitors and then perform another programmer-initiated 34-joule charge and interrogation. If the second charge time is again greater than or equal to 11.00 seconds or if the initial battery voltage is 4.97 volts or less, the device should be replaced.

If the battery voltage is not observed before the device's capacitors are charged, it must reach its required value within thirty minutes after charging.

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The patient should have X-rays and pacing/sensing thresholds taken every three months for the first year after implant and every six months thereafter to verify proper lead position and check for conductor fractures.

See the section titled "Elective Replacement and Potential Loss of Function Indicators" for more information about when to replace the PCD device.

1. Under unique conditions, a charge time of 2.33 seconds or its multiple may be reported as 2.33 seconds less than its actual value (e.g. a reported charge time of 0.00 seconds could actually be 2.33 seconds). If this occurs, wait five minutes before dumping the energy on the capacitors and perform another programmer-initiated 34 J charge and interrogation.

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GENERAL DEVICE INFORMATION

Magnet/Programming Head Operation

Applying and holding a magnet (Part No. 174105) and/or programming head over the device temporarily suspends the automatic detection and therapy capabilities. Using the "Cancel Magnet" function on the programmer will restore these detection capabilities while the magnet/programming head is in position.

CAUTION: Telemetry communication with the PCD device may cause inappropriate sensed events resulting in brief inhibition of bradycardia therapy. These sensed events may also count toward detection of VT or VF. Removing the programming or transtelephonic monitor head restores the device to normal function.

Placing a magnet over the PCD device does **not** inhibit VVI therapy.

Turning Off the PCD Device

To turn OFF the VT and VF capabilities of PCD device, press the "Nominal VVI" key and then the "Program" key on the programmer. This turns OFF VT and VF Detection and programs other parameters to the values listed in Table 4 below. This programming takes effect after any therapies in progress are delivered. This keystroke sequence can be used at any time after the device model number has been selected or a successful interrogation has been performed. The physician should interrogate the device after pressing the key to ensure that VT and VF Detection have been turned OFF.

To turn the PCD device back ON, follow the usual programming steps.

The table below lists the settings the PCD device is programmed to at the following events:

- At factory shipping,
- When "Nominal VVI" is programmed,
- When the VVI option under "Emergency VVI" is programmed,and
- When a "power-on reset" (an electrical reset) occurs.

Table 4. Nominal VVI Settings, Reset Parameter Values, Emergency VVI Option Settings, and Factory Shipped Settings

Parameter	Value
Mode	VVI
Pulse Width	0.49 ms
Sensitivity	0.6 mV
Amplitude	5.4 V
Refractory After Pace	320 ms
Pacing Rate	65 ppm
VT Detection & Therapies	OFF
VF Detection & Therapies	OFF

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Device Reporting Features

The PCD device has a number of reporting features that provide current programmed settings of pacing, sensing, and VT and VF Detection and Therapy. It also provides current functional status of the device and information about previous detected and treated VT and VF episodes.[1]

Programmed Parameters

Pacing and Sensing

The PCD device reports the pacing mode, rate, pulse width, and amplitude. It also gives the programmed sensitivity and refractory after pace.

VT Detection and Therapy

The PCD device reports the following about VT Detection and Therapy:

- VT Detection ON or OFF
- Interval Criterion settings (TDI and VT NID)
- Interval Stability Criterion ON or OFF
- Interval Stability Criterion settings
- Onset Criterion ON or OFF
- Onset Criterion settings
- Onset Counter ON or OFF
- VT Therapy types (Ramp, Burst, or Cardioversion) and their respective settings.

PACING AND SENSING

PACING MODE	VVI
PACING RATE	65 PPM
PACING PULSE WIDTH	0.49 MS
PACING AMPLITUDE	5.4 V
SENSITIVITY	0.3 MV
REFRACTORY AFTER PACE	320 MS

VT DETECTION AND THERAPIES

VT DETECT:	
VT DETECTION ENABLE	ON
# INTERVALS TO DETECT	16
VT DETECTION INTERVAL	400 MS
INTERVAL STABILITY	OFF MS
ONSET CRITERIA ENABLE	OFF
ONSET VALUE (R-R%)	81 %
ONSET COUNTER ENABLE	OFF
VT THERAPY #1:	
THERAPY TYPE	RAMP%
VT THERAPY ENABLE	ON
INITIAL # OF S PULSES	5
FIRST R-S INTERVAL	97 %
PER PULSE DECREMENT	10 MS
# OF SEQUENCES	8
MINIMUM INTERVAL	200 MS
VT THERAPY #2:	
THERAPY TYPE	BURST%
VT THERAPY ENABLE	ON
# OF S1 PULSES	6
S1-S1 INTERVAL	84 %
PER SEQUENCE DECREMENT	10 MS
# OF SEQUENCES	5
MINIMUM INTERVAL	200 MS
VT THERAPY #3:	
THERAPY TYPE	CARDIOVERSION
VT THERAPY ENABLE	ON
CV PULSE WIDTH	3.9 MS
CV ENERGY (JOULES)	3.0 J
CV CURRENT PATHWAY	SEQ
VT THERAPY #4:	
THERAPY TYPE	CARDIOVERSION
VT THERAPY ENABLE	ON
CV PULSE WIDTH	3.9 MS
CV ENERGY (JOULES)	34.0 J
CV CURRENT PATHWAY	SEQ

1. The data strips shown are examples.

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VF Detection and Therapy

The PCD device reports the following about VF Detection and Therapy:

- VF Detection ON or OFF
- VF Detection settings (FDI and VF NID)
- Defibrillation Therapy settings

VF DETECTION AND THERAPIES

VF DETECT:	
VF THERAPY ENABLE	ON
VF DETECTION INTERVAL	320 MS
# INTERVALS TO DETECT	18
VF DEFIBRILLATION THERAPY #1:	
VF THERAPY ENABLE	ON
DEFIB PULSE WIDTH	3.9 MS
DEFIB ENERGY (JOULES)	34.0 J
DEFIB CURRENT PATHWAY	SEQ
VF DEFIBRILLATION THERAPY #2:	
VF THERAPY ENABLE	ON
DEFIB PULSE WIDTH	3.9 MS
DEFIB ENERGY (JOULES)	34.0 J
DEFIB CURRENT PATHWAY	SEQ
VF DEFIBRILLATION THERAPY #3:	
VF THERAPY ENABLE	ON
DEFIB PULSE WIDTH	3.9 MS
DEFIB ENERGY (JOULES)	34.0 J
DEFIB CURRENT PATHWAY	SEQ
VF DEFIBRILLATION THERAPY #4:	
VF THERAPY ENABLE	ON
DEFIB PULSE WIDTH	3.9 MS
DEFIB ENERGY (JOULES)	34.0 J
DEFIB CURRENT PATHWAY	SEQ

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Status and Data

These reports provide the physician with the capability to acquire data on the device's activities/operations between office visits.

- The PCD device will determine and report its own internal status, e.g., what it has retained in memory, error messages, battery status, last charging time, and charging circuit status.
- The **VT Onset Counter** reports the number of instances when the Onset Criterion associated with VT detection was fulfilled. It only counts when VT Detection is also ON and either the Onset Criterion or Onset Counter is enabled.
- Following detection of a VT episode, the PCD device's **VT Episode Counter** adds one. This counter does not increase for subsequent detection(s) of the same VT episode. It keeps track of the number of detected VT episodes.
- If the PCD device determines the VT therapy was effective (see "VT Episode Termination and Determination of Therapy Efficacy"), the **VT Therapy Success Counter** (corresponding to the last delivered therapy) is increased by one. A counter exists for each of the four possible programmed therapies.[1]
- The **Number of VTs That the PCD was Ineffective** (in terminating) increases by one each time all programmed VT therapies are ineffective in terminating a detected VT episode.

DATA

PCD STATUS:	
MEMORY RETENTION	OK
CHARGE CIRCUIT	OK
LAST CHARGE TIME	3.12 SEC
BATTERY VOLTAGE	6.19 V
VT ONSET COUNTER	14
VT EPISODE AND THERAPY DATA:	
EPISODE COUNT	6
VT THERAPY #1 SUCCESS COUNT	3
VT THERAPY #2 SUCCESS COUNT	2
VT THERAPY #3 SUCCESS COUNT	1
VT THERAPY #4 SUCCESS COUNT	0
# OF VT'S PCD INEFFECTIVE	0
PCD EFFICACIOUS ON LAST VT	YES
LAST THERAPY USED	#3
# SEQ IN LAST PACE THERAPY	5
R-R AVG FOR LAST PACE THRPY	370 MS
VF EPISODE AND THERAPY DATA:	
EPISODE COUNT	5
VF THERAPY #1 SUCCESS COUNT	3
VF THERAPY #2 SUCCESS COUNT	2
VF THERAPY #3 SUCCESS COUNT	0
VF THERAPY #4 SUCCESS COUNT	0
# OF VF'S PCD INEFFECTIVE	0
PCD EFFICACIOUS ON LAST VF	YES
LAST THERAPY USED	#2

LAST EPISODE DETECTION SEQUENCE:

-19. R-R INTERVAL-920 MS
-18. R-R INTERVAL-910 MS
-17. R-R INTERVAL-230 MS
-16. R-R INTERVAL-210 MS
:
:
-0. R-R INTERVAL-210 MS
-0. VF DETECTED

EVENTS AFTER LAST THERAPY:

+0. VF THERAPY #2 DELIVERED
+1. R-R INTERVAL-650 MS
+2. R-R INTERVAL-920 MS
+3. R-R INTERVAL-920 MS
:
:
+10. R-R INTERVAL-920 MS
+10. THERAPY WAS SUCCESSFUL

1. This counter is also incremented if the VT therapy accelerated the rhythm to VF and the corresponding VF therapy is successful in terminating the VT episode prior to the next VT detection.

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The number of effective therapies plus the number of VT episodes in which the PCD was ineffective should equal the VT episode count. Exceptions to this may occur if a therapy is aborted (e.g., by a magnet application or by spontaneous termination of the VT episode during the first therapy's charging period), if therapies are initiated by the programmer during the episode, or if the device is interrogated prior to identification of VT termination.

- The **PCD Efficacy on the Last VT Episode** is also available, that is, whether the device was successful (8 consecutive paced or sensed beats greater than or equal to the TDI) on the last detected VT episode.
- The **Last VT Therapy Used** notes which programmed therapy was delivered last.
- The **Number of Sequences in the Last Pacing Therapy** reports which sequence within the last Burst or Ramp Therapy was delivered last. This information is useful because, from it (and with the next report), the physician can determine the interval and number of pulses of the last delivered therapy.[1]
- The **R–R Average for the Last Pacing Therapy** discloses the average of the last four intervals prior to delivery of the last Burst or Ramp sequence. When this information is coupled with knowledge of the programmed settings for the last pacing therapy and sequence counter of the therapy, the physician can determine the pulse intervals delivered during the last pacing therapy.[1]
- Following detection of a VF episode, the PCD device's **VF Episode Counter** is increased by one. This counter does not increase for each detection within the same VF episode.
- If the PCD device determines a VF therapy was effective (see "VF Episode Termination and Efficacy Determination"), **the Successful VF Therapy Counter** corresponding to the last delivered therapy is incremented by one. A counter exists for each of the four possible therapies.
- The **Number of VF Episodes in which the PCD device was Ineffective** is incremented by one each time all programmed VF therapies are delivered and determined to be ineffective in terminating a detected VF episode.

  The number of effective therapies plus the number of VF episodes in which the PCD device was ineffective should equal the total VF episode count. Exceptions to this may occur if a therapy is aborted by a magnet application, if therapies are initiated manually by the programmer during a VF episode, or if the device is interrogated prior to identification of VF termination.
- The **PCD Efficacy on the Last VF Episode** is also available from the PCD device.
- The **Last VF Therapy Used** notes which programmed VF therapy was last delivered.
- The **Last Episode Detection Sequence** retains data from 20 intervals just prior to the last detected VT/VF episode.
- The **Events After Last Therapy** section retains data from 10 intervals following the last VT/VF therapy of the last VT/VF episode.

1. These two counters are also updated by a manually-programmed Burst or Ramp therapy.

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Electrophysiological Study (EPS) Features

With programmer-initiated commands, the PCD device will produce up to four independently programmable premature stimuli. These stimuli may be used to induce a tachycardia for determining the patient's susceptibility to ventricular tachyarrhythmias and the efficacy of the device's programmed therapies (i.e., Burst, Ramp, or Cardioversion) to treat the induced tachycardia.

Also, a ramp or burst pacing sequence with very short intervals for more aggressive stimulation may be used to establish the efficacy of Defibrillation Therapy.

The PCD device has these manually controllable therapies:

- **Emergency therapies,** including Defibrillation, Cardioversion, Burst, and VVI nominal pacing parameters,
- Defibrillation therapy (**VFRx**), programmable as to pulse width, stored energy, and current pathway, and
- VT therapies (**VTRx**), programmable as to Burst, Ramp, or Cardioversion.

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Telemetry Features

The physician can acquire information about the present and past operation of the PCD device.

- Programmed Parameter Report, i.e., the programmed values to which the PCD device is currently set. See "Device Reporting Features" in "General Device Information" for more information on reports.
- Continuous, Real-Time Marker Channel™ telemetry, including the timing and categorization of sensed, paced, and therapeutic events (i.e., VF/VT/Normal). Refer to Figure 27 and the programmer technical manual for additional details.
- Continuous, Real-time Electrograms from either of two different sets of leads. EGM-Near-Field is taken from the PACE/SENSE to SENSE2 leads and EGM-Far-Field is taken from the PULSE1 to COMMON leads. (Far-Field electrograms are not available in two-electrode cardioversion/defibrillation systems because a plug is used in the PULSE1 connector port.)

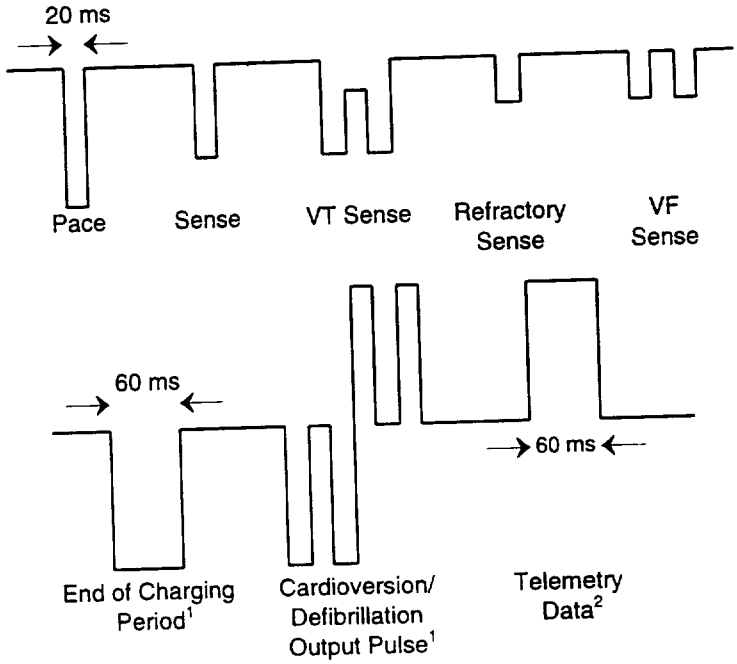

Figure 27. Representative Marker Channel Symbols

1. Interference generated during charging or pulse delivery may occasionally prevent these markers from appearing.

2. This indicates data transmission other than Marker Channel telemetry. Other markers may not appear or may falsely appear within 300 ms either side of this Telemetry Data marker.

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Permanent Telemetry Enable

This feature, which appears on the 9710 Programmer, is designed for future applications. At that time, it may be used to provide continuous telemetry (after removal of the programming head) for a programmable number of hours, or continuously. **This feature is normally programmed OFF.**

Radiopaque Identification

A radiopaque code block is visible on a standard X Ray as black characters on a white background. This code block may be used to identify the PCD device, Model 7217B, as follows:

Manufacturer:	Medtronic
Model Identification:	ZB (Model 7217B)
Engineering Series Number:	Follows the Model Identifier

Figure 28. Radiopaque I.D.

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Output Voltage and Delivered Energy

Programming Output Voltage For Cardioversion/Defibrillation

Table 5 converts stored energy (joules) to pulse amplitude (volts), based on a 75 ohm load.

Table 5. Converting Joules to Volts

Programmed Stored Energy (Joules)	Pulse Amplitude (Volts)	Programmed Stored Energy (Joules)	Pulse Amplitude (Volts)
34.0	753 (± 5%)	9.0	387 (± 5%)
32.0	732 (± 5%)	8.0	366 (± 5%)
30.0	708 (± 5%)	7.0	342 (± 5%)
28.0	684 (± 5%)	6.0	315 (± 5%)
26.0	660 (± 5%)	5.0	288 (± 5%)
24.0	633 (± 5%)	4.0	258 (± 5%)
22.0	606 (± 5%)	3.0	225 (± 5%)
20.0	579 (± 5%)	2.0	183 (± 5%)
18.0	549 (± 5%)	1.8	174 (± 16%)
16.0	516 (± 5%)	1.6	162 (± 16%)
15.0	501 (± 5%)	1.4	153 (± 16%)
14.0	483 (± 5%)	1.2	141 (± 16%)
13.0	465 (± 5%)	1.0	129 (± 16%)
12.0	447 (± 5%)	0.8	114 (± 16%)
11.0	429 (± 5%)	0.6	99 (± 16%)
10.0	408 (± 5%)	0.4	81 (± 16%)
		0.2	57 (± 16%)

Programming Pulse Width For Defibrillation

To achieve the most effective defibrillation therapy for the most patients, the output pulse should have approximately a 65% "tilt", which means the amplitude at the end of the pulse should drop 65% of the initial amplitude. Tilt values are dependent on the pulse width and pathway resistance. Table 6 below suggests what the pulse width should be programmed to as a function of the pathway resistance to obtain a 65% tilt. For example, when programming for SEQUENTIAL pulses where the two path resistances are 80 and 60 ohms, calculate the mean resistance (70 ohms) and use the SEQUENTIAL table to choose a pulse width of 4.4 ms. If programming for SIMULTANEOUS pulses where the path resistances are 90 and 70 ohms, approximate the resistance by using the product of the two path resistances divided by their sum ($6300 \div 160 \approx 39\ \Omega$). Then look at the SIMULTANEOUS/SINGLE table for 39 ohms and choose 4.9 ms. For a SINGLE pulse with a path resistance of 40 ohms, for example, use the SIMULTANEOUS/SINGLE table, look under 40 ohms, and choose 4.9 ms.

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Clinical experience has shown that the most commonly used defibrillation pulse width is 3.9 ms for SEQUENTIAL pathway and 6.3 ms for SIMULTANEOUS and SINGLE pathways.

Table 6. Pulse Widths for 65% Tilt

SEQUENTIAL		SIMULTANEOUS/SINGLE	
Resistance (ohms)*	Pulse Width (ms)	Resistance (ohms)**	Pulse Width (ms)
20-34	2.0	<19	2.0
35-42	2.4	20-21	2.4
43-50	2.9	22-25	2.9
51-58	3.4	26-29	3.4
59-66	3.9	30-33	3.9
67-74	4.4	34-37	4.4
75-82	4.9	38-41	4.9
83-89	5.4	42-45	5.4
90-97	5.9	46-48	5.9
98-102	6.3	49-52	6.3
103-110	6.8	53-56	6.8
111-118	7.3	57-59	7.3
119-126	7.8	60-63	7.8
—	8.1	64-100	8.1

*Use the mean of the two path resistances.
**For simultaneous, approximate the resistance—use the formula $\frac{R_1 \times R_2}{R_1 + R_2}$

Stored and Delivered Energy

Cardioversion and defibrillation therapies have three programmable parameters: stored energy, pathway, and pulse width. The stored energy determines the pulse amplitude (as shown in Table 5). The percentage of programmed stored energy that is applied to the lead system (that is, the delivered energy) depends on the programmed pathway, the programmed pulse width, and the pathway impedance. The percentage of programmed stored energy that is delivered increases when the programmed pulse width increases or the pathway impedance decreases.

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The percentage of delivered energy vs. programmed stored energy may be seen by referring to Figures 29 and 30. Increasing the programmed stored energy will have a proportional effect on the delivered energy. For example, if the pulse width, pathway, and pathway impedance are unchanged, doubling the stored energy doubles the delivered energy.

Figures 29 and 30 demonstrate the effect on the delivered energy with respect to the programmed stored energy, pulse width, pathway, and pathway impedance. One should not conclude, however, that two different settings delivering the same energy have the same effectiveness. Always verify the effectiveness of the new settings when reprogramming pulse width or current pathway.

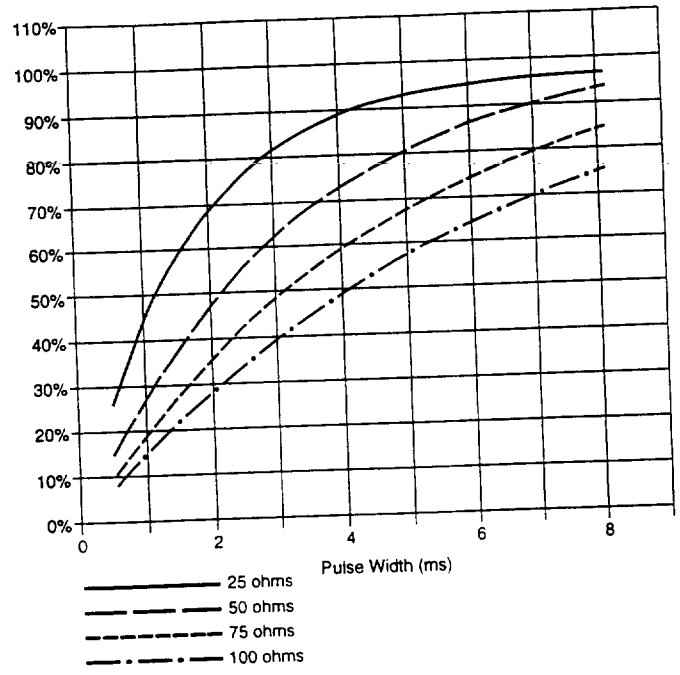

Figure 29. Percentage of Programmed Stored Energy Delivered Over a Single Pathway

If, for example, the programmed pulse width is 3.9 ms and the pathway impedance is 50 ohms, the percentage of delivered energy (compared to programmed stored energy), is about 72%. Increasing the pulse width to 6.3 ms with the same impedance will result in about an 88% delivered energy figure.

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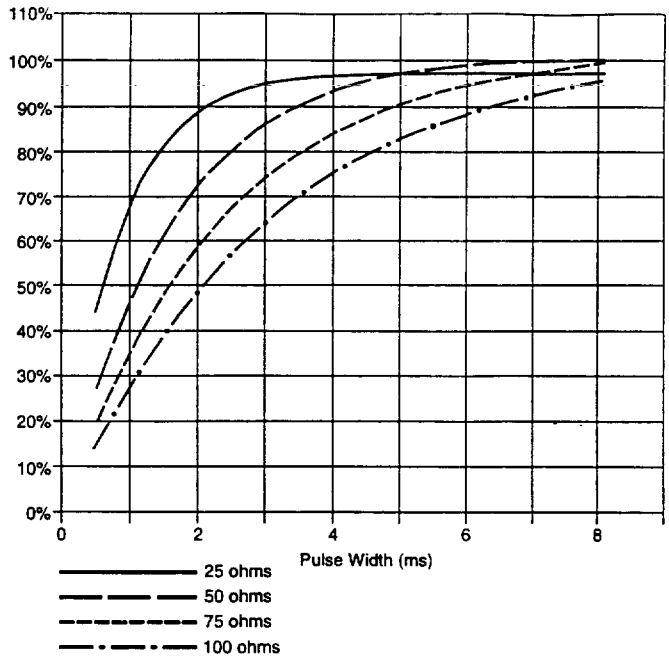

Figure 30. Percentage of Programmed Stored Energy Delivered Over Sequential or Simultaneous Pathways

Programming a sequential or simultaneous pathway may change the percentage of delivered energy. With the same examples as were used to illustrate Figure 29 where each pathway is 50 ohms, the percentages are about 93% and 99% respectively.

Output Waveforms

The illustrations that follow depict examples of waveforms that can be delivered by the PCD device during its programmable VT and VF therapies. Figures 31-33 represent the three programmable waveforms delivered during Cardioversion and Defibrillation Therapy. Figure 34 displays the waveform for Burst and Ramp therapies and bradycardia therapy, which are delivered at pacing energy levels. (Dashed voltage waveforms represent detected potentials generated from other leads. The examples assume 75 ohms as the resistance for cardioversion and VF pathways.).

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Cardioversion and Defibrillation
Sequential Current Pathway

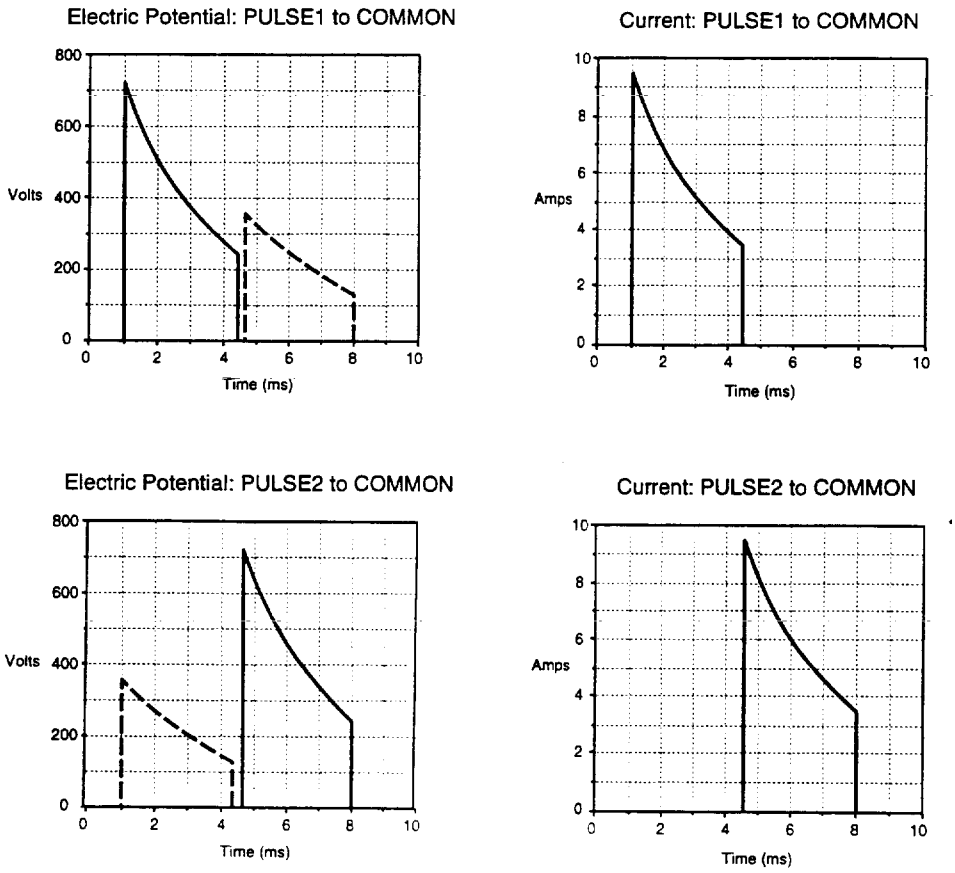

Figure 31. Output Waveforms (Sequential)

NOTES: 1. Dashed waveforms indicate potential reflected through the heart from the active electrode.

2. Current through the PACE/SENSE and SENSE2 electrodes will normally be less than 10 mA.

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Cardioversion and Defibrillation
Simultaneous Current Pathway

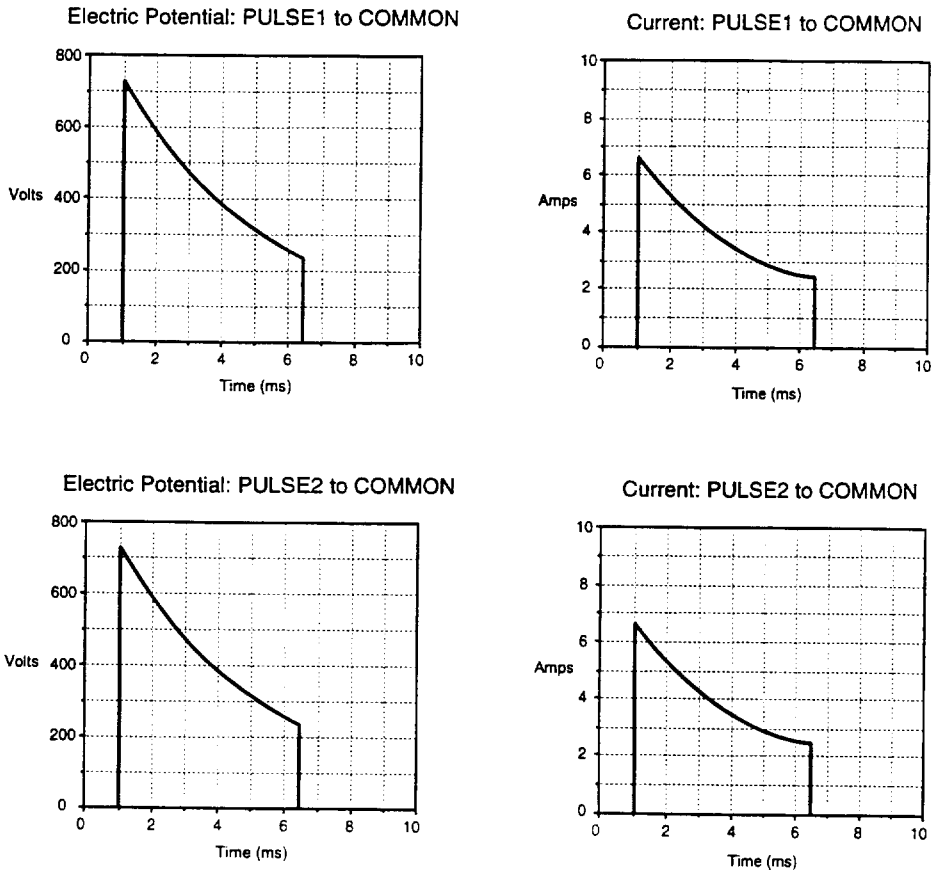

Figure 32. Output Waveforms (Simultaneous)

NOTE: Current through the PACE/SENSE and SENSE2 electrodes will normally be less than 10 mA.

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Cardioversion and Defibrillation
Single Current Pathway

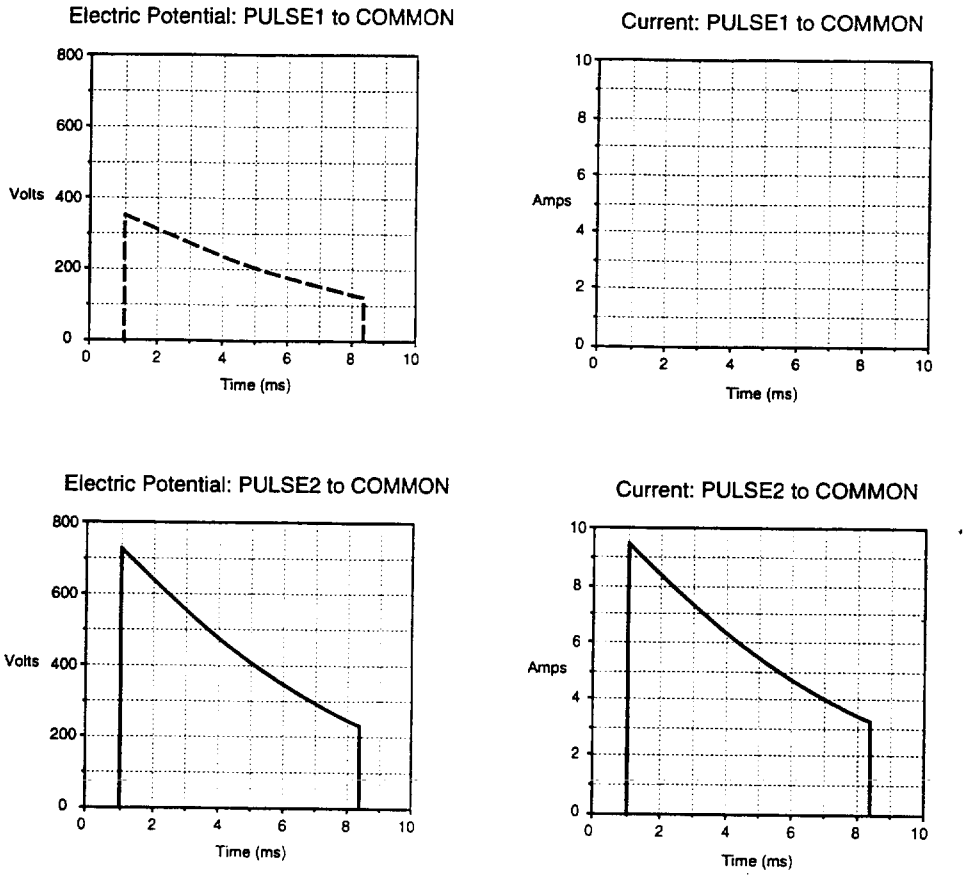

Figure 33. Output Waveforms (Single)

NOTES: 1. Dashed waveforms indicate potential reflected through the heart from the active electrode.

2. Current through the PACE/SENSE and SENSE2 electrodes will normally be less than 10 mA.

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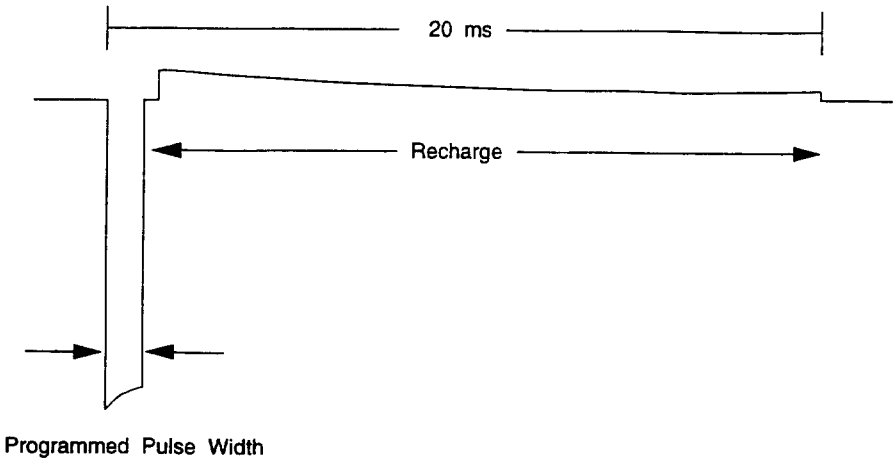

Figure 34. Output Waveform (Pacing)

WARNINGS AND PRECAUTIONS

Lead Systems

The Medtronic 7217B has been proven safe and effective when combined with Medtronic epicardial patch electrodes, Medtronic Transvene non-thoracotomy leads, or commercially available electrodes manufactured by Cardiac Pacemakers Incorporated (i.e. C10). No claims of safety and efficacy can be made with regard to other acutely or chronically implanted lead systems.

Disease Progression, Detection and Automatic VT and VF Therapies

The physician should be aware that even when there has been a satisfactory response to VT or VF therapies (i.e., Burst, Ramp, Cardioversion, or Defibrillation) during clinically conducted EP studies, underlying or accompanying disease or change in antiarrhythmic drug therapy may over time alter the heart's electrophysiologic characteristics. Thus, over time, the programmed automatic therapies may not only be ineffective but also deleterious to the patient (e.g., initiate an atrial tachyarrhythmia or accelerate a ventricular tachycardia to flutter or fibrillation). In addition, changing cardiac electrical characteristics may prevent detection of a tachyarrhythmia or may cause the pulse generator to misinterpret a normal rhythm as a clinically significant arrhythmia.

Implanted or Temporary Pacemakers

Previously implanted bradycardia pacemakers, tachyarrhythmia devices and leads should be explanted. The output pulses of an implanted device may adversely affect the tachyarrhythmia detection capabilities of the PCD device. If leads must be abandoned rather than removed they should be capped to ensure they will not become a pathway for currents to or from the heart. If a patient requires a separate atrial or dual chamber pacemaker for hemodynamic reasons, either permanent or temporary, consider the following to minimize potential interaction between the pacemaker and the PCD:

- Use only bipolar pacemakers that remain bipolar after exposure to high voltage shocks;
- Use pacemaker leads with close interelectrode spacing;
- Allow adequate space between the pacing lead electrodes and the defibrillation lead electrodes;
- Test the PCD device to determine if output pulses from the pacemaker are sensed by the PCD;
- Induce all the patients ventricular tachyarrhythmias and ventricular fibrillation with the pacemaker programmed to an asynchronous mode at maximum output to evaluate possible inhibition of detection by the PCD due to pacing artifacts;
- Program the pacemaker to the lowest amplitude allowable for capture chronically, the maximum sensitivity, and the minimum rate acceptable to the patient.

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Electromagnetic Interference (EMI)

Exposure to EMI may, under certain circumstances, prevent VT/VF detection or cause the PCD device to falsely detect a VT or VF and deliver an unneeded VT or VF therapy. The delivery of the therapy could, in turn, provoke an actual VT or VF. Additionally, since the PCD device communicates with the programmer by means of radio frequency telemetry, EMI may cause short telemetry interruptions. Under unique circumstances, EMI may cause an electrical reset of the device (see **Power On Reset**). **Keep PCD patients away from EMI sources, when and as long as any detection criteria are enabled.** Physicians should carefully weigh their decision to program the device to maximum sensitivity (0.3 mV), as it will increase the susceptibility to EMI sources. EMI sources include, but are not limited to, the following:

- Nuclear Magnetic Resonance Imaging (MRI) equipment
- Therapeutic diathermy
- Defibrillation equipment
- Electrocautery
- High-voltage systems
- Radio transmitters
- Theft prevention equipment
- Current-carrying conductors
- High-powered electromagnetic fields

Preventing Accidental Exposure to Maximum Voltage

To prevent an accidental discharge during implantation or explantation, the Model 7217B PCD device should be programmed so that VT and VF detection are both OFF.

In the event of a patient's death while the Model 7217B PCD device is implanted, the device should be explanted and returned to Medtronic. Prior to the explant procedure, **both VT and VF detection must be programmed OFF** to prevent the delivery of potentially hazardous shocks to medical or mortuary personnel. Medtronic requests that such individuals INTERROGATE THE PCD DEVICE AND PRINT A FULL REPORT BEFORE TURNING OFF DETECTION AND EXPLANTING THE DEVICE.[1]

Supraventricular Tachyarrhythmias

Depending on programmed detection and therapy settings, patients with supraventricular tachyarrhythmias (despite a drug regimen) may be inappropriately paced, cardioverted, or defibrillated. If the PCD device cannot distinguish such rhythms from ventricular tachyarrhythmias with available criteria, the physician must judge whether the use of the PCD device is advisable.

1. Consult the Technical Manuals for the Programmer and MemoryMod for details on turning OFF VT and VF detection.

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Because of the nature or frequency of conducted rapid atrial rhythms, the physician should carefully evaluate such rhythms and weigh the patient's needs against the benefits before implanting the PCD device. If the determining factor hinges on which therapies must be used, the physician should be aware that the total designed capacity for cardioversion and VF therapies is finite. The use of pacing level therapies, i.e., Burst and Ramp, will not appreciably alter the device's longevity.

Repeated, Multiple VT/VF Episodes

The physician must weigh the risks versus the benefits for patients who display a history of repeated and multiple VT episodes. Use discretion in the treatment of such episodes, since it may quickly deplete the battery of the PCD device.

The PCD device has a finite capacity for its high-energy therapies, i.e., cardioversion and defibrillation. The use of pacing level therapies, i.e., Burst and Ramp, will not appreciably alter the device's longevity.

Diathermy

Therapeutic diathermy should not be used at the implant site on patients who have a PCD device because of possible damage to the circuitry due to heating effects on the device.

Defibrillation

The Model 7217B PCD device may be damaged by direct or transthoracic defibrillatory discharges. When performing direct heart defibrillation, do not directly contact the exposed metal surface of any electrode with the paddles. When performing transthoracic defibrillation, do not place a paddle directly over the PCD device. Interrogate the PCD device after the use of direct or transthoracic defibrillation to determine the functional integrity of circuits and programmed parameters. Reprogramming may be necessary.

Patch electrodes, because they "insulate" a portion of the heart tissue, may unavoidably reduce the effectiveness of transthoracic defibrillation.

Use of a Magnet

Use only a Medtronic magnet (Part No. 174105) or programming head over the PCD device.

Positioning a magnet or the programming head of the Programmer over the Model 7217B PCD device temporarily suspends VT and VF Detection and makes the device subject to programming. Placing a magnet over the PCD device does **not** inhibit VVI therapy.

Electrocautery

Electrosurgical units should **never be used in the vicinity (i.e., six inches [15 cm] or closer)** of a Model 7217B PCD device and its associated lead system. Currents generated from electrosurgical units may cause permanent loss of output, induce ventricular

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fibrillation, or reset programmed parameters in these units (see "Effects of Electrosurgical Cautery and Defibrillation"). Where alternatives to electrocautery are available, these should be used.

Power On Reset

Certain conditions, (including but not limited to: exposure to EMI, electrocautery or transthoracic defibrillation) may lead to an electrical reset of the device. The table below lists the settings the PCD is reset to when a "power on reset" (POR) occurs. **Always interrogate the PCD device at the beginning and end of each follow-up session to verify and document that the programmed status of the device is as desired.** The device may be reprogrammed to desired parameters after the source of interference is removed.

If a POR has occurred, then the POWER ON RESET message should be cleared from the PCD device memory and the device reprogrammed to desired parameters. To clear the POWER ON RESET message, use the DATA key on the main menu of the programmer to display and clear the STATUS group.

Table 7. Power On Reset Parameter Values

Parameter	Value
Mode	VVI
Pulse Width	0.49 ms
Sensitivity	0.6 mV
Amplitude	5.4 V
Refractory After Pace	320 ms
Pacing Rate	65 ppm
VT Detection & Therapies	OFF
VF Detection & Therapies	OFF

Nonsterile Package

The sterile package should be inspected prior to opening. If the seal or package is damaged, contact your local Medtronic representative.

Damage to a PCD Device Prior to Implantation

The Model 7217B PCD device should not be implanted if dropped on a hard surface from a height of 12 inches (30 cm) or more.

Random Failures

All devices will ultimately cease to function due to normal depletion of the battery and may also fail at any time due to random component or battery failure which cannot be predicted prior to their occurrence. Also, the system may cease to function at any time due to lead-related problems such as dislodgement, fracture, fibrotic tissue formation, elevated thresholds, or medical complications.

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Infrequent Charging of the High-Voltage Capacitors

Infrequent charging of the high-voltage capacitors may cause the charging period to be longer than desired. **The use of the programmer-initiated charging command should be performed to 34 joules at every PCD follow-up visit.**

SIDE EFFECTS

Possible side effects include, but are not limited to, the following: body rejection phenomena including local tissue reaction; muscle and nerve stimulation; pericarditis; infection; lead dislodgement; erosion of the PCD device, leads, or adaptor through the skin; and adverse psychological effects, which may include psychologic intolerance to the PCD device, imagined pulsing, dependency, fear of inappropriate pulsing, and fear that pulsing capability may be lost.

POTENTIAL ADVERSE EFFECTS

The following potential adverse effects may arise during and after implantation of a PCD device: myocardial irritability at implant, which might cause premature ventricular contractions (PVCs), supraventricular tachycardia, or fibrillation; cardiac tamponade or loss of sensing due to perforation of the myocardium at implant; acute hemorrhage due to venous perforation; infection; thrombus formation and subsequent pulmonary embolization caused by the presence of intravascular leads; loss of system function due to battery failure or other component failure; inability to reprogram the pulse generator because of programmer failure; false sensing, inappropriate pulsing, and/or inhibition of normal electrical conduction due to dislodged or fractured leads, case fracture, or electronic component failure; interruption of desired function due to electrical or magnetic interference, including nuclear magnetic resonance (NMR) and diathermy and lithotripsy when used near the site of the pulse generator and leads, and system failure due to ionizing radiation; erosion or extrusion of the pulse generator; fibrotic tissue growth; fluid accumulation; keloid formation; and formation of hematomas or cysts.

EFFECTS OF ELECTROMAGNETIC INTERFERENCE

The Model 7217B PCD device is designed to limit the effects from most common sources of electromagnetic interference (EMI). Because many forms of EMI exist, it is impossible to characterize all of them here. In general, VT and VF Detection should, if possible, be programmed OFF before subjecting the patient to procedures that induce strong electromagnetic fields.

Paired sensing between the PACE/SENSE and SENSE2 leads makes the Model 7217B PCD device relatively insensitive to signals of non-cardiac origin. It is important to maintain a distance no greater than one (1) cm between the two electrodes to minimize EMI effects. The patient should be advised to avoid strong electromagnetic fields such as those listed in Table 8. Such signals could be interpreted by the device as being of cardiac origin and be detected as a tachyarrhythmia with subsequent delivery of VT or VF therapies.

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Table 8. Potential Complications

Source	Effects/Precautions
Standard fluoroscopy radiation for imaging	No Effect
Microwave diathermy/ovens	No Effect[1]
Therapeutic diathermy	Heating of circuitry. Must be avoided directly over the device; program VT/VF Detection OFF.
Transthoracic defibrillation	Effectiveness of transthoracic defibrillation may be affected by the implanted PCD system; possible circuit damage or loss of output if ≥ 400 J or < 15 cm from the PCD device; increased pacing threshold; decreased R-wave amplitude; resetting of programmed parameter values (see "Power On Reset" on page 82).
Direct defibrillation	Effectiveness of direct defibrillation may be affected by the implanted PCD system; potential circuit damage to the PCD device, loss of output, increased pacing threshold, decreased R-wave amplitude, resetting of programmed parameter values. Avoid direct contact of the paddles with the exposed coils of the patch electrodes.
Electrosurgical cautery	Possible triggering of VT/VF detection and/or therapies; within 15 cm of the PCD system, the complications may include: potential circuit damage to the PCD device, loss of output, increased pacing threshold, decreased R-wave amplitude, or resetting of programmed parameter values. Program VT/VF Detection OFF to avoid inadvertent detection.
Ionizing radiation	Possible damage to circuitry. Should be avoided or device shielded; see "Hospital or Medical Environment." May mimic R-waves and inhibit output or initiate VT/VF detection and therapies. Program VT/VF Detection OFF to avoid inadvertent detection.
Domestic electrical equipment, car engine, airport screening equipment	No adverse effect with conventional, properly grounded and operating devices. However, excessive levels of EMI may cause VT/VF detection.
Pulsed energy; leakage current	May mimic R-waves and inhibit output or cause VT/VF detection.

1. Up to 200 Volts peak/meter.

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Potential Complications (Continued)

Source	Effect/Precautions
Continuous strong interference	May mimic R-waves and inhibit output or cause VT/VF detection.
Continuous strong magnetic field	Undesired suspension of VT/VF detection; possible damage to PCD circuitry, if charging occurs.
Metal portions of the electrodes touching each other	A short circuit may occur during defibrillation or cardioversion resulting in permanent damage to the device's high-energy output circuitry.

Effects of Electrosurgical Cautery and Defibrillation

The use of electrocautery (within 15 cm) or direct defibrillation may cause permanent damage to the device.

Under certain conditions, the use of direct defibrillation or electrosurgical cautery in the vicinity of a Model 7217B PCD System (i.e., device and lead/electrodes) may cause the device to be set to its reset parameter values (see Table 4 in "General Device Information").

Program VT/VF Detection OFF during electrosurgical cautery to avoid triggering of VT/VF therapy.

Following the use of direct or transthoracic defibrillation or electrosurgical cautery, interrogate the device and print a full summary to verify and document that the programmed status of the device is as desired.

NOTE: Always interrogate the device at the beginning and end of each follow-up session and print a full summary to verify and document that the programmed status of the PCD device is as desired.

Hospital or Medical Environment

Exposure to normal diagnostic levels of x-ray and fluoroscopic radiation should not affect the Model 7217B PCD device.

The Model 7217B PCD device SHOULD NOT BE DIRECTLY IRRADIATED by therapeutic levels of ionizing radiation (such as produced by cobalt or linear accelerators used for cancer treatment) because of risk of permanent damage to the device's circuitry. If such therapy is required in the vicinity of the device, the device should be shielded (with VT/VF detection OFF) and its operation and various functions confirmed following treatment.

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Home or Job Environment

The Model 7217B PCD device should not be affected by the normal operation of electrical equipment such as household appliances, electrical machine shop tools, microwave ovens, spark-ignited internal combustion engines, radio frequency transmitting systems, or microwave frequency transmitting systems.

NOTE: Such effects will normally not be observed if proper electrode spacing (i.e., no greater than 1 cm between the PACE/SENSE and SENSE2 electrodes and with the corresponding leads routed together) is provided at implant.

- Medtronic should be consulted when device wearers will be in areas where contact with current-carrying conductors is possible or when they must come near high-powered, electromagnetic fields radiated by arc-welding units, induction furnaces, resistance welders, etc.

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GENERAL WARNING

The Medtronic® Implantable Pacer Cardioverter Defibrillator Device (the "Device") and the Medtronic Implantable Leads (the "Leads") are implanted in the extremely hostile environment of the human body. This environment places severe limitation on the design and function of the Device and Leads. These limitations unavoidably reduce the effectiveness and longevity of the Device and Leads despite the exercise of due care in design, component selection, manufacture, and testing prior to sale.

The Device includes a nonseparable power source that will ultimately cease to function due to exhaustion or premature failure thereby necessitating removal of the Device. The Leads are necessarily very small in diameter and very flexible, which unavoidably increases the likelihood of breakage or breach of their insulation. Other reasons for failure of the Device or Leads include, but are not limited to: body rejection phenomena; physiological variations in patients; medical complications, including antiarrhythmic drugs; Lead displacement; Lead fracture; fibrotic tissue formation; erosion of the Device or Lead through body tissue; infection; perforation of an artery or heart; random component failure; or interference from transmitters, tools, appliances, instruments, equipment, electrocautery, external defibrillators or other devices that use electricity, ionizing radiation, or electromagnetic wave transmission.

Complications that may be associated with the use of the Device and Leads include, but are not limited to: failure to detect ventricular tachycardia or ventricular fibrillation; failure to terminate ventricular tachycardia or ventricular fibrillation; delivery of a pacing or shock therapy when no ventricular arrhythmia is present, which could precipitate an episode of ventricular tachycardia or ventricular fibrillation; acceleration of a ventricular arrhythmia; failure to capture after a shock delivery; constrictive pericarditis; discomfort or pain during or following the delivery of electrical shock; or tissue or muscle burns at the site of the electrodes.

Consequently, no representation or warranty is made that failure or cessation of function of the Device or Leads will not occur, that the body will not react adversely to the implantation of the Device or the Leads, that medical complications will not follow the implantation of the Device or the Leads, that the Device and Leads will effectively restore adequate cardiac function, or that implantation of the Device and Leads will prevent sudden death. See the Medtronic Warranty packaged with the product for the terms and conditions of the warranty.

SERVICE

Medtronic employs highly trained representatives and engineers located throughout the world to serve you and, upon request, to provide training to qualified hospital personnel in the use of Medtronic products. In addition, Medtronic maintains a professional staff of consultants to provide technical and medical consultation to product users. For supplemental information, contact your local Medtronic representative, or call or write Medtronic at the appropriate address or telephone number listed on the back cover.

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GLOSSARY OF TERMS

The following definitions and/or descriptions are used in this manual.

Anode: Positive "pole" of the current pathway. PULSE1 and/or PULSE2 are the anodes for delivery of cardioversion and defibrillation therapies.

Auto-Adjusting Sensitivity: The device automatically adjusts the programmed sensitivity to a less sensitive value following signal detection on the sensing leads. This prevents the sensing of T-waves when sensitive thresholds are used.

Acceleration: The criteria for determination that a VT has accelerated after delivery of a therapy. Acceleration is defined as a decrease by 60 ms or more in the average cardiac cycle length from the initial VT detection cycle length.

Automatic: When the desired detection and therapy are programmed ON, the device delivers the therapy (without manual intervention) after all detection criteria are met.

Blanking Period: The period during which the PCD device does not sense events. Blanking periods occur after each paced, sensed, or therapy event and during and after a charging period is completed.

Burst: A VT therapy in which the device delivers a sequence of rate-adaptive, equal-interval pulses. The first pulse in the sequence is delivered at a programmable percentage of the tachycardia cycle length. Subsequent pulses in the same sequence are delivered at this same interval.

Cancel Magnet: A programming command that overrides the effect (on VT and VF Detection) of positioning a programming head over the device. This command reinstates automatic VT and VF Detection while the programming head is in place.

Cardioversion: Describes the VT therapy type in which the PCD device delivers a programmable pulse that is synchronized to a ventricular sensed event.

Cathode: Negative "pole" of the current pathway. COMMON is the cathode for delivery of cardioversion and defibrillation therapies.

Charge: A programming command that allows the manual initiation of the capacitor charging cycle. The length of this cycle is an indication of the condition of the PCD device battery.

Charge Circuit Inactive: A change in device function after three consecutive Charging Periods are equal to 35 seconds. In this state, the device disables:

- All automatic VT and VF Detection and Therapies,
- Programmer-initiated therapies (except Emergency Burst Pacing),
- Programmer-initiated EPS, premature stimuli, and fibrillation stimuli,
- Programmer-initiated Charging Periods.

Charging Period: The period during which the PCD device stores the programmed energy (charge) in capacitors so that it can rapidly deliver a cardioversion or defibrillation therapy.

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Committed: Once a charging cycle is initiated for defibrillation therapy, a shock will be delivered. The therapy may be aborted by applying a magnet; however, timing of magnet application will determine whether therapy is aborted.

COMMON: The electrode that serves as the cathode for cardioversion and defibrillation therapies, and as the anode for pacing therapies.

Current Pathway: The path followed by a Cardioversion or Defibrillation pulse(s) when discharged across cardiac tissue, i.e., between an anode and cathode.

Defibrillation: A therapy consisting of electrical shock to terminate ventricular fibrillation. The device attempts to synchronize the shock to a ventricular depolarization, and if unsuccessful, delivers the shock asynchronously. Automatic VF Therapy can be programmed up to a series of four attempts to terminate a VF episode.

Detection: The condition in which the device has determined the presence of electrical events that fulfill all programmed VT or VF criteria.

Disabled: A permanently programmed state in which detection and/or therapies are not available (OFF condition). These functions can only be re-enabled via a programming sequence.

Dump: A programming command that discharges the manually-charged capacitor into a load circuit in the device.

Effective Therapy: The PCD device considers a VT or VF therapy effective if, after the therapy, the device recognizes the termination of the episode prior to redetection, i.e., the continuation of the original arrhythmia.

EGM (Electrogram): The signal, transmitted via telemetry, of an electrogram taken from the device's lead system.

Elective Replacement Indicator: The telemetered battery voltage at which replacement of the device is recommended. It does not indicate that the device has altered its operation in anyway.

Emergency-VVI: A programming step that allows quick access to manual initiation of Defibrillation, Burst, Cardioversion, or VVI Nominal Therapy.

Enable: Allows or turns ON the function: e.g., allows VT and VF Detection and Therapies to carry out the designed capacity for detecting and terminating VT/VF episodes.

ETCD: External Tachyarrhythmia Control Device.

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Fibrillation Detection Interval (FDI): The interval in milliseconds that measured cardiac intervals must be less than or equal to in order to meet the ventricular fibrillation detection criteria.

Interval Criterion: The programmable VT Detection Criterion that is designed to detect a sustained high ventricular rate by measuring each cardiac cycle length and comparing it to the programmed Tachycardia Detection Interval.

Interval Stability Criterion: The programmable VT Detection Criterion that allows the PCD device to screen out irregular ventricular rhythms and/or unstable VTs.

Marker Channel: A programmer-generated set of symbols that allows real-time visualization of sensing, pacing, detection, and therapy events occurring within the device.

Number of Intervals to Detect (NID): The programmable number of measured cardiac intervals that must meet the FDI or TDI criteria for detection to occur. Displayed on the programmer screen as #INT.

Non-Committed: Post completion of charging for cardioversion, the device attempts to confirm the presence of VT and synchronize to an R-wave; if this is not possible, therapy will not be delivered.

Onset Criterion: The programmable VT Detection Criterion that permits the PCD device to differentiate between a sudden or abruptly starting tachycardia and one with a gradually increasing rate such as sinus tachycardia.

Paced Events: Output pulses (of pacing energy levels) from the PCD device.

Pacing Therapies: Two VT therapies, Burst and Ramp, are pacing therapies designed to deliver pulses at pulse widths and amplitudes the same as those programmed for bradycardia therapy.

PCD Ineffective: The PCD device is considered ineffective for VT or VF if, after all therapies have been delivered, the device redetects the arrhythmia prior to recognition of the episode's termination.

Potential Loss of Function Indicator: The telemetered voltage at which immediate replacement of the PCD device is recommended. In this situation the potential for altered or loss of function is present.

PULSE1, PULSE2: The defibrillation electrodes that serve as anodes for cardioversion and defibrillation therapy.

Ramp: A VT Therapy in which the device delivers a sequence of rate-adaptive, decreasing-interval pulses. The first interval is a programmable percentage of the detected VT cycle length. Each subsequent interval is decremented from the preceding interval by a programmable value. For each sequence the device automatically increases the number of pulses by one.

Redetection: After the delivery of VT/VF Therapy the device monitors the cardiac cycle length for continued fulfillment of the programmed detection criteria. Fulfillment of this criteria (redetection) is required before the next therapy will be delivered.

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Refractory Period: The period after paced, sensed, or therapy events during which events are not used for detection, synchronization, etc., but are used to restart a blanking period. The PCD device can sense events during this time, but not during the related blanking period. Events sensed during the refractory period are called "refractory sensed events."

Rounding: When attempting to detect a tachyarrhythmia, the PCD device rounds down to the nearest 10 ms while measuring the cardiac cycle length. However, it rounds up or down to the nearest 10 ms interval when using the measured interval to average or calculate percentages of intervals, e.g., during Burst or Ramp Therapies or when the Onset Criterion is active.

Sensed Event: The recognition by the PCD device circuitry of electrical activity on the paired leads (PACE/SENSE to SENSE2) that exceeds the programmed sensitivity threshold. Sensed events are either refractory sensed events or non-refractory sensed events, i.e., events sensed outside a refractory period. Non-refractory sensed events may also be categorized as VT, VF, or normal sensed events.

Sequence: The programmable feature that indicates the number of attempts that will be made by a given Ramp or Burst therapy to terminate the tachycardia.

Sequential Pulse Cardioversion or Defibrillation: The programmable therapy designed to terminate a VT/VF episode, consisting of two high-voltage pulses delivered one after the other across two different pathways.

Simultaneous Pulse Cardioversion or Defibrillation: The programmable therapy designed to terminate a VT/VF episode, consisting of two high-voltage pulses delivered at the same time across two different pathways.

Single Pulse Cardioversion or Defibrillation: The programmable therapy designed to terminate a VT/VF episode, consisting of one high-voltage pulse delivered across one pathway.

Suspend: Temporary inactivation of detection functions by placing the programming head over the device. Cancel Magnet or lifting the programming head reactivates detection if it was previously programmed ON. Detection functions are also suspended after all therapies are delivered.

Synchronization Sequence: In both Cardioversion and Defibrillation Therapy, the process conducted after the completion of charging when the PCD device attempts to identify the leading edge of an R-wave or ventricular event with which to synchronize the delivery of a high-energy output. In Cardioversion therapy, this period is also used to confirm the continued presence of the VT.

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Tachycardia Detection Interval (TDI): The interval in milliseconds that measured cardiac intervals must be less than to meet the ventricular tachycardia detection criteria. Note: The intervals must also be greater than the FDI.

Termination: The PCD device considers a VT of VF episode "terminated" whenever it detects eight consecutive cardiac cycles longer than the TDI or FDI, respectively.

Therapy Type: Defines the kind of delivered therapy, i.e., Burst, Ramp, Cardioversion, or Defibrillation.

Therapy Sequence: A single attempt to terminate a VT with pacing level stimuli. The term applies to VT therapy types in which a single therapy can consist of a programmable number of Burst or Ramp sequences.

Therapy: The device operation to treat a detected VT or VF. A single therapy consists of a cardioversion or defibrillation shock or a sequence of pacing level treatments, i.e., Burst or Ramp.

VF Episode: The period during which the device considers VF in progress, i.e., from the time of initial VF detection until the criteria for VF termination are recognized by the PCD device.

VT Episode: The period during which the device considers VT in progress, i.e., from the time of initial VT detection until the criteria for VT termination are recognized by the PCD device.

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SPECIFICATIONS[a,b]

Programmable Functions	Capability	Increments	Programmer Default[c]	Tolerance	Other Notes
Sensing/Pacing					
Mode	VVI				Only mode available
Pacing Rate[d]	30-64, 65, 66-82, 85, 86, 88, 90 ppm	2 ppm	65 ppm	± 1 ppm	
Pulse Width	0.03–1.59 ms	0.03 ms	0.49 ms	– 0.0, + .03 ms	
Sensitivity[e,f]	0.3–2.4 mV	0.3 mV	0.3 mV	± 0.15 mV ± 0.20 mV ± 0.25 mV ± 0.40 mV	For 0.3 mV For 0.6 mV For 0.9–1.5 mV For 1.8–2.4 mV
Pulse Amplitude	2.8 and 5.4 V		5.4 V	2.5 & 5.2 V min	
Refractory After Pace	320–480 ms	40 ms	320 ms	– 20, + 0 ms	
VT Detection					
Enable	ON/OFF		OFF		
VT Detection Interval[g]	280–600 ms	10 ms	400 ms	± 1 ms	TDI should be at least 40 ms longer than FDI
Number of Intervals to Detect	4-52	4	16		NID value applies to all VT Detections
Onset Criterion	ON/OFF		OFF		
R-R Percent[g]	56–62, 66–87, 91–97%	3%	81%	± 0.5%[h,i]	
Onset Counter	ON/OFF		OFF		
Interval Stability[g]	OFF, 30–130 ms	10 ms	OFF	± 1 ms[h]	

a. Due to Medtronic's continuing deveopment, it is not possible to list all currently available programming configurations. See the appropriate Medtronic programmer manual for specific details.
b. Parameter and tolerance values apply at 37° C and 510 ohm load at time of manufacture. Values may vary depending on the specific test procedures used.
c. Programmer default values are associated with the Model 9788 MemoryMod.
d. Escape interval equals pulse interval (–10, + 50 ms).
e. With a 40 ms sine^2 waveform.
f. When using the Cenelec waveform, the rated sensing threshold value will be 1.5 times the rated sine^2 sensing threshold value.
g. With a periodic (constant amplitude and wave shape) signal.
h. Does not include an additional (-0, +10 ms) rounding tolerance associated with each interval measurement.
i. Does not include an additional ± 5 ms rounding tolerance associated with an R-R average calculation.

Programmable Functions	Capability	Increments	Programmer Default	Tolerance	Other Notes
VF Detection					
Enable	ON/OFF		OFF		
VF Detection Interval[a,b]	240-400 ms	10 ms	320 ms	± 1 ms	FDI should be at least 40 ms less than TDI
Number of Intervals to Detect	6-30	6	18		
VT Therapies	0-4				
Burst					
Enable	ON/OFF		OFF		
Number of S_1 Pulses	1–15	1	6		
S_1–S_1 Interval	50–62, 66–87, 91–97%	3%	84%	± 0.5%[c]	
Number of Sequences	1–15	1	5		
Decrement per Sequence	0–40 ms	10 ms	10 ms	± 1 ms	
Minimum Pulse Interval[d]	150–300 ms	10 ms	200 ms	± 1 ms	
Ramp					
Enable	ON/OFF		OFF		
Initial Number of S_1 Pulses	1-15	1	5		
First R–S Interval	50–62, 66–87, 91–97%	3%	97%	± 0.5 %[c]	
Decrement per Pulse	0–40 ms	10 ms	10 ms	± 1 ms	
Number of Sequences	1–15	1	8		
Minimum Pulse interval[d]	150–300 ms	10 ms	200 ms	± 1 ms	

a. With a periodic (constant amplitude and wave shape) signal.
b. When VF Detection is enabled, the programmed setting for this parameter serves as the minimum interval to identify a VT event.
c. Tolerance does not include rounding tolerances associated with the R–R interval measurement (–0,+10 ms), R–R average calculation (± 5 ms), and the stimulation interval calculation (± 5 ms).
d. The Minimum Pulse Interval selected applies to both Burst and Ramp therapies and is used for all programmed therapies and sequences.

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Programmable Functions	Capability	Increments	Programmer Default	Tolerance	Other Notes
Cardioversion					
Enable	ON/OFF		OFF		
Current Path	Single, Simultaneous, or Sequential		Sequential		
Pulse Width	0.5–2.0 ms 2.4–5.9 ms 6.3–7.8 & 8.1 ms	0.5 ms 0.5 ms 0.5 ms	6.3 ms	+0.2, –0.1 ms +0.2, –0.1 ms +0.2, –0.1 ms	
Energy (Stored)	0.2–1.8 joules 2.0–15.0 joules 16.0–34.0 joules	0.2 J 1.0 J 2.0 J	0.6 J[a]	± 35% ± 15% ± 15%	Peak voltage with 75 ohm load: ± 16% ± 5% ± 5%
VF Therapy	0–4				
Enable	ON/OFF		OFF		
Current Path	Single, Simultaneous, or Sequential[b]		Sequential		
Pulse Width	2.0 & 2.4–5.9 ms 6.3–7.8 & 8.1 ms	0.5 ms 0.5 ms	6.3 ms	+0.2, –0.1 ms +0.2, –0.1 ms	
Energy (Stored)	0.2–1.8 joules[c] 2.0–9.0 joules[c] 10.0–15.0 joules 16.0–34.0 joules	0.2 J 1.0 J 1.0 J 2.0 J	34 J	± 35% ± 15% ± 15% ± 15%	Peak voltage with 75 ohm load: ± 16% ± 5% ± 5% ± 5%
VT Manual Prescriptions					
Burst	See Above				Programmer-initiated therapies (Manual Prescriptions) do not involve the automatic detection criteria. Only one pacing sequence or therapy per command.
Ramp	See Above				
Cardioversion	See Above				
VF Manual Prescriptions					
Defibrillation	See Above				
Electrophysiological Studies[d]					Delivered:
S_1–S_1	300–2000 ms	10 ms	600 ms	± 2 ms	in VVI Mode
S_1–S_2	150–600 ms	10 ms	400 ms	± 1 ms	Asynchronously
S_2–S_3	150–600 ms	10 ms	OFF	± 1 ms	Asynchronously
S_3–S_4	150–600 ms	10 ms	OFF	± 1 ms	Asynchronously
Number of S_1	1–20	1	8		
	20–95	5			

a. Default setting is 34.0 J for therapy #3 and #4
b. The programmed current path applies to all four VF therapies.
c. Energy range available only for Therapies #1 and #2.
d. Specifications may vary with the specific Medtronic programming system used.

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Programmable Functions	Capability	Increments	Programmer Default	Tolerance	Other Notes
Electrophysiological Studies (continued)					
High Rate Pacing (Fib)					
Manual–Interval	100-400 ms	10 ms	400 ms	± 1 ms	
Automatic					
Interval Limit	100–200 ms	10 ms	200 ms	± 1 ms	
	210–250 ms	20 ms		± 1 ms	
	300–400 ms	50 ms		± 1 ms	
Telemetry					
Permanent	OFF, 1-63 hrs Continuous	1 hr	OFF		Based on 4,000 events per hour
Type	Marker Channel		Marker Channel		
	EGM–Near Field				PACE/SENSE to SENSE2
	EGM–Far Field				PULSE1 to COMMON
Manual Capacitor Charging					Peak voltage with 75 ohm load
	0.2–1.8 J	0.2 J		± 35%	± 16%
	2.0–15.0 J	1.0 J		± 15%	± 5%
	16.0–34.0 J	2.0 J		± 15%	± 5%

Nonprogrammable Functions	Capability	Tolerance	Other Notes
Blanking	120 ms[a,b]	–20, +0 ms[c]	After sensed event
	320 ms	–20, +0 ms[c]	After paced event
	300 ms	–20, +90 ms[c]	After Charging Period
	300 ms	–20, +0 ms[c]	After VT/VF therapy or failure to synchronize
Refractory	200 ms	–20, +0 ms[c]	After sense, during CV Synchronization Sequence
	400 ms	–20, +90 ms[c]	After Charging Period
	520 ms	–20, +0 ms[c]	After VT/VF therapy or failure to synchronize
VF Synch Period	500 ms	± 1 ms	If no sensed event, the defibrillation shock is delivered
Escape Interval	1000 ms	±2 ms	After VT/VF therapy
Maximum Allowable Charging Period	34.95 seconds	+20, –10 ms	For cardioversion and VF therapy

a. Using a periodic (constant amplitude and waveform) signal
b. Measured from the time of the previous sensed event.
c. Based on a 40 ms sine^2 waveform at twice the programmed sensitivity threshold.

Nonprogrammable Functions	Capability	Tolerance	Other Notes
Time Between Sequential Pulses	244 µsec	± 225 µsec	
Disabling of VT Detection	64 events		After a VF detection
Rate Limit (Protective Feature)	120 ppm	± 20 ppm	Does not apply during therapies or programmed high rates
Input Impedance (min)	50 Kohms		

Data	Range	Tolerance	Other Notes
PCD Status			
Memory Retention	OK, Reset (by Power Inadequate, Memory Loss, Both)		
Charge Circuit	OK, Timeout, Inactive		
Last Charge Time	10 ms – 34.95 seconds	+ 20, – 10 ms	
Battery Voltage	Measured Voltage	± 200 mV	
VT Onset Counter	0–65,535		
VT Episode and Therapy Data			
Episode Count	0–255[a]		
VT Therapy Success Count	0–255[a]		Reports for each of 4 therapies
Number of VTs PCD Ineffective	0–255[a]		
PCD Efficacious on Last VT	YES/NO		
Last Therapy Used	0–4		
Number of Sequences in Last Therapy	1–15		Applies to Burst and Ramp therapies only
R-R Average for Last Pace Therapy	None, 150–600 ms		Applies to Burst and Ramp therapies only

a. An increment to a counter that causes the value to exceed the maximum will cause the counter to go to the minimum value.

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Nonprogrammable Functions	Capability	Tolerance	Other Notes
VF Episode and Therapy Data			
Episode Count	0–255[a]		
VF Therapy Success Count	0–255[a]		Reports for each of 4 therapies
Number of VFs PCD Ineffective	0–255[a]		
PCD Efficacious on Last VF	YES/NO		
Last Therapy Used	0-4		
Last Episode Sequence	20 intervals		Prior to last VT or VF episode detection
Cycle Length Intervals	100 – 2000 ms	+ 12, –2 ms	
Last Therapy Sequence	10 intervals		Following last VT or VF therapy delivered during last episode
Mechanical Dimensions			
Size: Height	101 mm		
Length	70 mm		
Width	20 mm		
Mass	197 grams		
Displacement Volume	113 cc		
External Shield	Titanium		
Battery	Lithium Silver Vanadium Oxide		(6.4 V nominal)
Factory Preset Parameters	As indicated on Package Labeling		

a. An increment to a counter that causes the value to exceed the maximum will cause the counter to go to the minimum value.

Medtronic

Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576
Telephone: (612) 574-4000
Cable: Medtronic Telex: 29-0598
FAX: (612) 574-4879

March 26, 1993

Office of Device Evaluation
PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

RECEIVED
29 MAR 93 12 02
FDA/CDRH/ODE/DMC

Re: Transvene Lead System, PMA Amendment
(Document Control Number P920015)

A031

The purpose of this submission is to respond to the deficiencies described in FDA's letter, dated March 17, 1993, see Attachment 1. Deficiency responses are presented in Attachment 2. An updated Summary of Safety and Effectiveness is provided in Attachment 3.

Information provided in this amendment includes clinical experience of 757 patients through February 1, 1993. Additional information is provided on virtually all clinical Transvene system implants, N = 1330, relative to patient complications and observations (including lead dislodgements), patient deaths and survival. This is provided in deficiency response #8. Again, the data cutoff date for these 1330 patients is February 1, 1993. A stand-alone, Clinical Summary Report is provided in Attachment 4 for convenient reference.

Clinical data presented in this amendment continues to demonstrate the PCD Transvene system performs as specified and is, therefore, safe and effective for its intended use. Results include 99.3 percent survival from SCD at one year. Additionally, Transvene system perioperative mortality and hospital stay compares dramatically to that of epicardial systems, 0.7% mortality and 7 days in hospital, versus 5.3 percent mortality and 11 days in hospital, respectively.

Copies of Transvene labeling (technical manuals) are provided in Attachment 5 for reference.

The existence of this PMA Amendment and the data and other information it contains are confidential, and the protection afforded to such confidential information by 18 USC 1905 and other applicable laws is hereby claimed.

Three copies of this PMA Amendment are provided. Should additional information be required by the Agency, please contact the undersigned.

Sincerely yours,

MEDTRONIC, INC.

Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
(612) 574-4688
(612) 574-6424 FAX

Attachment

7

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Attachment 3: Updated Summary of Safety and Effectiveness, March 26, 1993 182

Attachment 4: Clinical Summary Report 269

Attachment 5: Transvene Lead Technical Manuals

Appendix A: Nonclinical Testing Transvene Models 6963, 6966, 6999

Appendix B: Technical Report for Medtronic, Inc.

Appendix C: Medtronic Product Performance Report, February 1993

000203

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

MAR 17 1993

Ms. Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

RE: P920015
Transvene™ Lead System
Filed: April 1, 1992
Amended: September 21, 1992

Dear Ms. Marrone:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial scientific review of the above referenced premarket approval application (PMA). We regret to inform you that on the basis of this review, we have concluded that the PMA lacks information needed to complete the review and determine whether there is reasonable assurance that the device is safe and effective for its intended use.

We recognize the potential public health significance of this device and acknowledge the separate discussions underway to expedite the review. However, because of this lack of information, review of the PMA cannot continue and, accordingly, we have listed the following significant deficiencies which require the responses as indicated:

1. To clearly establish the purpose of the clinical data in the PMA application, please provide the following:

   a. the hypothesis and the objectives of your clinical study;

   b. a discussion of (i) how your clinical study addresses the use of a control, which is relevant to all clinical studies, (ii) the appropriateness of the AICD™ as a historical control, and (iii) your rationale for not using a concurrent control during an implantable cardioverter defibrillator (ICD) study;

   c. the endpoints of your study; and

   d. how the data provided in the PMA application support the specified endpoints.

3

2. Based on data provided in your PMA application, please prepare table(s) which include a side-by-side comparison of the PCD® Transvene™ and the PCD® Epicardial System and the PCD® Transvene™ and Ventak P AICD™ populations. The table must also include the inclusion and exclusion criteria which were used for each study. You must include a discussion of how these data may or may not represent a valid comparison, and other comments which justify and support the use of these groups as controls.

3. An update of the PMA clinical study population must be provided. The update must include the data as presented in the PMA application, and must include the clinical experience in the use of the new anchoring sleeves, which are aimed at decreasing the incidence of dislodgement, and a summary of the clinical experience (spontaneous treatment efficacy of ventricular tachycardia (VT) and ventricular fibrillation (VF), observations and complications, number of patient deaths and overall survival) of the patients followed for a year or more.

4. Please provide a clear description of how you identified the "patient who did not meet the implant criteria." Please discuss your implant criteria and how implant testing attempted to satisfy protocol requirements.

5. Of the 214 patients who did not meet the implant criteria and yet were implanted with the device, 170 patients had successful defibrillation with 24 Joules (J). Please provide an update of the clinical experience on these patients, as described in item 3 above. Also, please discuss how your proposed labeling will address this protocol deviation. Will implant criteria be changed?

6. There were 20 patients among the 214 who did not meet the implant criteria and were implanted without the 10 J safety margin. An update of the spontaneous episode experience in the treatment of VT and VF in these patients and the overall survival must be provided.

7. Table IK-4, page 151, compares the patients meeting the implant criteria to those who did not meet the criteria. However, many of the percentages were presented without numerical support. Please provide the appropriate numbers.

8. Please provide an update on the patients who are implanted with the Transvene™ System and were not counted in the PMA population. The update must include a summary of the clinical experience as referenced in item 3 above.

9. Based on your study protocol, please differentiate between defibrillation threshold (DFT) testing and lowest energy to defibrillate (LED) testing. Based on the individual patient report forms of the 757 patients, how many patients underwent what is described as DFT testing and how many had LED testing? Samples of the patient report forms showing the scheme of testing which was

CC64

categorized as DFT and LED testing must be provided. Please discuss how the DFT and LED data were reported and presented in the PMA application.

10. There is a statistically significant difference between the mean DFT obtained with the RV-CS-SQ lead configuration and the mean DFT obtained with the other lead configurations. How do you account for this difference? Was the DFT as reported and discussed for all lead configurations obtained using an identical or similar scheme? Please discuss. You must document that there were no significant differences between the scheme for performing DFT and LED testing between the Transvene™ and PCD® Epicardial patient populations, if that is the case.

11. Please elaborate on how the comparison of DFTs obtained from the PCD® Epicardial Lead study and the Transvene™ study can be considered as a valid comparison in that the majority of the patients (574 (75.3 percent)) in the Transvene™ study were programmed with the sequential pathway and 178 (23.4 percent) were programmed via the simultaneous pathway. The majority of the patients (496 (65.2 percent)) in the PCD® Epicardial study were programmed with the single pathway. Based on your PCD® Epicardial study, please discuss the DFTs or energy requirements obtained with the use of the single defibrillation pathway versus the sequential and simultaneous pathways.

12. Please discuss the time between detection and delivery of therapy of the Transvene™ System versus the PCD® Epicardial System.

13. On page 125 of the application, please explain and/or discuss what is meant by "a 2:1 VF sensing margin", how it is determined, and if the patients met the criteria.

14. Of the 329 patients who were followed for 6 months, 130 patients had spontaneous episodes. What was the average number of VT and VF episodes per patient? Of the patients followed for a year, how many had spontaneous episodes of VT and VF and what was the mean number of episodes per patient in this group?

15. On page 130, Table IF-4, you report that there were 5362 episodes of VT successfully terminated. On page 131, paragraph 2, you state that 25 patients experienced 45 (0.8 percent) episodes of sinus tachycardia or atrial fibrillation. Are these patients included in the success or failure category? Nine hundred and sixty-four episodes of VF were reported, however, 75 episodes were not actual VF. You must clarify how the successful and ineffective therapies and failures are discerned and categorized. Please prepare a table which includes a category of ineffective therapies with actual patient numbers and percentages. In addition, what assurance is there that an episode of supraventricular tachycardia or atrial fibrillation is not misinterpreted as VT or VF by the physician and considered a successful therapy?

16. Table IM-6, page 173 must be modified to include a column on inappropriate therapy or therapies delivered as the device was programmed so that the percentages add up to 100 percent.

17. On page 162, Table IL-2 lists a category "Fail to Cardiovert/Defibrillate" as 0.8 percent. Please clarify. If a patient survives an episode of an inappropriate therapy, is it categorized as a success? Please discuss. The tables must include percentages with the representative numerical support.

18. There were 38 inactive patients reported in Table IH-1, however, 34 patients were reported to be no longer active. Please clarify.

19. Please discuss how the 1 year sudden cardiac death survival, as reported in Table IF-2 page 128, was calculated. The numbers and an explanation of patient classification must be included. Was every patient included who had a prior cardiac arrest regardless of the arrhythmia?

20. On page 177, the number of patients must be provided so that the percentages and calculated p-values can be confirmed.

21. Table IV-C, page 649 of the original submission shows a comparison of patient variables for the three lead systems and provides p-values for the variables tested, but the hypothesis was not clearly stated. Please state the hypothesis and discuss the p-values obtained when reporting by primary indication, and the chi-square test of the data set and how it was computed.

22. For purposes of justification of data pooling and data analysis of Table IV-C, please discuss why the multiple statistical significant difference was not adjusted at a 0.05 significance level using a more widely accepted procedure such as the Hochberg procedure (Dunnett and Tarnhoue: A Step-up Multiple Test Procedure, Journal of the American Statistical Association, March, 1992, Vol 87: pp.162-170).

23. You claim that confidence interval analysis was performed to compare the overall mortality of the PCD● and AICD™ populations. What was the confidence interval?

24. Please clarify and/or discuss the following regarding Table XB-1, page 378, Volume 2:

    a. the total number of patients in the Ventak P population (292) versus those reported by primary indication (291); and

    b. a chi-square test of primary indication, using the StatXact computer software, yields a p-value of nearly 0. This is statistically significant, indicating the PCD● and Ventak P populations are significantly different.

25. Please discuss the incidence of inappropriate therapies reported as observations in the Transvene™ study. It appears as if there has only been a slight improvement over the PCD® Epicardial study as it relates to programming and patient management (drug therapy). Please discuss the experience of both studies and how the labeling supports effective programming of the device parameters and the use of the Onset and Stability algorithms. How many patients in the Transvene™ study have the Onset and Stability algorithms programmed ON? At what interval during the study were the majority of patients programmed with the algorithms? Your experience in the treatment of induced and spontaneous episodes with use of the algorithms must be discussed.

26. Please discuss the "device related" complications reported for the Transvene™ and the PCD® Epicardial System.

27. Please describe in detail the complications reported in the patients followed for a year.

28. There was a substantial increase in the number of infections reported in the Transvene™ study. Even though you discussed why there was an increase, based on your experience, how will your labeling address the procedures for reduction in the number of infections? Please validate these procedures.

29. A discussion of your experience in the use of the different entry sites for the placement of the Transvene™ leads, and how your labeling assists in the selection of an entry site, must be provided.

30. Of the 22 deaths, 15 systems were explanted and returned for analysis. The results of the analyses (PCD® and Transvene™ leads) must be provided. What did device interrogation reveal? How many of the 41 Transvene™ lead systems which were explanted were returned and analyzed? How long were the leads implanted? A description of the protocol for analysis and the results of the analyses on all leads and devices must be provided. The PMA application must document how your study has addressed the need for the return and analysis of all Transvene™ leads and the PCD®.

31. Please discuss the circumstances surrounding the death of the patient who died (b)(4) months post implant. What did interrogation of the device reveal?

32. Of the perioperative deaths, how many devices were programmed OFF? Please discuss the circumstances surrounding each death. The number of perioperative deaths must be reported in a table and be identified as sudden cardiac, non-sudden cardiac or non-cardiac. Were there other deaths when the device was programmed OFF?

33. You state that there have been no reported patient deaths in the group with a 1 year sudden cardiac death survival and overall

actuarial survival of 100 percent. Does this include the perioperative deaths and the patients who have been followed out for a year?

34. Please provide an engineering drawing of each Transvene™ lead model which identifies the segments of the lead and a description of the tests that each segment and the full lead body underwent.

35. Since flex testing exerts a considerable amount of stress on the lead, and is essential to life testing, why was it considered that (b)(4) cycles at a bend radius of (b)(4) inch per lead model over a 12 month period would be sufficient? Describe how the full lead and different segments were flexed. Did you do a finite element stress analysis to validate the flex testing stress?

36. In light of the failure of your platinum sputtered polyurethane bradycardia pacing leads, and since the Transvene™ lead Model 6966 is also a platinum sputtered polyurethane lead, please provide documentation regarding the failure mechanism of the pacing leads and all relevant information pertaining to these cases. How can we be assured that the failure may be restricted to the bradycardia pacing leads? Based on your testing to date regarding the pacing leads and the testing of the Model 6966 lead, discuss the potential and the probability of failure of the Model 6966 lead. A side by side comparison of the Model 6966 and the 4,000 series bradycardia pacing leads must be provided. The comparison must include material, design, dimensions, function, tests performed and a schematic drawing.

37. A copy of the Summary of Safety and Effectiveness which includes the updated data must be provided.

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period up to 180 days. As provided by 21 CFR 814.37(c), you may decline to submit a major amendment requested by FDA in which case the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

As provided under 21 CFR 814.44(g), FDA will consider this PMA to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA amendment. You may, however, amend the PMA within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA with in the 180-day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA and will be assigned a new number.

You may amend the PMA to provide the above requested information (12 copies), voluntarily withdraw the PMA (3 copies), direct CDRH to complete processing the PMA without the submission of additional information (3 copies) or request an extension. The required copies of the amended PMA should include the FDA reference number for this PMA and should be submitted to the following address:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

Upon receipt of an amendment adequately addressing the above requests or a written response declining to submit the requested amendment, CDRH may schedule an advisory panel meeting at which your PMA will be reviewed. You will be notified of the location and date of this meeting should one be necessary. In order to provide adequate time for CDRH and advisory panel review, information received by FDA less than 6 weeks in advance of any scheduled advisory committee meeting will not be considered or reviewed at the meeting and may delay consideration of your PMA until a subsequent advisory committee meeting.

If you have questions concerning this deficiency letter, please contact Doris Terry at (301) 427-1018 or Arnold Alpert, Ph.D., at (301) 427-1186.

Sincerely yours,

F. Alan Andersen

F. Alan Andersen, Ph.D.
Acting Director
Office of Device Evaluation
Center for Devices and
Radiological Health

01

1. **To clearly establish the purpose of the clinical data in the PMA application, please provide the following:**

   a. **the hypothesis and the objectives of your clinical study;**

   RESPONSE:

   The hypothesis and objectives of the Medtronic Transvene clinical study are as follows. Note that this has been presented in each clinical summary report provided to FDA over the past two years including our previous deficiency responses provided on September 18, 1992.

   Hypothesis

   The objectives of the Transvene clinical study, described below, are intended to demonstrate the hypothesis that the Transvene PCD system is safe and effective in treating VT and VF, versus the null hypothesis that the system is not safe and effective in the treatment of VT and VF tachyarrhythmias.

   Objectives

   The safety and efficacy of the Transvene system is/was determined by:

   - Evaluating the sensitivity and specificity of the PCD device with Transvene lead systems to detect episodes of VT and VF, and to evaluate the ability of the system to appropriately discriminate between VT/VF and other potentially nonmalignant rhythms.

   - Monitoring the efficacy of the PCD device with Transvene lead systems in treating VT and VF episodes. VT/VF therapy efficacy is determined as the ratio of successful termination of episodes detected to the total number of episodes detected in which one or more therapies were delivered (successful termination/number of detected episodes with therapy delivered). Investigators are able to choose from any of the available leads and VT/VF therapies that the efficacy was first evaluated acutely.

   - Evaluating the performance of the Model 6966, 6963 and 6999 Transvene leads.

- Estimating the one year SCD and overall survival of the patients implanted with the PCD® Transvene™ System.

- Monitoring the patient selection criteria and patient management methods required by the PCD device and Transvene leads.

- Evaluating the safety and effectiveness of the Model 5355 ETCD device when used during the implant procedure. Specifically, tachyarrhythmia episode induction, detection, termination and ease of use are analyzed.

- Evaluating the safety and performance of the Model 9710 programmer and the Model 9788 MemoryMod software cartridge in programming sensing and therapy parameters and the appropriate delivery of noninvasive electrophysiologic stimulation.

b. **a discussion of (i) how your clinical study addresses the use of a control, which is relevant to all clinical studies, (ii) the appropriateness of the AICD™ as a historical control, and (iii) your rationale for not using a concurrent control during an implantable cardioverter defibrillator (ICD) study;**

RESPONSE:

i. **how your clinical study addresses the use of a control, which is relevant to all clinical studies,**

Background

The PCD Epicardial System, is a tiered therapy device that, combines features of bradycardia support pacing, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. This system has incorporated programmability and multiple detection and therapeutic options that allows the titration of device therapy to a patient's specific clinical arrhythmia history.

The PCD Epicardial System requires a thoracotomy for implantation because of the need to insert epicardial patch leads. This exposes the patient to surgical risk and potentially limits the type of patient who may be considered for implant of the system. The need for a simpler and safer implantation technique is widely recognized. The incorporation of a nonthoracotomy lead system, such as

the PCD Transvene System, should decrease the potential perioperative and long term mortality and morbidity associated with current epicardial system implantation approaches.

The PCD Epicardial System and PCD Transvene System are identical except for the implanted defibrillation lead system. Thus the performance of the PCD device, and associated support equipment, is similar in the two systems and therefore a comparison of clinical experience should focus on those areas where the lead system implanted may impact clinical outcome. This would include spontaneous VT/VF episode efficacy, complication/observation rates and patient survival.

The Use of a Control

Medtronic provides a comparison of the PCD Transvene System clinical experience to the reported PCD Epicardial System clinical experience. **A historical control comparison was performed using the Medtronic clinical database on the PCD Epicardial System since patients were being enrolled in the two studies concurrently and the patient indications, implant criteria and clinical data requirements were identical for the two patient groups.**

At the start of the PCD® Transvene™ System clinical study a randomized controlled study was not performed since the investigators felt strongly that it was not clinically appropriate to randomize to a surgical procedure when a less invasive implant procedure was available. The investigators believed that the ability for Medtronic to do a historical control comparison between the PCD® Transvene™ and PCD® Epicardial System would provide sufficient data to allow a comparison of the clinical outcome of the two patient groups. A historical comparison would be appropriate

A historical comparison to the Ventak-P Epicardial System was also feasible since it was the most similar system that was market released and the patient indications were similar to that of both the PCD® Transvene™ and PCD® Epicardial Systems.

The premise of the PCD® Epicardial and Transvene™ studies was to demonstrate that if a patient was evaluated at

implant and shown to meet implant criteria, that they would be reliably defibrillated over time, and therefore, have a high probability of survival from SCD regardless of which lead system or defibrillation pathway was chosen. The Epicardial System is a valid comparison since the same PCD® was used in both systems, the same indications were used, the same implant criteria, the same protocol and data requirements and the studies were performed concurrently at the same centers. There is no other system that is currently market released that is a better, or more applicable control. We have shown for both studies that freedom from SCD at one year is at least equivalent to that afforded by the commercially available AICD for patients who meet the implant criteria regardless of lead system. All of the transvenous defibrillation systems that are available are currently under investigation and, as such, limited or no data exists with which to compare our performance.

The investigators believe that there is a class of patients who cannot tolerate the thoracotomy required for the utilization of the epicardial patch lead defibrillation lead system and who are at high risk of sudden cardiac death. For these patients, the PCD Transvene System is the only therapy available. Because of the surgical risks and postsurgical complications associated with epicardial lead system, implantation in the following patient groups may not be possible:

(1) patients in whom there is no indication for concomitant cardiovascular surgery at the time of ICD System implant;

(2) patients with severe pulmonary disease who cannot tolerate prolonged anesthesia or an open chest procedure;

(3) patients with severe congestive heart failure (ejection < 40%) who are at increased risk for perioperative mortality post a thoracotomy procedure;

(4) patients who may eventually require open chest procedures for treatment of their coronary artery disease or cardiac transplant.

For these patients, the PCD Transvene System is the only therapy available. The PCD Transvene System simplifies and greatly reduces the risk associated with lead introduction, making therapy available to these patient

groups. Because there is no need to open the chest of these patients, options for future therapy remain available; e.g. CABG is associated with decreased morbidity and mortality if there has been no prior open chest surgery. **Thus randomization would not be feasible or clinically or ethically appropriate in these patient groups.**

ii. **the appropriateness of the AICD™ as a historical control, and**

The AICD clinical experience was compared to that of the Transvene system, i.e., the AICD served as a control of sorts, because the AICD system **was the only commercially available, FDA approved ICD system,** at the time of our analysis and documentation of the PCD® Epicardial and Transvene™ clinical experience. The Ventak-P System was chosen since it was the most similar to PCD® and the patient indications were similar. For purposes of comparison, the Ventak-P epicardial system patient population described in the (Ventak-P) Summary of Safety and Effectiveness, P890061, dated May 2, 1991, was used. A copy of this summary was obtained through the Freedom of Information Act.

A detailed comparison has been provided in the Transvene PMA application and subsequent amendments. It is also provided in this amendment, see Deficiency Response Number 2.

iii. **your rationale for not using a concurrent control during an implantable cardioverter defibrillator (ICD) study;**

A concurrent market release control was not used because of the reasons previously stated in Deficiency Response 1.b.(i) and because another transvenous defibrillation lead system was/is not commercially available. Other manufacturers simply do not allow their systems, clinical or market release, to be used by competitors due to the need to protect trade secrets. A concurrent control was also not used because an appropriate historical control was available, that is, the PCD Epicardial System. The PCD® Epicardial System is an appropriate historical control. Since patients were being enrolled in the two studies concurrently, the patient indications, implant criteria and clinical data requirements were identical for the two groups.

Specifically, the PCD Epicardial System uses the same tiered therapy device that combines features of bradycardia support pacing, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. This system has incorporated programmability and multiple detection and therapeutic options that allows the titration of device therapy to a patient's specific clinical arrhythmia history.

The PCD Epicardial System and PCD Transvene System are identical except for the implanted defibrillation lead system. Thus, the performance of the PCD device and associated support equipment, is similar in the two systems and therefore a comparison of clinical experience should focus on those areas where the implanted lead system may impact clinical outcome.

Analysis provided in this clinical update, and also provided in previous Transvene PMA documents, shows that the incorporation the of nonthoracotomy defibrillation system has maintained the type of therapy available for the treatment of recurrent VT/VF and decreased the potential mortality and morbidity associated with epicardial implant approaches while maintaining the positive impact of ICD therapy on VT/VF episode efficacy and patient survival.

This analysis is thoroughly discussed in this amendment. See Deficiency Response Number 1 and the Clinical Update.

c. the endpoints of your study; and

d. **how the data provided in the PMA application support the specified endpoints.**

RESPONSE:

The following is a description of the endpoints of the Transvene clinical study and how the data collected support these endpoints.

Endpoint: Freedom from sudden cardiac death (SCD) and all cause mortality as shown through one-year survival.

Endpoint: Treatment efficacy of spontaneous VT/VF episodes.

Data supporting these endpoints are as follows. (See also the Clinical Update included in this PMA amendment.)

Patient Deaths

- The estimated one-year survival probabilities for Sudden Cardiac Death, Non-Sudden Cardiac Death, all Cardiac Deaths and Noncardiac Death were found to be 99.5%, 96.2%, 95.8%, and 98.1%, respectively.

  The incorporation of programmable VT/VF detection and therapies has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

- The sudden cardiac death survival of 99.5% at one year is comparable to that of the AICD™ patient population 98.0%.

- There have been no deaths due to a PCD Device malfunction.

- Overall survival at 93.3% is better than that afforded by the Ventak-P Epicardial System.

Complications/Observations

- Complications were reported in 19.4% of the patient population and observations were reported in 23.8% of the patient population.

- The incidence of complications was comparable to that of the market released AICD™ system in the categories of ineffective VT/VF therapy, pocket infection and pocket erosion, and was lower than the AICD™ in the category of inappropriate delivery of VT/VF therapy.

Patient Indications

- All of the patients entered into clinical evaluation met at least one of the primary indications. Sudden cardiac death (SCD) was the primary indication in 37.1% of the patients, recurrent ventricular tachycardia (VT) was the primary indication in 49.8% of the patients and SCD/VT was the primary indication in 13.1% of the patients.

- The number of patients (60.5%) receiving VT/VF therapy for spontaneous episodes of ventricular arrhythmias supports the conclusion that the patient selection criteria

are appropriate and that the PCD Transvene System was implanted in patients who benefit from this therapy.

- The one year sudden cardiac death survival rates for the SCD patient group was 100.0%, for the VT patient group 99.4% and the SCD/VT patient group 98.6%.

VT/VF Detection and Therapy Performance

- The PCD Transvene System properly detects and treats VT as demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VT was 98.4%.

- The PCD Transvene System properly detects and treats VF as demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VF was 98.4%.

- There were no reported patient deaths due to the nondetection of a spontaneous VT or VF episode by the PCD Transvene System.

PCD Transvene System Performance

- The PCD Transvene System components (Model 7216A/7217B and Model 6884/6966, 6881/6963, 6895/6999 Transvene leads) have performed according to design and specification and are, therefore, considered safe and effective in the indicated patient population.

Clinical Experience Summary Conclusions

The PCD Transvene System is a tiered therapy device which combines features of bradycardia pacing support, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. The incorporation of these features has allowed the physician to titrate the ICD therapy to meet specific patient clinical needs, allowed fewer shocks to be delivered for recurrent ventricular tachycardia because of antitachycardia pacing features, allowed fewer cases of inappropriate therapy delivery due to programmable detection and allowed a sudden cardiac death survival rate identical to the Ventak-P Epicardial System.

The PCD Transvene System, due to the elimination of the need for a thoracotomy, has provided a marked improvement in both the

perioperative and overall patient mortality as compared to the PCD Epicardial System. In addition, due to the decreased perioperative morbidity and mortality, the post implant hospital stay has been decreased to a mean of 7.6 days as opposed to a mean of 10.6 days ($p = 0.001$) for the PCD Epicardial System.

Medtronic asserts and the PCD Transvene investigators unanimously agree that the findings of the clinical study support the conclusion that the Medtronic Tachyarrhythmia Control System and the Transvene Cardioversion and Defibrillation Electrodes are safe and effective in the indicated patient population.

2. **Based on data provided in your PMA application, please prepare table(s) which include a side-by-side comparison of the PCD® Transvene™ and the PCD® Epicardial System and the PCD® Transvene™ and Ventak P AICD™ populations. The table must also include the inclusion and exclusion criteria which were used for each study. You must include a discussion of how these data may or may not represent a valid comparison, and other comments which justify and support the use of these groups as controls.**

RESPONSE:

The efficacy and safety of implantable cardioverter defibrillator (ICD) therapy for recurrent ventricular tachycardia (VT) and ventricular fibrillation (VF) has been well established. The Ventak-P Epicardial System provides cardioversion and defibrillation therapy for VT and hemodynamically unstable VT. However, this type of therapy may not be optimal for patients with stable, well tolerated VT that is amenable to antitachycardia pacing due to the pain associated with cardioversion shock therapy. The need to incorporate programmability, multiple detection and therapeutic options has lead to the development of the PCD® Device.

However the Ventak-P Epicardial System and PCD® Epicardial System are implanted only with a defibrillation lead system requiring a thoracotomy. The PCD® Transvene™ System allows the implantation of an ICD System without the potential increased perioperative morbidity and mortality associated with a thoracotomy. This allows the application of ICD therapy in patients who may not otherwise be candidates for this type of therapy.

In the PCD® Transvene™ System PMA Application a comparison of the PCD® Transvene™ System clinical experience was made to both the Ventak-P Epicardial System and the PCD® Epicardial System. (Reference: Clinical Experience Report Section X, Comparison to AICD Clinical Results and Section XI, Comparison to PCD® Epicardial System Clinical Results). A comparison to the Ventak-P Epicardial System was done because this was the only FDA approved ICD System available at the time of the original submission. A comparison to the PCD® Epicardial System was done since this system incorporated the same tiered therapy ICD Device as well as being a concurrent clinical study.

The comparison between the Ventak-P Epicardial System and the PCD® Transvene™ System was limited in scope due to the availability of clinical data from the Ventak-P Epicardial System Summary of Safety and

Effectiveness but included patient characteristics, implant defibrillation thresholds, incidence of spontaneous VT/VF episodes, incidence of complications and one year actuarial survival.

The comparison between the PCD® Transvene™ System and the PCD® Epicardial System included patient characteristics, implant data, implant defibrillation thresholds, programmed parameter status, spontaneous VT/VF episode efficacy, incidence of complications and observations and one year actuarial survival.

At the start of the PCD® Transvene™ System clinical study a randomized controlled study was not performed since the investigators felt strongly that it was not clinically appropriate to randomize to a surgical procedure when a less invasive implant procedure was available. The investigators believed that the ability for Medtronic to do a historical control comparison between the PCD® Transvene™ and PCD® Epicardial System would provide sufficient data to allow a comparison of the clinical outcome of the two patient groups. A historical comparison would be appropriate since patients were being enrolled in the two studies concurrently and the patient indications, implant criteria and clinical data requirements were identical for the two patient groups.

A historical comparison to the Ventak-P Epicardial System was also feasible since it was the most similar system that was market released and the patient indications were similar to that of both the PCD® Transvene™ and PCD® Epicardial Systems.

The **indications for the Ventak-P Epicardial System** are:

1. Patients who have survived at least one episode of cardiac arrest presumably due to hemodynamically unstable ventricular tachycardia unassociated with acute myocardial infarction; and

2. Patients who have experienced recurrent ventricular tachyarrhythmias in the absence of previous arrest and are inducible into sustained hypotensive ventricular tachycardia or fibrillation despite conventional antiarrhythmia drug therapy.

The patient **indications for the PCD® Transvene™ and PCD® Epicardial System** are as follows:

1. Patients who have survived at least one episode of cardiac arrest presumably due to a ventricular tachyarrhythmia not caused by an acute myocardial infraction; or

2. Patients with recurrent sustained ventricular tachycardia that remain inducible via programmed electrical stimulation or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

The **Ventak-P Epicardial System is contraindicated** in the following patients:

1. Patients who ventricular tachyarrhythmias may have a reversible cause;
2. Patients who require a pacemaker that causes Ventak-P pulse generator nondetection or oversensing;
3. Patients whose ventricular tachyarrhythmias occur so frequently that device's batteries would be depleted soon after implantation; and
4. Patients who are prone to supraventricular tachyarrhythmias despite conventional drug therapy.

The PCD® Transvene™ and PCD® Epicardial System are contraindicated in the following patient groups:

1. Patients with transient ventricular tachyarrhythmias due to reversible causes;
2. Patients with transient ventricular tachyarrhythmias due to other causes such as acute myocardial infarction; and
3. Sole use of detection and treatment of atrial arrhythmias.

The following tables provide a side-by-side comparison of the PCD® Transvene™ System to both the Ventak-P Epicardial System and the PCD® Epicardial System. These tables are identical to those presented in the PCD® Transvene™ System PMA application but have been updated to reflect clinical experience with the PCD® Transvene™ System with a data cutoff of 2/1/93. The clinical experience with the PCD® Epicardial System reflects a data cutoff of 1/5/93 and the Ventak-P Epicardial System clinical experience is that presented in the Summary of Safety and Effectiveness that is available via the Freedom of Information Act.

A comparison of the Ventak-P Epicardial System clinical experience and the PCD® Transvene™ System clinical experience indicates that the devices are being used in patients with similar cardiovascular disease history. There is a statistical difference in the primary indication for implant between the two systems. There were more patients that had Sudden Cardiac Death as their primary indication in the PCD® Transvene™ System population than the AICD Epicardial System population ($p = 0.001$).

Cox regression analysis was performed to see what effect gender, primary indication and system implanted (PCD® Transvene™ or PCD® Epicardial) had on survival outcome. This analysis showed that for overall

survival at one year the system implanted had an influence on the probability of survival but gender and primary indication had no influence.

Thus, since primary indication has no impact on survival outcome, the PCD® Transvene™ System and Ventak-P Epicardial System can be compared. There was a statistical difference (Confidence Interval Analysis) in one year overall survival between the PCD® Transvene™ (94.2%) and AICD Epicardial System (90.8%). This difference is due to the implanted defibrillation lead system.

The mean DFT value at implant of the PCD® Transvene™ System falls well below the maximum output (34J) of the PCD® Device and is comparable to that reported with the Ventak-P Epicardial System.

The percentage of patients receiving therapy from the PCD® Transvene™ System is comparable to that reported with the Ventak-P Epicardial System. However, greater than 90% of the VT episodes are treated by antitachycardia pacing in the PCD® Transvene™ System versus cardioversion shocks in the Ventak-P Epicardial System experience. This reduction in shocks is a clinical benefit to the patients.

The reported incidence of most complications is comparable between the two systems. The incorporation of programmable VT/VF detection has decreased the delivery of inappropriate therapy for sinus tachycardia and/or atrial fibrillation with a rapid ventricular response. The incorporation of programmable VT/VF detection and therapy algorithms has not resulted in an increase in reported complications.

The reported Sudden Cardiac Death survival rates in the two patient groups is comparable (PCD® Transvene™ System - 99.7%; Ventak-P System - 98.6%). This indicates that the programmable features within the PCD® Transvene™ System have improved the types of therapy available for the treatment of recurrent VT and VF while maintaining a positive impact on sudden cardiac death survival.

More importantly, the overall one year actuarial survival for the PCD® Transvene™ System was 94.2% as compared to 90.8% for the Ventak-P Epicardial System. This difference was primarily due to the improvement in the reported perioperative mortality in the PCD® Transvene™ System patient population.

The PCD® Transvene™ System incorporates additional detection and therapy features as compared to market released Ventak-P Epicardial System and has been used in a comparable patient population. In that patient population the PCD® Transvene™ System has allowed for fewer

shocks to be delivered because of the antitachycardia pacing features, fewer cases of inappropriate therapy delivery due to programmable detection and a comparable sudden cardiac death survival rate.

In addition, the elimination of a thoracotomy for implant in the PCD® Transvene™ System has improved the perioperative mortality and overall one year survival when compared to the Ventak-P Epicardial System.

A comparison of PCD® Transvene™ System clinical experience and PCD® Epicardial System clinical experience indicates that the devices are being used in patients with similar cardiovascular disease history. There is a statistical difference in the primary indication for implant between the two systems. There were more patients that had Sudden Cardiac Death as their primary indication in the PCD® Transvene™ System population than the PCD® Epicardial System population ($p = 0.002$). However, as with the Ventak-P Epicardial System analysis indicated that this difference in indication did not have an impact on patient outcome.

The mean DFT value at implant of the PCD® Transvene™ System falls well below the maximum output (34J) of the PCD® device and are comparable to those obtained with the PCD® Epicardial System.

The differences in PCD® device programmed status in the two groups is a reflection of the patients receiving the PCD® Transvene™ System and the defibrillation energy requirements of a nonthoracotomy lead system. However, despite differences in the programmed status, the PCD® device performed safely and effectively in both patient groups.

The spontaneous VT episode efficacy for the PCD® Transvene™ System was 98.4% which was comparable to that reported with the PCD® Epicardial System, 98.3%. The spontaneous VF episode efficacy for the PCD® Transvene™ System was 98.4% which again was comparable to that reported with the PCD® Epicardial System, 98.7%. Thus the incorporation of a nonthoracotomy lead system had no effect on the efficacy of the PCD® Device in detecting and terminating spontaneous VT/VF episodes.

The reported incidence of complications is comparable between the two systems. The reported incidence of observations was statistically lower in the PCD® Transvene™ System.

Finally, the reported Sudden Cardiac Death survival rates in the two patient groups is statistically the same (PCD® Transvene = 99.5%; PCD® Epicardial = 98.9%). However, there is statistical improvement in the overall survival in the PCD® Transvene™ System patient population. There was a significant improvement in overall survival in the patients

receiving a PCD® Transvene™ System. The Overall one year actuarial survival includes death from all causes. The overall one year survival for patients receiving the PCD® Transvene™ System was 93.3%.

This is significantly improved as compared to the overall one year actuarial survival for the PCD® Epicardial System (88.6%) [p = 0.004]. This improvement in overall survival is primarily due to the marked improvement in perioperative mortality, the PCD® Transvene™ System having a 0.7% perioperative mortality versus the a perioperative mortality of 5.3% in the PCD® Epicardial System. This improvement in perioperative mortality is primarily due to the elimination of the need for a thoracotomy and its associated morbidity and mortality.

Comparison of the clinical performance and survival outcome of the PCD® Transvene™ System versus both the PCD® Epicardial and Ventak-P Epicardial Systems indicates that the PCD® Transvene™ Systems performs similarly while providing important patient benefit. The PCD® Transvene™ System eliminates the need for a thoracotomy for the implantation of defibrillation lead systems. This directly improves the overall patient survival by decreasing the perioperative patient morbidity and mortality when compared to the PCD® Epicardial System and Ventak-P Epicardial System. This is added benefit however is not gained at the expense the PCD® Transvene™ System efficacy in treating spontaneous VT/VF episodes when compared to the PCD® Epicardial System.

PCD® Transvene™ System Comparison of Patient Characteristics PCD® versus AICD		
	PCD®	**Ventak-P**
Number of Patients	757	292
Mean Follow-Up Time	11.7 months	6.8 months
% Males **% Females**	610 (81%) 147 (19%)	231 (79%) 61 (21%)
Mean Age	59.4 years	61.5 years
Primary Indication:* **SCD** **VT** **SCD/VT**	 281 (37%) 377 (50%) 99 (13%)	 49 (16%) 169 (59%) 73 (25%)
Coronary Artery Disease	561 (74%)	228 (78%)
Mean Ejection Fraction	35.6%	34%
Drug Therapy at Implant	42%	45.0%
Concomitant Surgery	0%	18.0%

* Statistically Significant ($p \leq 0.05$)

Table 2-1: Comparison of Patient Characteristics, PCD® versus Ventak-P 2/1/93

PCD® Transvene™ System Comparison of Implant Defibrillation Thresholds PCD® versus AICD		
	PCD®	**AICD**
Mean DFT	14.8J	13.4J

Table 2-2: Comparison of Implant DFT, PCD® versus Ventak-P -2/1/93

PCD® Transvene™ System Comparison of Incidence of Spontaneous VT/VF Episodes PCD® versus AICD		
	PCD®	AICD
Number of Patients with VT/VF Episode	458 (60.5%)	137 (46.9%)

Table 2-3: Comparison of Incidence of Spontaneous VT/VF Episodes: PCD® vs Ventak-P 2/1/93

PCD® Transvene™ System Comparison of Complication/Observation Rates PCD® versus AICD		
Category	PCD®%	AICD%
Fail to Cardiovert/Defibrillate	2.3%	4.1%
Inappropriate/Problematic VT/VF Therapy Delivery	9.6%*	20%
Pocket Infection (explant)	2.9%	2.2%
Erosion	0.8%	0.7%

* Includes Observations only; there were no Complications in this category.

Table 2-4: Comparison of Complication/Observation Rates: PCD® Transvene™ System vs AICD Epicardial System - 2/1/93

PCD® Transvene™ System Comparison of Patient Death Classifications PCD® versus AICD		
	PCD®	AICD
Sudden Cardiac	5	4
Non-Sudden Cardiac	30	8
Noncardiac	16	6
Unknown	-	1
TOTAL	51	19
Perioperative	5	8

Table 2-5: Comparison of Patient Death Classifications: PCD® versus AICD - 2/1/93

PCD® Transvene™ System Comparison of One Year Actuarial Survival PCD® versus AICD		
	PCD®	AICD
Sudden Cardiac Survival	99.7%	98.6%
Overall Survival*	94.2%	90.8%
Perioperative Mortality*	0.7%	2.7%

* Statistically Significant ($p \leq 0.05$)

Table 2-6: Comparison of Actuarial Survival: PCD® versus AICD - 2/1/93

PCD® Transvene™ System Comparison of Patient Characteristics		
	PCD® Transvene™ System	**PCD® Epicardial System**
Number of Patients	757	742
Mean Follow-Up Time	11.7 months	16.3 months
% Males*	610 80.6%	637 85.8%
% Females	147 19.4%	105 14.2%
Mean Age	59.4 years	59.6 years
Primary Indication*		
SCD	281 37.1%	214 28.8%
VT	377 49.8%	405 54.6%
SCD/VT	99 13.2%	123 16.6%
Cardiovascular History		
Coronary Artery Disease	561 74.1%	569 76.7%
Cardiomyopathy	238 13.1%	222 29.9%
Mean Ejection Fraction	35.6%	34.0%
Number of Drugs Failed*	2.3	3.0

* Statistically Significant ($p \leq 0.05$)

Table 2-7: Comparison of Patient Characteristics, PCD® Transvene™ System versus PCD® Epicardial System - 2/1/93

PCD™ Transvene™ System Performance Comparison Implant Pace/Sense Parameters		
Parameter	**PCD® Transvene™ System**	**PCD® Epicardial System**
Pacing Threshold*	0.87 V (0.1-3.6V)	0.98 V (0.2-5.3 V)
R Wave Amplitude*	14.2 mV (1.3-32 mV)	13.5 mV (2.2-37.2 mV)
Slew Rate*	1.66 v/S (0.25-9.8 v/S)	1.38 v/S (0.15-7.2 v/S)
Resistance*	575 ohms (264-1381 ohms)	438 ohms (157-1206)

* Statistically Significant ($p \leq 0.05$)

Table 2-8: PCD® Transvene™ System: Comparison of Implant Pace/Sense Parameters - 2/1/93

PCD® Transvene™ System Performance Comparison Chronic Pace/Sense Parameters		
Parameter	**PCD® Transvene™ System**	**PCD® Epicardial System**
Electrogram Amplitude	10.0 mV (0.5 - 25 mV)	9.5 mV (0.5 - 40 mV)
Pulse Width Threshold	0.24 ms (0.03-1.59 ms)	0.24 ms (0.03-1.59 ms)

Table 2-9: PCD® Transvene™ System: Comparison of Chronic Pace/Sense Parameters - 2/1/93

PCD® Transvene™ System Performance Comparison Implant Defibrillation Thresholds	
System	**Mean DFT**
PCD™ Transvene™ System*	14.8J
PCD™ Epicardial System	9.8J

* (b)(4) (b)(4)

Table 2-10: PCD® Transvene™ System: Comparison of Implant DFT - 2/1/93

PCD® Transvene™ System Performance Comparison Programmed Defibrillation Pathway		
Defibrillation Pathway	**PCD® Transvene™ System**	**PCD® Epicardial System**
Sequential	574 (75.3%)	251 (33.0%)
Simultaneous	178 (23.4%)	14 (1.8%)
Single	10 (1.3%)	496 (65.2%)

Table 2-11: PCD® Transvene™ System: Comparison of Programmed Defibrillation Pathway - 2/1/93

PCD® Transvene™ System Performance Comparison		
Spontaneous VT Episodes		
	PCD® Transvene™ System	**PCD® Epicardial System**
Mean Follow-Up	11.7 months	16.3 months
Number of Episodes	10,027	20,061
% Overall Efficacy	98.4%	98.3%
% Unsuccessful VT Termination	0.7%	1.0%
Spontaneous VF Episodes		
	PCD® Transvene™ System	**PCD® Epicardial System**
Mean Follow-Up	11.7 months	16.3 months
Number of Episodes	1982	2636
% Overall Efficacy	98.4%	98.7%
% Unsuccessful VF Termination	0.3%	0.5%

Table 2-12: PCD® Transvene™ System: Comparison of Spontaneous VT/VF Episode Efficacy - 2/1/93

PCD® Transvene™ System PCD® Transvene™ System versus PCD® Epicardial System Reported Complications		
Reported Complications	**PCD® Transvene™ System (N = 757)**	**PCD® Epicardial System (N = 742)**
Increased Defibrillation Requirements	1.2%	0.5%
Inappropriate Therapy	-	2.2%
Pace/Sense Related	0.8%	3.5%
Infection Related - Explant	2.9%	2.3%
Lead Related	15.1%	2.8%
Device Related	0.5%	0.9%

Table 2-13: Reported Complications: PCD® Transvene™ System versus PCD® Epicardial System - 2/1/93

PCD® Transvene™ System PCD® Transvene™ System versus PCD® Epicardial System Reported Observations		
Reported Observations	**PCD® Transvene™ System (N = 757)**	**PCD® Epicardial System (N = 742)**
Ineffective Therapy	1.1%	1.1%
Inappropriate Therapy	9.6%	13.6%
Pace/Sense Related	9.0%	14.0%
Infection Related	5.3%	2.5%
Lead Related	2.3%	1.2%
Device Related	-	-

Table 2-14: Reported Observations: PCD® Transvene™ System versus PCD® Epicardial System - 2/1/93

PCD® Transvene™ System Death Classifications PCD® Transvene™ System versus PCD® Epicardial System		
Death Classification	**PCD® Transvene™ System (N=757)**	**PCD® Epicardial System (N=742)**
Sudden Cardiac	5	24
Non-Sudden Cardiac	30	54
All Cardiac	35	78
Noncardiac	16	34
TOTAL	51	112
Perioperative Deaths	5	39

Table 2-15: Death Classifications: PCD® Transvene™ System versus PCD®Epicardial System - 2/1/93

PCD® Transvene™ System Comparison of Actuarial Survival PCD® Transvene™ System versus PCD® Epicardial System			(b)(4)
One Year Survival	**PCD® Transvene™ System**	**PCD® Epicardial System**	
Number of Patients	757	742	
Sudden Cardiac	99.5%	98.9%	
Non-Sudden Cardiac	96.2%	96.7%	(b)(4)
All Cardiac	95.8%	95.7%	
Noncardiac	98.1%	98.0%	
Overall*	93.3%	88.6%	
Perioperative Mortality*	0.7%	5.3%	

* (b)(4) (b)(4)

Table 2-16: Comparison of Actuarial Survival: PCD® Transvene™ System versus PCD® Epicardial System - 2/1/93

3. **An update of the PMA clinical study population must be provided. The update must include the data as presented in the PMA application, and must include the clinical experience in the use of the new anchoring sleeves, which are aimed at decreasing the incidence of dislodgement, and a summary of clinical experience (spontaneous treatment efficacy of ventricular tachycardia (VT) and ventricular fibrillation (VF), observations and complications, number of patient deaths and overall survival) of the patients followed for a year or more.**

RESPONSE:

A. The update of the PMA clinical study population is attached. This population consists of 757 patients entered into the Clinical Trial as of 6-24-92 and followed through 2-1-93 with a mean implant duration of 11.7 months.

B. Clinical Experience of Patients with Two Anchoring Sleeves

Analysis has been completed on 234 patients implanted with the Transvene system using leads that are packaged with two anchoring sleeves. **(NOTE: These 234 patients were enrolled in the Clinical Trial after 6-24-92 and are not included in the 757 patient population).** Table 3-1 contains a data summary for the 234 patients. This group of patients has similar characteristics to the 757 patient population in most areas with a slightly higher percentage of patients with VT reported as the primary indication for implant than the 757 group of patients (60.7% vs 49.8%).

PCD® Transvene™ System Data Summary of Patients with Two Anchoring Sleeves	
Number of Patients	234
Number, % Male Number, % Female	192 82.1% 42 17.9%
Mean Age	60.8 yrs
Primary Indication: SCD VT SCD/VT	 75 32.1% 142 60.7% 17 7.2%
Coronary Artery Disease	180 76.9%
Mean Ejection Fraction	33.1% (N=212)

Table 3-1: PCD® System Data Summary for Patients with Two Anchoring Sleeves

Of these 234 patients, 186 have completed their 1 month follow-up and 49 have completed their 3 month follow-up. There has been one lead dislodgement in this group of patients.

Since the introduction of the dual anchoring sleeve the incidence of lead dislodgement has been dramatically reduced.

C. Clinical Experience of Patients Followed For Greater Than or Equal To One Year

Table 3-3 provides a data summary on the patients followed for a year or more. This table includes patient characteristics, defibrillation pathway configuration, mean LED and DFT, spontaneous VT and VF experience and efficacy. The characteristics of this subset of patients are similar to the original 757 patient population. Patients followed for a year or more had a slightly lower percentage of patients having a history of coronary artery disease (69.2% vs 74.1%) and a slightly higher mean ejection fraction (38% vs 35.6%). The differences are small and are not suspected to have an impact on implant duration or survival. Note that since by definition all patients have been followed for at least one year, the overall survival rate and the sudden cardiac survival rate is 100% at one year.

PCD™ Transvene™ System Data Summary	
	Patients with 12 months of Follow-up
Number of Patients	393
Device Months Follow-up	6454.6
Mean Follow-up Time	16.3 mo
Maximum Follow-up Time	37.4 mo
Number, % Male Number, % Female	310 78.9% 83 21.1%
Mean Age	58.8 yrs
Primary Indication: SCD VT SCD/VT	 150 38.2% 191 48.6% 52 13.2%
Coronary Artery Disease	272 69.2%
Mean Ejection Fraction	357 38.0%
Defibrillation Pathway: Sequential Simultaneous Single	 296 74.9% 93 23.6% 6 1.5%
Mean LED	15.6J (N=365)
Mean DFT	14.3J (N=184)
Spontaneous VT: Number of Patients Number of Episodes % Success	 186 6338 99.0% (6273/6338)
Spontaneous VF: Number of Patients Number of Episodes % Success	 176 1105 98.6% (1090/1105)

Table 3-3: PCD™ System Data Summary - Transvene™ Patients with 12 month Follow-up - 2/1/93

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There have been a total of 7 patient deaths reported in this subset of patients. The deaths occurred greater than 12 months from the date of implant. Table 3-4 summarizes how these patient deaths have been classified.

PCD™ Transvene™ System Summary of Death Classifications in Patients followed for a Year or more	
Classifications	**Number of Deaths**
Sudden Cardiac	0
Non-Sudden Cardiac	4
Noncardiac	3
TOTAL	7

Table 3-4: PCD™ Transvene™ System - Summary of Death Classifications - 2/1/93

Complications and Observations in the patients followed for 1 year or more

The use of a multiprogrammable implantable cardioverter defibrillator (ICD) device allows the physician to resolve most relevant medical events by noninvasively changing programmed parameters thus, avoiding invasive procedures. However, there will continue to be certain relevant medical events which will require invasive procedures for resolution.

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following definitions:

COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

As of February 1, 1993, of the 393 patients with implant durations of greater than or equal to one year, there have been a total of 89 complications reported in 76 patients and 122

observations reported in 99 patients in the PCD™ Transvene™ System patient population. Thus, 19.3% (76/393) of the patients had a clinical event reported which was categorized as a complication vs 19.4% (147/757) in the overall population and 25.2% (99/393) of the patients had a clinical event reported which was categorized as an observation vs 23.8% (180/757) in the overall population.

Table 3-5 summarizes the reported PCD® Transvene™ System complications and observations by category. The reported complications and observations are recognized clinical events that may occur with **any** of the current ICD devices. These complications and observations are discussed in the PCD® device and Transvene™ manual. **None of the reported complications or observations have resulted in a patient death.**

PCD® Transvene System Reported Complications/Observations in Patients followed for 1 Year or more: By Category		
Category	**Complications**	**Observations**
	Num (% of Pts)	Num (% of Pts)
Increased Defibrillation Requirements	3 (0.8%)	2 (0.5%)
Inappropriate VF Therapy Delivery	-	10 (2.5%)
Inappropriate VT Therapy Delivery	-	40 (10.2%)
Loss of Capture	2 (0.5%)	6 (1.5%)
Oversensing	-	29 (7.4%)
Undersensing	-	-
Skin Erosion	2 (0.5%)	1 (0.3%)
Pocket Infection	5 (1.3%)	7 (1.8%)
Seroma	1 (0.3%)	9 (2.3%)
Hematoma	1 (0.3%)	7 (1.8%)
Pneumothorax	2 (0.5%)	1 (0.3%)
Pacemaker Syndrome	-	1 (0.3%)
Perforation	1 (0.3%)	-
Subclavian Vein Thrombosis	-	1 (0.3%)
Lead Fracture	6 (1.5%)	-
Subcutaneous Patch Crinkling	5 (1.3%)	3 (0.8%)
Early Device Explant	3 (0.8%)	-
Total Lead Dislodgement	56 (14.2%)	6 (1.5%)
Total	**89**	**122**

Table 3-5: PCD Transvene System: Reported Complications and Observations - 2/1/93

Table 3-6 contains a description of the lead dislodgements that have occurred in less than 30 days and in greater than 30 days.

PCD® Transvene System Reported Complications/Observations in Patients followed ≥1 Year Lead Dislodgements <30 days and >30 days N=393			
Complications		Observations	
<30 days	>30 days	<30 days	>30 days
27 (6.9%)	29 (7.4%)	0 (0)	6 (1.5%)

Table 3-6: PCD Transvene System: Lead Dislodgements occurring <30/>30 days in patients followed for greater than or equal to one year as of 2/1/93

There have been a total of 29 lead dislodgements reported in patients at greater than 30 days. None of the lead dislodgements resulted in an ineffective therapy for a spontaneous VT or VF episode or patient death. Lead dislodgements were documented by fluoroscopic examination during electrophysiologic evaluation, chest x-ray obtained during routine follow-up, or during pacing/sensing threshold evaluation during routine follow-up. In all 29 cases, reoperation was required to reposition the lead and reestablish an effective defibrillation lead system.

Lead dislodgements are not specific to the PCD® Transvene™ System and have been reported with dual chamber pacemakers and the current market released implantable cardioverter defibrillator (ICD) system. The early history of dual chamber pacemakers witnessed a high lead dislodgement rate of at least 20% (Smyth, PND, et al. Permanent perivenous atrial sensing and pacing with a new J-shaped lead. J Thoracic Cardiovascular Surgery. 1976;72:565-570). Winkle, et al reported that the incidence of dislodgement of the superior vena cava spring leads with the current market release ICD system to be 6.3%. (Winkle, et al. Automatic Implantable Cardioverter-Defibrillator: Efficacy, Complications, and Survival in Patients with Malignant Ventricular Arrhythmias. JACC. June 1988; Vol.11, No.6:1278-86).

In summary, this group represents the majority of the overall population and characteristics of the 393 patients with implant durations of greater than or equal to one year were similar to the overall population.

4. **Please provide a clear description of how you identified the "patient who did not meet the implant criteria." Please discuss your implant criteria and how implant testing attempted to satisfy protocol requirements.**

RESPONSE:

For purposes of the PCD® Transvene™ and Epicardial Systems, the implant criteria was defined as successful VF termination at least 3 times in 4 attempts with the final lead configuration with an output energy of 18 Joules or less.

"Patients who did not meet implant criteria" were defined as:

- Patients who had less than 3 successful VF terminations at 18 Joules or less;
- Patients in whom the lowest energy of success was greater than 18 Joules;
- Patients in whom either 1 or 2 successful VF terminations with the final lead configuration were obtained at 18 Joules or less; and,
- Patients in whom ventricular tachycardia or ventricular flutter was induced at the time of implant.

The PCD® Transvene™ and Epicardial Systems were evaluated through successive inductions and treatment of ventricular tachyarrhythmias according to study protocol. The protocol asked for a minimum of 3 inductions of VF in order to demonstrate reliable defibrillation efficacy at 18 Joules. If the first lead system evaluated successfully defibrillated the patient three consecutive times at 18 Joules or less, the implant criteria would have been satisfied and the implant could be completed. Additional inductions were required if the first lead system was not efficacious at 18 Joules. Performing additional inductions to obtain a defibrillation threshold was **not** a protocol requirement. The attached figure represents the recommended Defibrillation Efficacy Protocol used in lead evaluation testing for the PCD® Transvene™ and Epicardial Systems.

There is a class of patients who cannot tolerate the thoracotomy required for the utilization of the epicardial patch lead defibrillation lead system and are at high risk of sudden cardiac death. Because of the surgical risks and postsurgical complications associated with the implant of an epicardial lead system, implantation in the following patient groups may not be desirable or possible:

(1) Patients in whom there is no indication for concomitant cardiovascular surgery at the time of ICD implant;

(2) Patients with severe pulmonary disease who cannot tolerate prolonged anesthesia or an open chest procedure;

(3) Patients with severe congestive heart failure (ejection fraction < 40%) who are at increased risk for perioperative mortality post a thoracotomy procedure;

(4) Patients who may eventually require open chest procedures of treatment of their coronary artery disease or cardiac transplant.

For these patients, the PCD® Transvene™ System is the only therapy available. The PCD® Transvene™ System simplifies and greatly reduces the risk associated with lead introduction, making therapy available to these patient groups. Because there is no need to open the chest of these patients, options for future therapy remain available; e.g. CABG is associated with decreased morbidity and mortality if there has been no prior open chest procedure.

The investigators felt that for these patients a 10 Joule safety margin between the lowest energy of success (24J) and the maximum output (34J) of the PCD® Device provided adequate defibrillation efficacy evaluation. The investigators used this 10 Joule safety margin as a benchmark based on the clinical experience discussed in the article, Troup, et al. The Implanted Defibrillator: Relation of Defibrillating Configuration and Clinical Variables to Defibrillation Threshold. Journal of American College of Cardiology, 1985; 6:1315-1321. The investigators felt that for these patients the risk associated with not meeting the recommended implant criteria was outweighed by the benefit of not having to undergo an epicardial system implant with a thoracotomy approach and its associated morbidity and mortality.

To determine whether a patient can be defibrillated reliably with a particular lead system, VF must be induced and successfully terminated at least 3 times in 4 attempts with a stored output energy of 18 Joules or less. The following protocol should be followed in assessing defibrillation efficacy:

Defibrillation Efficacy Protocol
(b)(4)

(b)(4)

Lead system testing will be accomplished using an External Cardioverter/Defibrillator (ECVD), Model 2394 or Model 5355.

NOTE: The following precautions should be observed when initiating and treating episodes of ventricular tachyarrhythmias with the Model 2394 External Cardioverter/ Defibrillator:

5. Of the 214 patients who did not meet the implant criteria and yet were implanted with the device, 170 patients had successful defibrillation with 24 Joules (J). Please provide an update of the clinical experience on these patients, as described in item 3 above. Also, please discuss how your proposed labeling will address this protocol deviation. Will implant criteria be changed?

RESPONSE:

Table 5-1 provides the patient characteristics for 170 patients who did not meet the implant criteria but had successful defibrillation at 24 joules and received the PCD™ Transvene™ System.

PCD™ Transvene™ System Patients Meeting Implant Criteria vs 170 Patients with Successful Defibrillation at 24J		
Patient Characteristics		
Number of Patients	170	543
Mean Follow-Up	9.6 months	12.3 months
Male*	151 (88.8%)	422 (77.7%)
Female	19 (11.2%)	121 (22.3%)
Mean Age	59.8 yrs	59.4 yrs
Indication*		
SCD	63 (37.1%)	209 (38.5%)
VT	77 (45.3%)	78 (51.2%)
SCD/VT	30 (17.6%)	56 (10.3%)
Cardiovascular History		
CAD	137 (77.7%)	396 (72.9%) 173
Cardiomyopathy	58 (34.1%)	(31.9%)
Mean EF*	32.7%	36.3%
NYHA Class		
I	45 (27.6%)	164 (30.9%)
II	90 (55.2%)	278 (52.4%)
III	24 (14.7%)	82 (15.4%)
IV	4 (2.5%)	7 (1.3%)

* Statistically Significant ($p \leq 0.05$)

Table 5-1: PCD™ Transvene™ System: Patients Meeting Implant Criteria N = 170 Patient Characteristics - 2/1/93

There was a statistically significant difference in the number of males ($p=0.002$), the number of patients with the primary indication of VT ($p=0.032$), and the mean EF ($p=0.007$) between the groups above however these differences are not clinically significant.

In order to determine if the patient's not meeting implant criteria had higher risk for morbidity and mortality, a comparison of their clinical outcome was made with those patients who did meet the implant criteria. This comparison is provided in Table 5-2. There were no statistical or clinically significant differences in outcome as observed below.

PCD™ Transvene™ System Patients Not Meeting Implant Criteria 170 Patients with Successful Defibrillation at 24J		
Implant Data		
Number of Patients	170	543
Spontaneous VT Episode Efficacy	98.5%	98.7%
Spontaneous VF Episode Efficacy	99.4%	98.7%
Number of Patient Deaths	11	37
Perioperative Mortality	0.6%	0.7%
One Year Survival		
Sudden Cardiac	99.4%	99.5%
Non-Sudden Cardiac	98.6%	95.8%
All Cardiac	98.0%	95.4%
Noncardiac	96.3%	98.5%
Overall	93.8%	93.2%

Table 5-2: PCD™ Transvene™ System: Patients Not Meeting Implant Criteria N = 170 - Clinical Outcome - 2/1/93

Complications and Observations: Patients Not Meeting Implant Criteria N = 170

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following definitions:

COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

Of the 170 patients with successful defibrillation at 24 Joules, as of February 1, 1993, there have been a total of 41 complications reported in 33 patients and 34 observations reported in 31 patients in the PCD™ Transvene™ System patient population. Thus, 19.4% (33/170) of the patients had a clinical event reported which was categorized as a complication and 18.2% (31/170) of the patients had a clinical event reported which was categorized as an observation. The percent of patients with complications reported in the overall population of 757 patients was 19.4% (147/757), the same percentage as in this subgroup of 170. There were 23.8% (180/757) of the patients in the overall population with reported observations, a slightly higher percentage than in this subgroup of 170 patients. Table 5-3 summarizes the reported PCD® Transvene™ System complications and observations by category. The reported complications and observations are recognized clinical events that may occur with any of the current ICD devices. These complications and observations are discussed in the PCD® device and Transvene™ manual. **None of the reported complications or observations have resulted in a patient death.**

PCD® Transvene System Reported Complications/Observations Patients Not Meeting Implant Criteria 170 Patients with Successful Defibrillation at 24J		
Category	**Complications**	**Observations**
	Num (% of Pts)	Num (% of Pts)
Increased Defibrillation Requirements	5 (2.9%)	-
Inappropriate VF Therapy Delivery	-	-
Inappropriate VT Therapy Delivery	-	10 (5.9%)
Loss of Capture	-	5 (2.9%)
Oversensing	-	7 (4.1%)
Undersensing	-	-
Skin Erosion	-	-
Pocket Infection	3 (1.8%)	2 (1.2%)
Seroma	2 (1.2%)	3 (1.8%)
Hematoma	1 (0.6%)	2 (1.2%)
Pneumothorax	-	-
Pacemaker Syndrome	-	-
Perforation	1 (0.6%)	-
Subclavian Vein Thrombosis	1 (0.6%)	1 (0.6%)
Lead Fracture	2 (1.2%)	-
Subcutaneous Patch Crinkling	2 (1.2%)	1 (0.6%)
Early Device Explant	1 (0.6%)	-
Total Lead Dislodgement	23 (13.5%)	3 (1.8%)
Total	41	34

Table 5-3: PCD Transvene System: Reported Complications and Observations - 2/1/93

Table 5-4 contains a description of the lead dislodgements that have occurred in less than 30 days and in greater than 30 days in the 170 patients.

PCD® Transvene System Reported Complications/Observations Lead Dislodgements <30 days and >30 days Patients Not Meeting Implant Criteria 170 Patients with Successful Defibrillation at 24J			
Complications		Observations	
Num (% of Pts)		Num (% of Pts)	
<30 days	>30 days	<30 days	>30 days
9 (5.3%)	14 (8.2%)	1 (0.6)	2 (1.2%)

Table 5-4: PCD Transvene System: Lead Dislodgements <30/>30 days - 2/1/93

There have been a total of 14 lead dislodgements reported in patients at greater than 30 days. None of the lead dislodgements resulted in an ineffective therapy for a spontaneous VT of VF episode or patient death. Lead dislodgements were documented by fluoroscopic examination during electrophysiologic evaluation, chest x-ray obtained during routine follow-up, or during pacing/sensing threshold evaluation during routine follow-up. In the overall patients population of 757, lead dislodgement was reported in 6.5% of the patients implanted for >30 days which is slightly lower than in this subset of patients, 8.2%, which are included in the analysis of the overall population. In all 14 cases, reoperation was required to reposition the lead and reestablish an effective defibrillation lead system.

Lead dislodgements are not specific to the PCD® Transvene™ System and have been reported with dual chamber pacemakers and the current market released implantable cardioverter defibrillator (ICD) system. The early history of dual chamber pacemakers witnessed a high lead dislodgement rate of at least 20% (Smyth, PND, et al. Permanent perivenous atrial sensing and pacing with a new J-shaped lead. J Thoracic Cardiovascular Surgery. 1976;72:565-570). Winkle, et al reported that the incidence of dislodgement of the superior vena cava spring leads with the current market release ICD system to be 6.3%. (Winkle, et al. Automatic Implantable Cardioverter-Defibrillator: Efficacy, Complications, and Survival in Patients with Malignant Ventricular Arrhythmias. JACC. June 1988; Vol.11, No.6:1278-86).

In summary, there are no clinically significant differences in the characteristics and/or most importantly in outcome of the 170 patients

that did not meet implant criteria but were successfully defibrillated with 24 joules and those meeting implant criteria. Based on these data, the recommended defibrillation efficacy implant requirements will be revised to the following:

Two consecutive successful defibrillations with the final lead configuration with a stored output energy of 24 Joules or less; or

Three successful defibrillations in four attempts with the final configuration at a stored output energy of 24 Joules or less.

6. **There were 20 patients among the 214 who did not meet the implant criteria and were implanted without the 10 J safety margin. An update of the spontaneous episode experience in the treatment of VT and VF in these patients and the overall survival must be provided.**

RESPONSE:

There were 20 patients in whom the implant procedure was terminated due to poor patient condition. These patients received a PCD® Transvene™ System without at least a 10 Joule defibrillation safety margin. The mean ejection fraction of this group was 26.9%, indicating a more severe underlying cardiovascular disease, and may have contributed to the physicians decision to terminate the implant procedure prior to meeting the recommended defibrillation implant criteria.

Of these 20 patients, VT or VF has been induced at chronic follow-up visits in 16 patients (80%) and in all cases successful defibrillation with the implanted PCD® Transvene™ System was documented.

The overall spontaneous VT episode efficacy for the patient group was 98.9%. While the overall spontaneous VF episode efficacy for the patient group was 96.0%. Examination of the spontaneous VF episodes indicated that one patient experienced atrial fibrillation that was detected as VF and in whom all four programmed VF therapies were ineffective. This patient's antiarrhythmic drug therapy was modified and there were no further reports of ineffective therapies.

There have been no patients in this patient population who have experienced an actual spontaneous VF episode where all four programmed VF therapies failed to terminate the episode.

There have been two reported patient deaths, both of which were classified as non-sudden cardiac secondary to end stage heart failure. The one year sudden cardiac death survival in this patient population is 100% while the overall one year survival was 85.5%. This lower overall one year survival may be due to the lower mean ejection fraction and poorer cardiac status of this group.

The clinical outcome (which is summarized in the Table 4-1) of these twenty patients was not adversely affected by not meeting the recommended defibrillation implant criteria since there were no reports of failure to terminate a spontaneous VF episode and the overall one year sudden cardiac death survival was 100%.

PCD® Transvene™ System Patients Not Meeting Implant Criteria Due to Patient Condition	
Number of Patients	20
Mean EF	26.9%
# Patients with Induced VT/VF	16 (80%)
Spontaneous VT Episode Efficacy	98.9%
Spontaneous VF Episode Efficacy	96.0%
One Year Sudden Cardiac Death Survival	100%
One Year Overall Survival	85.5%

Table 4-1: PCD® Transvene™ System: Patients Not Meeting Implant Criteria Due to Poor Patient Condition

7. **Table IK-4, page 151, compares the patients meeting the implant criteria to those who did not meet the criteria. However, many of the percentages were presented without numerical support. Please provide the appropriate numbers.**

RESPONSE:

The spontaneous VT and VF episode efficacy and perioperative mortality presented in table IK-4 are percentages, but the survival calculations are probabilities. The survival probabilities are calculated using a life-table survival analysis. For verification of survival probabilities, the data necessary to do calculations is available upon request. The following table is IK-4 with a June 24, 1992 data cutoff, providing you the additional numerical support for percentages where appropriate.

PCD® Transvene™ System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Implant Data		
Data	Meeting Criteria	Not Meeting Criteria
Number of Patients	543	214
Number of Successful VT Episodes Number of VT Episodes Spontaneous VT Episode Efficacy	3619 3657 99.0%	1743 1773 98.4%
Number of Successful VF Episodes Number of VF Episodes Spontaneous VF Episode Efficacy	708 715 99.0%	258 260 99.2%
Number of Patient Deaths	18	4
Perioperative Mortality	4 0.7%	1 0.5%
One Year Actuarial Survival Sudden Cardiac Non-Sudden Cardiac All Cardiac Noncardiac Overall	 100.0% 96.4% 96.4% 99.2% 94.9%	 99.3% 98.6% 97.9% 100.0% 97.4%

Table IK-4: PCD® Transvene™ System: Patients Not Meeting Implant Criteria versus Patients Meeting Implant Criteria - Comparison of Clinical Outcome - 6/24/92

8. **Please provide an update on the patients who are implanted with the Transvene™ System and were not counted in the PMA population. The update must include a summary of the clinical experience as reference in item 3 above.**

RESPONSE:

Overview of Clinical Experience for Transvene Population of 1330 Patients

This response covers a total of 1335 implants in 1330 patients of the PCD™ Device with the Transvene™ Defibrillation Lead System. The patients included in this report includes the 757 patients described in the original PMA application and an additional 573 patients that have been implanted in the U.S. from 6/25/92 to 2/1/93. The first implant occurred internationally on October 20, 1989, and the first implant in the U.S. occurred on October 16, 1990.

The mean implant duration for this patient population is 8.0 months and ranges from implant to 37.4 months. The cumulative implant duration is 10,653.7 months.

The patient population (N=1330) enrolled in the clinical trial was predominately male (81.6%) with a mean age of 60.4 years. In half of the patients (54.5%), the primary indication for implant was recurrent, sustained ventricular tachycardia without an episode of sudden cardiac death. Sudden Cardiac Death was the primary indication for 34.7% of the patients and SCD in combination with recurrent, sustained VT was the primary indication in 10.8%. Coronary artery disease was the primary heart disease in 76.2% of the patient population with a mean reported ejection fraction of 34.3% Table 8-1 provides a data summary on these patients. Although there is a slightly higher percentage of patients with the primary indication of VT, 54.5% vs 49.8% (PMA patient population), there are no substantial differences or trends noted from the original PMA population.

PCD™ Transvene™ System Data Summary of Updated Population N = 1330	
Number of Patients	1330
Device Months Follow-up	10,653.7 mo
Mean Follow-up Time	8.0 mo
Maximum Follow-up Time	37.4 mo
Number, % Male Number, % Female	1085 81.6% 245 18.4%
Mean Age	60.4 yrs
Primary Indication: SCD VT SCD/VT	 462 34.7% 725 54.5% 145 10.8%
Coronary Artery Disease	1014 73.4%
Mean Ejection Fraction	1194 34.3%
Defibrillation Pathway: Sequential Simultaneous Single	 980 73.4% 341 25.5% 14 1.1%
Mean LED	16.4J (N = 1236)
Mean DFT	15.4J (N = 496)
Spontaneous VT: Number of Patients Number of Episodes % Success	 424 11577 98.1%
Spontaneous VF: Number of Patients Number of Episodes % Success	 427 2453 98.6%
One Year SCD Survival	99.3%
Overall Survival	93.0%

Table 8-1: PCD™ Transvene System: Data Summary - Updated Pts. (1330) - 2/1/93

Complications and Observations

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following definitions:

COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

Of the 1330 patients, as of February 1, 1993, there have been a total of 225 complications reported in 195 patients and 275 observations reported in 228 patients in the PCD™ Transvene™ System patient population. Thus, 14.7% (195/1330) of the patients had a clinical event which was categorized as a complication and 17.1% (228/1330) of the patients had a clinical event which was categorized as an observation.

Table 8-2 summarizes the reported PCD® Transvene™ System complications and observations by category. In almost all categories, the percentage of patients in which a complication or observation was reported has decreased compared to the original PMA patient population of 757. The percentage of patients with lead dislodgements reported has substantially decreased from 12% with a complication to 8.8% and 1.6% with an observation to 0.9%. No new categories of complications or observations were reported. The reported complications and observations are recognized clinical events that may occur with **any** of the current ICD devices. These complications and observations are discussed in the PCD® device and Transvene™ manual. **None of the reported complications or observations have resulted in a patient death.**

PCD® Transvene System Reported Complications/Observations By Category N = 1330		
Category	**Complications**	**Observations**
	Num (% of Pts)	**Num (% of Pts)**
Increased Defibrillation Requirements	14 (1.1%)	8 (0.7%)
Inappropriate VF Therapy Delivery	-	17 (1.3%)
Inappropriate VT Therapy Delivery	-	68 (5.1%)
Loss of Capture	6 (0.5%)	16 (1.2%)
Oversensing	1 (0.1%)	83 (6.2%)
Undersensing	-	-
Skin Erosion	5 (0.4%)	1 (0.1%)
Pocket Infection	30 (2.3%)	12 (0.9%)
Seroma	10 (0.8%)	20 (1.5%)
Hematoma	12 (0.9%)	23 (1.7%)
Pneumothorax	2 (0.2%)	1 (0.1%)
Pacemaker Syndrome	-	2 (0.2%)
Perforation	7 (0.5%)	-
Subclavian Vein Thrombosis	1 (0.1%)	6 (0.5%)
Lead Fracture	9 (0.7%)	-
Subcutaneous Patch Crinkling	7 (0.5%)	5 (0.4%)
Early Device Explant	4 (0.3%)	-
Total Lead Dislodgement (n = 1330)	117 (8.8%)	12 (0.9%)
Total	**225**	**275**

Table 8-2: PCD Transvene System: Reported Complications/ Observations (n = 1330) - 2/1/93

Table 8-3 contains a description of the lead dislodgements that have occurred in less than 30 days and in greater than 30 days. As noted earlier, the percentage of patients in which a complication or observation regarding lead dislodgement was reported has decreased from the original PMA patient population of 757.

PCD® Transvene System Reported Complications/Observations Lead Dislodgements <30 and >30 days (N=1330)				
Category	Complications		Observations	
	Num (% of Pts)		Num (% of Pts)	
	<30 days	>30 days	<30 days	>30 days
RV Lead Dislodgement n=1314	19 (1.4%)	13 (1.0%)	0 (0)	1 (0.1%)
CS Lead Dislodgement n= 387	19 (4.9%)	11 (2.8%)	2 (0.5%)	2 (0.5%)
SVC Lead Dislodgement n=989	16 (1.9%)	36 (3.6%)	1 (0.1%)	6 (0.6%)
Total Dislodgement n=1330	57 (4.3%)	60 (4.5%)	3 (0.2%)	9 (0.7%)

Table 8-3: PCD Transvene System: Lead Dislodgements <30/>30 days (n=1330) - 2/1/93

There have been a total of 60 lead dislodgements reported in patients at greater than 30 days. None of the lead dislodgements resulted in an ineffective therapy for a spontaneous VT of VF episode or patient death. Lead dislodgements were documented by fluoroscopic examination during electrophysiologic evaluation, chest x-ray obtained during routine follow-up, or during pacing/sensing threshold evaluation during routine follow-up. In all 60 cases, reoperation was required to reposition the lead and reestablish an effective defibrillation lead system.

Lead dislodgements are not specific to the PCD® Transvene™ System and have been reported with dual chamber pacemakers and the current market released implantable cardioverter defibrillator (ICD) system. The early history of dual chamber pacemakers witnessed a high lead dislodgement rate of at least 20% (Smyth, PND, et al. Permanent perivenous atrial sensing and pacing with a new J-shaped lead. J Thoracic Cardiovascular Surgery. 1976;72:565-570). Winkle, et al reported that the incidence of dislodgement of the superior vena cava spring leads with the current market release ICD system to be 6.3%. (Winkle, et al. Automatic Implantable Cardioverter-Defibrillator: Efficacy, Complications, and Survival in Patients with Malignant Ventricular Arrhythmias. JACC. June 1988; Vol.11, No.6:1278-86).

Patient Deaths

The positive impact of implantable cardioverter defibrillator (ICD) therapy on sudden cardiac death mortality has been well documented in the medical literature. The use of device therapy for the treatment of recurrent ventricular arrhythmias has become an accepted and important clinical tool. An analysis of the sudden cardiac death survival in the PCD™ Transvene™ System patient population was performed.

For purposes of the clinical study, each of the patient deaths was categorized using the following definitions:

Non-Cardiac:	Deaths that occurred where the primary cause of death was determined to be non cardiac in nature, e.g. stroke, cancer, etc.
Cardiac:	Deaths that occurred where the primary cause of death was determined to be cardiac in nature.
Non-Sudden:	Deaths that occur greater than one hour after the onset of symptoms.
Sudden:	Deaths that occur within one hour of the onset of symptoms or where the death is unwitnessed. Sudden cardiac deaths were also categorized as being **Witnessed** or **Unwitnessed.**
Perioperative:	Deaths that occur within thirty days of implant.
System Related:	A death which results from a malfunction (operation not according to design specification) of a PCD™ System component, or as a result of a device induced arrhythmia, or an interaction between a PCD™ System component and the patient.
Procedure Related:	A death which occurs as a result of a procedure required to implant, follow or test a PCD™ System.

All deaths and significant complications have been and will continue to be reviewed by a committee comprised of PCD™ Transvene™ System investigators and other physicians. Two committees (Clinical Event Review Committees) have been formed, one to review North American deaths and complications, and the other to review European clinical events. The primary purpose of these reviews was to determine whether

the PCD™ System was related to the deaths or significant complications that have occurred and, if so, what changes may be required to prevent such events in the future.

There have been a total of 68 patient deaths reported in the PCD™ Transvene™ System patient population. Table 8-4 summarizes how these patient deaths have been classified.

PCD™ Transvene™ System Summary of Death Classifications (n = 1330)	
Classifications	**Number of Deaths**
Sudden Cardiac	10
Non-Sudden Cardiac	37
Noncardiac	21
TOTAL	68

Table 8-4: PCD™ Transvene™ System - Summary of Death Classifications (n = 1330) - 2/1/93

None of the patient deaths were attributed to a malfunction of the PCD™ Transvene™ System.

Actuarial survival analysis on the PCD™ Transvene™ System was done on all patients who were either evaluated for implantation or in whom the device was implanted. Thus, the analysis is done from the perspective of **intention to treat.** Those patients in whom the PCD™ Device was OFF at the time of death or in whom no device was implanted **are** included in the survival analysis. Those patients that were screened for a PCD™ Transvene™ System but failed to receive a Transvene™ system are not included in this analysis.

Projected one year survival calculations for the various death classifications are provided in Table 8-5. **The actuarial projections include perioperative deaths only in the calculation of one year survival from death due to all causes (shown in the row labelled Overall).** The perioperative death rate defined as deaths which occurred within thirty days of implant was 0.8% (10/1330) which is considerably less than the perioperative mortality for the PCD™ System with Epicardial leads (5.3% - 39/742).

PCD™ Transvene™ System One Year Actuarial Survival	
Sudden Cardiac Death	99.3%
Non-Sudden Cardiac	96.3%
All Cardiac	95.6%
Noncardiac	98.1%
Perioperative	0.8%
Overall	93.0%

Table 8-5: PCD™ Transvene™ System - One Year Actuarial Survival - 2/1/93

The positive impact of the PCD™ Transvene™ System on patient mortality is clearly obvious from this analysis. The sudden cardiac death survival rate the total patient group (n = 1330) is 99.3%. This is a marked improvement when compared with the reported survival of similar patient groups treated with drug therapy alone of between 34% and 73% at one year.

In conclusion, the data above for the 1330 patients implanted and followed through 2-1-93 is similar to the 757 PMA patient population as expected. Although lead dislodgement is not an unexpected complication and patients are routinely evaluated during follow-up procedures at follow-up visits, in order to minimize the incidence of lead dislodgement, the dual anchoring sleeve has been introduced and the incidence of lead dislodgement has drastically decreased. The one year actuarial survival results continue to be stable, above 99% for SCD and efficacy rates continue at greater than 98%.

9. **Based on your study protocol, please differentiate between defibrillation threshold (DFT) testing and lowest energy to defibrillate (LED) testing. Based on the individual patient report forms of the 757 patients, how many patients underwent what is described as DFT testing and how many had LED testing? Samples of the patient report forms showing the scheme of testing which was categorized as DFT and LED testing must be provided. Please discuss how the DFT and LED data were reported and presented in the PMA application.**

RESPONSE:

The study protocol asks the investigator to determine the efficacy of the implanted lead system with the external test device prior to connecting the leads to the implantable PCD® device. The minimum amount of testing required to demonstrate lead system efficacy is 3 of 4 successful defibrillations at 18 Joules. The protocol asks that investigators go beyond this minimal level and perform testing using a step down procedure. Investigators attempt defibrillation at energy levels lower than 18 Joules in order to establish a defibrillation threshold. In order to make defibrillation testing uniform among the investigators, the protocol asks that testing be done using a common step down protocol. This protocol is as follows:

(b)(4)

(b)(4)

All investigators were asked to perform this step down testing, but the investigator was allowed to stop the step down testing, or waive it completely, if, in the investigators opinion, the patient could not tolerate

additional VF inductions. Since testing did not always follow this step down protocol, two terms were developed to accurately report defibrillation efficacy, Lowest Energy of Defibrillation (LED) and Defibrillation Threshold (DFT). They are defined as follows:

Lowest Energy of Defibrillation (LED):
LED is defined as the lowest programmed energy that successfully defibrillated the heart with the implanted lead system.

Defibrillation Threshold (DFT):
DFT is defined as the lowest programmed energy which successfully defibrillated the heart provided there is a failure at an energy below the lowest success or a success at $\leq$ 5J.

Based on these definitions all patients with a DFT also have an LED but not every patient with an LED has a DFT.

Several examples of the type of data used in this analysis is presented below. The first example shows successful completion of the step-down protocol with the first lead system tested. By having a success at 5 Joules this patient has both a DFT and LED of 5 Joules. This example also shows the various codes used in this section of the data forms.

5. Lead Evaluation Log **DFT and LED = 5 Joules**

Lead System Number	Episode Number	Therapy Number	Induced Rhythm	Therapy Data*	Post Therapy Rhythm	
(b)(4)						

(b)(4)

The next example shows a failure at 5 Joules. This patient, therefore, has a DFT and LED of 10 Joules.

5. Lead Evaluation Log **DFT and LED = 10 Joules**

Lead System Number	Episode Number	Therapy Number	Induced Rhythm	Therapy Data*	Post Therapy Rhythm	
(b)(4)						

(b)(4)

The next example is one where the investigator decided to stop lead evaluation before reaching an energy low enough to demonstrate failure to defibrillate. The implant criteria was met since there was three successes at 18 Joules or less. Since a failure was never demonstrated, we are unable to calculate a DFT, only an LED. The LED in this example is 10 Joules.

5. Lead Evaluation Log **LED = 10 Joules**

Lead System Number	Episode Number	Therapy Number	Induced Rhythm	Therapy Data*	Post Therapy Rhythm	
(b)(4)						

(b)(4)

Typically, more than one lead system is evaluated. The lead systems are described on the previous page of the "Lead System Evaluation Data Form" and identified by number. Every induction and therapy delivered into the lead system is recorded on the "Lead Evaluation Log". This is an example of a difficult patient that required two modifications to the lead system before an efficacious system was found. This patient had an LED of 18 Joules and no DFT. Since defibrillation testing was not performed at an energy less than 18 Joules, a failure level was not established.

MEDTRONIC CONFIDENTIAL

5. Lead Evaluation Log LED = 18 Joules						
Lead System Number	Episode Number	Therapy Number	Induced Rhythm	Therapy Data*	Post Therapy Rhythm	
(b)(4)						

(b)(4)

Table VID-8 on page 213 of the PMA clinical report shows the LED for the lead configurations tested at implant. Below is an updated Table VID-8 based on 757 patients.

PCD™ Transvene™ System Lowest Energy of Defibrillation	
All Lead Systems: N	703
Mean	16.0
Std. Dev.	5.1
Maximum	34
Minimum	0.6
RV-SVC-SQ: N	456
Mean	16.7
Std. Dev.	4.8
Maximum	34
Minimum	3
RV-CS-SQ: N	210
Mean	14.6
Std. Dev.	5.6
Maximum	34
Minimum	0.6
RV-CS-SVC: N	37
Mean	15.2
Std. Dev.	4.9
Maximum	34
Minimum	10

Table VID-8: PCD™ Transvene™ System - Lowest Energy of Defibrillation - 6/24/92

Seven-hundred-three (703) patients had at least one successful defibrillation with the lead system implanted during lead system testing. During the remaining 59 implant procedures (762-703=59) the patient either could not be induced into VF during implant lead testing, only V-Flutter or VT, or testing of the final lead system was waived due to patient condition.

A subset of patients were evaluated with the step-down protocol and either had a defibrillation failure at an energy below 18 Joules or was successful at 5 Joules. A defibrillation threshold (DFT) was calculated in this group of patients. This calculation was performed by Medtronic's statisticians from the information recorded on the study data forms. DFT is defined as the lowest programmed energy which successfully defibrillated the heart provided there is a failure at an energy below the lowest success or a success at $\leq$ 5J. There was no requirement to find the lowest DFT possible in a particular patient.

DFT's were obtained during 316 of the 762 implant procedures presented in this report. Table VID-9 on page 215 of the PMA clinical report contains the DFT's obtained during implant testing.

PCD™ Transvene™ System
Defibrillation Threshold (DFT)

(b)(4)

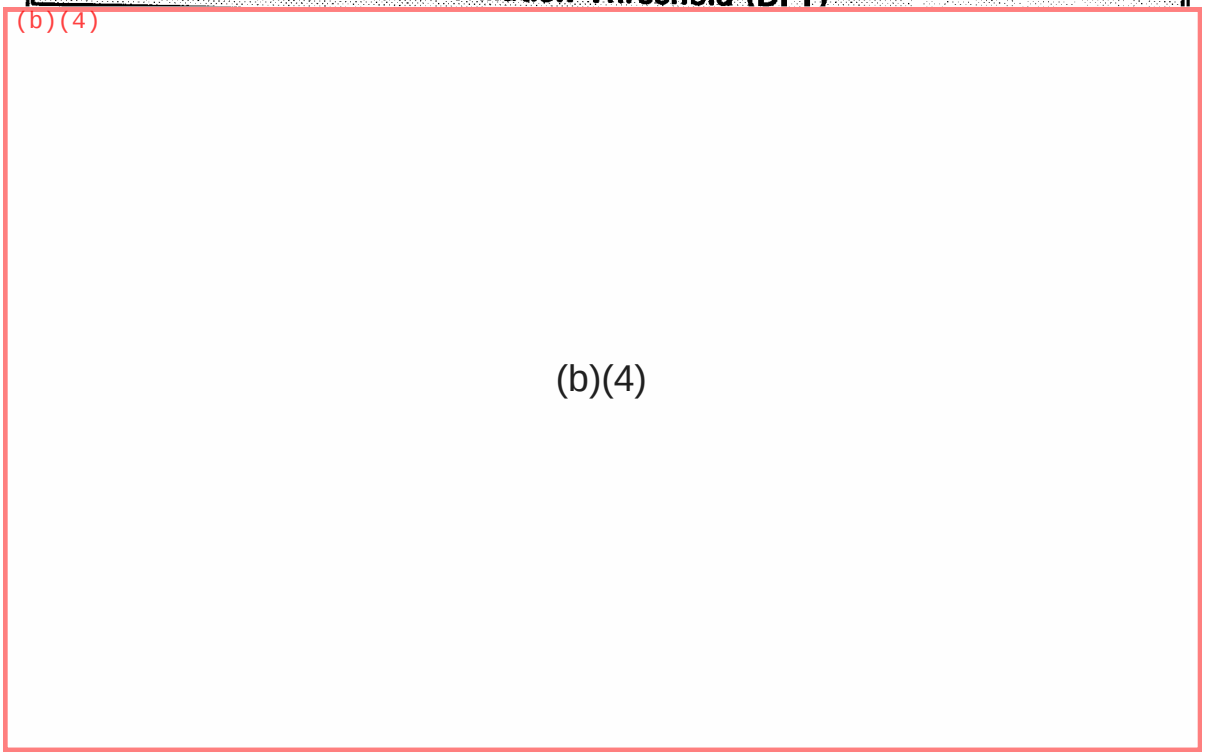


Table VID-9: PCD™ Transvene™ System - Defibrillation Threshold - 6/24/92

In summary the Lowest Energy of Defibrillation (LED) is defined as the lowest programmed energy that successfully defibrillated the patient with the implanted lead system. Defibrillation Threshold (DFT) is defined as the lowest programmed energy which successfully defibrillated the heart provided there is a failure at an energy below the lowest success or a success at $\leq$ 5J. An LED was determined during 703 of the 762 implant procedures included in the September 18, 1992 clinical update. In 316 of these implant procedures we were also able to calculate a DFT. Three-hundred-eighty-seven (387) (703-316=387) implant procedures had only an LED determined, since a failure level was never established.

10. **There is a statistically significant difference between the mean DFT obtained with the RV-CS-SQ lead configuration and the mean DFT obtained with the other lead configurations. How do you account for this difference? Was the DFT as reported and discussed for all lead configurations obtained using an identical or similar scheme? Please discuss. You must document that there were no significant differences between the scheme for performing DFT and LED testing between the Transvene™ and PCD® Epicardial patient populations, if that is the case.**

RESPONSE:

There was a statistically significant difference between the mean DFT obtained with the RV-CS-SQ lead configuration and the mean DFT obtained with the other lead configurations. Since there were no differences in the patient population implanted with any of the 3 lead configurations, this may be a configuration that results in lower DFTs than the other configurations. In theory, this may be due to better defibrillation current distribution throughout the myocardium. There is no intent to show that a lower DFT results in a better patient outcome. The premise of the PCD® Epicardial and Transvene™ studies was to demonstrate that if a patient was evaluated at implant and shown to meet implant criteria, that they would be reliably defibrillated over time, and therefore, have a high probability of survival from SCD regardless of which lead system or defibrillation pathway was chosen. We have shown that freedom from SCD at one year is at least equivalent to that afforded by the commercially available AICD for patients who meet the implant criteria regardless of lead system. As was described in Deficiency Response No. 5. Our data demonstrates that there is no difference in outcome between patients who met our 18J implant criteria (3/4 at $\leq$ 18J) or those with a 10J safety margin (at least one success at 24J). The DFT as reported for all Transvene™ and all Epicardial Systems was obtained using the same testing scheme. Please see Deficiency Response Number 9 for a thorough discussion of DFT and LED testing.

As previously discussed in the response to Deficiency #4, implanted defibrillation lead systems were evaluated through successive inductions and treatment of ventricular tachyarrhythmias according to study protocol. The protocol asked for a minimum of 3 inductions of VF in order to demonstrate defibrillation efficacy. The attached table represents the recommended Defibrillation Efficacy Protocol that was used to evaluate **all** lead configurations.

The recommended implant criteria and Defibrillation Efficacy Protocol was **identical** for both the PCD® Transvene™ and Epicardial Systems. References from the investigational plan (provided in IDE submissions for both systems) for the PCD® Transvene™ and Epicardial Systems are attached.

To determine whether a patient can be defibrillated reliably with a particular lead system, VF must be induced and successfully terminated at least 3 times in 4 attempts with a stored output energy of 18 Joules or less. The following protocol should be followed in assessing defibrillation efficacy:

Defibrillation Efficacy Protocol
(b)(4)

(b)(4)

Lead system testing will be accomplished using an External Cardioverter/Defibrillator (ECVD), Model 2394 or Model 5355.

NOTE: The following precautions should be observed when initiating and treating episodes of ventricular tachyarrhythmias with the Model 2394 External Cardioverter/ Defibrillator:

32

070

08/10/92
UPDATE-
NTL

INVESTIGATIONAL PLAN

MODEL 7217B PCD
PACER-CARDIOVERTER-DEFIBRILLATOR WITH
NON-THORACOTOMY LEAD SYSTEMS

A. STUDY PURPOSE

(b)(4)

(b)(4)

To determine whether a patient can be defibrillated reliably with a particular lead system, VF must be induced and successfully terminated at least 3 times in 4 attempts with a stored output energy of 18 Joules or less. The following protocol should be followed in assessing defibrillation efficacy:

Defibrillation Efficacy Protocol

(b)(4)

(b)(4)

Lead system testing will be accomplished using an External Cardioverter/Defibrillator (ECVD), Model 2394 or Model 5355.

NOTE: The following precautions should be observed when initiating and treating episodes of ventricular tachyarrhythmias with the Model 2394 External Cardioverter/ Defibrillator:

4/6/92
PVE

INVESTIGATIONAL PLAN

MODEL 7217B PCD
PACER-CARDIOVERTER-DEFIBRILLATOR SYSTEM
WITH EPICARDIAL PATCH LEADS

(b)(4)

(b)(4)

(b)(4)

(b)(4)

DEFIBRILLATION EFFICACY PROTOCOL

(b)(4)

(b)(4)

075

11. Please elaborate on how the comparison of DFTs obtained from the PCD® Epicardial Lead study and the Transvene™ study can be considered as a valid comparison in that the majority of the patients (574 (75.3 percent)) in the Transvene™ study were programmed with the sequential pathway and 178 (23.4 percent) were programmed via the simultaneous pathway. The majority of the patients (496 (65.2 percent)) in the PCD® Epicardial study were programmed with the single pathway. Based on your PCD® Epicardial study, please discuss the DFTs or energy requirements obtained with the use of the single defibrillation pathway versus the sequential and simultaneous pathways.

RESPONSE:

The premise of the PCD® Epicardial and Transvene™ studies was to demonstrate that if a patient was evaluated at implant and shown to meet implant criteria, that they would be reliably defibrillated over time, and therefore, have a high probability of survival from SCD regardless of which lead system or defibrillation pathway was chosen. The Epicardial System is a valid comparison since the same PCD® was used in both systems, the same indications were used, the same implant criteria, the same protocol and data requirements and the studies were performed concurrently at the same centers. There is no other system that is currently market released that is a better, or more applicable control. We have shown for both studies that freedom from SCD at one year is at least equivalent to that afforded by the commercially available AICD for patients who meet the implant criteria regardless of lead system. All of the transvenous defibrillation systems that are available are currently under investigation and as such, limited or no data exists with which to compare our performance. A discussion of DFTs or energy requirements obtained with the use of the single defibrillation pathway versus the sequential and simultaneous pathways is found in the PCD® Epicardial IDE G870102. In Section VII, Page 25 of the Clinical Summary report, it was shown that the DFTs were similar. A copy of that page is provided here for your convenience. The two patch (single pathway) DFT mean was 10.5J. The three patch (sequential/simultaneous) DFT mean was 8.8J. There was no difference in the outcome of patients with either of the systems.

Table VII-7 illustrates the lowest energy of defibrillation (LED) and defibrillation threshold (DFT) for the implanted lead systems. As noted previously, the implant criteria for the PCD™ Device was 3 of 4 episodes of VF successfully terminated at 18 Joules or less with a given lead configuration. As the DFT and LED indicate, VF was reliably terminated at an energy below the maximum output (34 Joules) of the PCD Device.

PCD Epicardial System Defibrillation Efficacy by Lead System		
Implant Frequency	**LED**	**DFT**
All Lead Systems	11.9J	9.8J
2 Patch System	12.5J	10.5J
3 Patch System	10.6J	8.8J

Table VII-7: PCD Epicardial System Defibrillation Efficacy by Lead System - 5/14/92

Of the 742 patients screened for a PCD Epicardial System, 92 patients (12.4%) received the system despite not meeting the recommended defibrillation implant criteria. The investigators felt in every case that the testing performed at the time of implant, though it did not meet the recommended implant criteria, demonstrated adequate defibrillation efficacy for implantation of the PCD Epicardial System.

A safety margin of at least 10 Joules between the successful defibrillation energy (24 J or less) and the maximum output of the PCD Device (34 Joules) was provided in 90% of the patients. The investigators utilized this 10 Joule safety margin as a benchmark based on the clinical experience discussed in the article, Troup., et al. The Implanted Defibrillator: Relation of Defibrillating Lead Configuration and Clinical Variables to Defibrillation Threshold. Journal of American College of Cardiology 1985; 6:1315-1321.

It is important to note that there was no statistical difference in overall spontaneous VT/VF episode efficacy and one year sudden cardiac death survival in patients who did not meet the recommended defibrillation implant criteria versus those patients who did meet the recommended implant criteria.

12. Please discuss the time between detection and delivery of therapy of the Transvene™ System versus the PCD® Epicardial System.

RESPONSE:

The time between the start of detection and delivery of therapy is dependent on the programmable VT/VF detection and therapy parameters and **not** on the implanted defibrillation lead system.

A representative VT episode duration can be determined by using the most frequently programmed parameters for VT detection and therapy during the clinical trial. For both the PCD® Transvene™ and Epicardial System the most frequent VT detection and therapy parameters were as follows:

(b)(4)

(b)(4)

For both the PCD® Transvene™ and Epicardial System, the majority (90%) of spontaneous VT episodes were terminated with VT Therapy #1. Using the above listed parameters a VT episode would last 8.4 seconds in patient receiving one sequence of antitachycardia pacing and 25.2 seconds in a patient requiring all three sequences for termination of the VT episode. Note, that after each delivery of a pacing sequence the PCD® Device needs to redetect ventricular tachycardia. If VT Therapy #2 (cardioversion) was required for termination of the episode, the episode duration would be 32.6 seconds.

A representative VF episode duration can be determined by using the most frequently programmed parameters for VF detection and therapy during the clinical trial. For both the PCD® Transvene™ and Epicardial System the most frequent VF detection and therapy parameters were as follows:

(b)(4)

(b)(4)

For both the PCD® Transvene™ and Epicardial System, the majority (90%) of spontaneous VF episodes were terminated with VF Therapy #1. Using the above listed parameters a VF episode would last 11.8 seconds in patient requiring VF Therapy #1 for successful reversion. If VF Therapy #2 was required for termination of the episode, the VF episode duration for both the PCD® Transvene™ and Epicardial System would be 20.6 seconds.

Since both the PCD® Transvene™ and Epicardial System patients were programmed to similar VT/VF detection and therapy parameters as well as the majority of spontaneous VT/VF episodes being terminated with Therapy #1, there is no difference in the time between start of detection and delivery of therapy for the two systems.

13. On page 125 of the application, please explain and/or discuss what is meant by "a 2:1 VF sensing margin", how it is determined, and if the patients met the criteria.

RESPONSE:

As previously described in the PCD® Transvene™ System PMA application as well as responses to deficiencies on the PCD® Epicardial System (PMA P900061, Submission dated 10/30/91), analysis of appropriate sensing and detection of VF is performed at the time of implant as well as during the course of follow-up. The goal of this testing is to ensure appropriate VF sensing and detection on an acute and chronic basis.

During defibrillation testing, the Model (b)(4) is programmed to a sensitivity value of (b)(4) which is (b)(4) times the nominal sensitivity setting (b)(4) of the Model (b)(4) Device. During VF inductions, the VF electrogram and corresponding Marker Channels which are available from the Model (b)(4) and (b)(4) are monitored and the majority of the VF signals (b)(4) should have an amplitude equal to or greater than (b)(4)

For the sensitivity parameter, the programming recommendations recommend a programmed value of (b)(4) Using the described testing, this would provide a (b)(4) sensing margin. In other words, appropriate sensing of VF was documented at a value (b)(4) times **less** sensitive than the programmed value and would provide a (b)(4) step safety margin when the PCD® Device is programmed to (b)(4) If the PCD® Device was programmed to a sensitivity value of (b)(4) the described testing would provide a 2:1 VF sensing margin. In other words, appropriate VF sensing was documented at a value (b)(4) times **less** sensitive than the programmed value and would provide a (b)(4) step safety margin when the PCD® Device is programmed to (b)(4) In both of these cases, implant testing and sensitivity value programming allows for changes in the VF electrogram amplitude without impacting appropriate VF sensing and detection.

All of the patients who received the PCD® Transvene™ System met the 2:1 VF sensing margin. At the last known follow-up, 76.6% of the patients were programmed to (b)(4) sensitivity (b)(4) VF sensing margin) and 22.3% were programmed to (b)(4) (b)(4) VF sensing margin). In addition, there have been no reports of undersensing during induced episodes of VF as well as no reported patient deaths due to lack of detection of a spontaneous VF episode.
This clinical experience indicates that the recommended VF sensing implant criteria has provided safe and effective evaluation of VF sensing at implant and ensured chronic appropriate VF sensing.

14. **Of the 329 patients who were followed for 6 months, 130 patients had spontaneous episodes. What was the average number of VT and VF episodes per patient? Of the patients followed for a year, how many had spontaneous episodes of VT and VF and what was the mean number of episodes of VT and VF and what was the mean number of episodes per patient in this group?**

RESPONSE:

Using the June 24, 1992 data cutoff there were 329 patients followed for 6 months or longer. Of the 329 patients, 130 patients had a spontaneous VT episode with a mean of 28.9 (3752/130) episodes per patient and 120 patients had a spontaneous VF episode with a mean of 5.6 (667/120) episodes per patient. A total of 179 patients had either spontaneous VT or VF episodes with a mean of 24.7 (4419/179) episodes per patient.

Of the 115 patients followed for 12 months or longer, 60 patients had a spontaneous VT episode with a mean of 29.5 (1770/60) episodes per patient and 37 patients had a spontaneous VF episode with a mean of 6.7 (248/37) episodes per patient. A total of 67 patients had either spontaneous VT or VF episodes with a mean of 30.1 (2018/67) spontaneous episodes per patient.

15. **On page 130, Table IF-4, you report that there were 5,362 episodes of VT successfully terminated. On page 131, paragraph 2, you state that 25 patients experienced 45 (0.8 percent) episodes of sinus tachycardia or atrial fibrillation. Are these patients included in the success or failure category? Nine hundred and sixty-four episodes of VF were reported, however, 75 episodes were not actual VF. You must clarify how the successful and ineffective therapies and failures are discerned and categorized. Please prepare a table which includes a category of ineffective therapies with actual patient numbers and percentages. In addition, what assurance is there that an episode of supraventricular tachycardia or atrial fibrillation is not misinterpreted as VT or VF by the physician and considered a successful therapy?**

RESPONSE:

For purposes of this clinical trial, spontaneous VT and VF episodes were defined as those episodes that **satisfied the programmed** VT and VF detection criteria. Specifically, all programmed VT and VF detection criteria must be fulfilled to detect an episode. Successful termination of the episode was defined as satisfying the VT/VF episode termination criteria. All spontaneous VT and VF episodes detected and treated by the PCD® Device are used in determining therapy efficacy. An ineffective episode is defined as VT or VF episode detected by the PCD® Device in which all four programmed therapies failed to successfully terminate the episode. Spontaneous episode efficacy is determined by the following ratio: **Number of TOTAL Episodes Successfully Terminated by PCD® Device/Number of TOTAL Episodes Detected by the PCD® Device.** The attached PCD® Device telemetry printouts provide examples of how spontaneous episode efficacy is determined.

For those episodes where all four programmed VT/VF therapies failed to terminate the episode, the clinical follow-up data form was reviewed for investigator's comments on the episode. The investigator reviewed the patient's symptoms at the time of the episode as well as the stored episode information provided by the PCD® Device and indicates on the clinical dataform whether the ineffective therapy was due to a nonventricular tachyarrhythmia such as sinus tachycardia or atrial fibrillation. If there is no such indication on the clinical dataform, it is assumed that the ineffective therapy was for a spontaneous VT or VF episode. It should be noted that for all current ICD Systems, the delivery of inappropriate therapy for atrial fibrillation or sinus tachycardia is a known risk of the therapy.

The Table 15-1 summarizes the spontaneous VT/VF episode experience on 757 patients with a cutoff date of February 1, 1993. The discussion that follows provides additional data on these episodes.

PCD® Transvene™ System Spontaneous VT and VF Episode Experience		
Spontaneous VT Experience		
Category	**# Episodes**	**# Patients**
Overall Experience	10,027	316
Successfully Terminated Experience	9864/10,027 (98.4%)	256
Ineffective Episode Experience	163/10,027 (1.6%)	60
Ineffective Episode Due to Atrial Fibrillation	33/10,027 (0.3%)	16
Ineffective Episode Due to Sinus Tachycardia	62/10,027 (0.6%)	23
Ineffective Episode Due to VT	68/10,027 (0.9%)	21
Spontaneous VF Episode Experience		
Category	**# Episodes**	**# Patients**
Overall Experience	1982	317
Successful Terminated Experience	1951/1982 (98.4%)	301
Ineffective Episode Experience	31/1982 (1.6%)	16
Ineffective Due to Atrial Fibrillation	11/1982 (0.55%)	4
Ineffective Due to Sinus Tachycardia	7/1982 (0.4%)	4
Ineffective Due to Afib and Sinus Tachycardia	4/1982 (0.2%)	1
Ineffective Due to Lead Performance	2/1982 (0.1%)	2
Ineffective at Monitored Death	2/9182 (0.1%)	1
Ineffective Episode Due to VF	5/1982 (0.25%)	4

Table 15-1: PCD® Transvene™ System Spontaneous Episode Experience - 2/1/93

Spontaneous VT Episode Experience

To date, 10,027 spontaneous episodes of VT have been detected by the PCD® Device in 316 patients. Most spontaneous VT episodes (90.7%) were successfully treated with VT Therapy #1 and 98.4% were successfully treated with one of the four programmable VT therapies.

Sixty patients experienced 163 episodes in which the PCD® Device was ineffective in terminating a spontaneous episode of VT despite delivery of all four programmed therapies. Sixteen (16) patients experienced 33 episodes of atrial fibrillation with a rapid ventricular response that was not "successfully treated" by the PCD® Device. Twenty-three (23)

patients experienced 62 episodes of sinus tachycardia that was not "successfully treated" by the PCD® Device. It should be noted, that the possibility of inappropriate VT therapy delivery due the detection of atrial fibrillation with rapid ventricular response or sinus tachycardia that meets the programmed VT detection criteria is a known risk for all current ICD Systems.

And finally, twenty-one patients experienced 68 episodes of spontaneous VT in which the programmed VT therapies were ineffective in terminating a spontaneous episode. No patient deaths occurred as a result of ineffective VT therapy. Reprogramming and pharmacologic intervention resolved these events. The table provided at the end of this response summarizes this experience.

Spontaneous VF Episode Experience

To date, 1982 spontaneous episode of VF have been detected by the PCD® device in 317 patients. Most (89.1%) spontaneous VF episodes were successfully treated with VF Therapy #1 and 98.4% were successfully treated with one of the four programmable VF therapies.

Sixteen (16) patients experienced 31 episodes in which the PCD® Device was ineffective in terminating a spontaneous VF episode of VF despite delivery of all four programmed VF therapies. Four (4) patients experienced 11 episodes of atrial fibrillation with a rapid ventricular response that was not "successfully treated" by the PCD® Device. Four (4) patients experienced 7 episodes of sinus tachycardia that was not "successfully treated" by the PCD® Device. One patient experienced 4 episodes of both atrial fibrillation and sinus tachycardia that was not "successfully treated" by the PCD® Device. It should be noted, that the possibility of inappropriate VT therapy delivery due the detection of atrial fibrillation with rapid ventricular response or sinus tachycardia that meets the programmed VT detection criteria is a known risk for all current ICD Systems.

In addition, there were three (3) patients who experienced ineffective therapy for a spontaneous VF episode due to lead performance or secondary to a terminal event. One patient experienced one episode of ineffective VF therapy due to lead dislodgement, a second patient experienced one episode of ineffective VF therapy due lead fracture which generated "noise" which was classified by the PCD® Device as "VF" and the third patient experienced two episodes of ineffective therapy at the time of his monitored death.

And finally, four patients experienced 5 episodes of spontaneous VF in which the programmed VF therapies were ineffective in terminating a

spontaneous VF episode. In three patients, these events were resolved with reprogramming or pharmacologic intervention and as of the last known follow-up these patients remain alive and have had no further ineffective VF therapies.

The last of the four patients experienced cardiac arrest at home and was found by the paramedics to be in sinus rhythm. While on monitor the patient developed VF and the PCD® Device appropriately detected and terminated the episode. However, the patient developed EMD and upon admission to the ER was pronounced dead on arrival.

The overall success rate of the PCD® Transvene™ System in terminating spontaneous episodes of either VT or VF was 98.4%. Table 15-2 provides as summary of spontaneous episode efficacy.

PCD® Transvene™ System Spontaneous VT/VF Episode Efficacy	
Spontaneous VT Episodes	
Number of Episodes	10,027
% Overall Efficacy	98.4% (9864/10,027)
% Unsuccessful Due to VT	0.7% (68/10,027)
% Unsuccessful Due to Non VT Arrhythmias	0.9% (95/10,027)
Spontaneous VF Episodes	
Number of Episodes	1982
% Overall Efficacy	98.4% (1951/1982)
% Unsuccessful Due to VF	0.3% (5/1982)
% Unsuccessful Due to Non VF Arrhythmias	1.3% (26/1982)

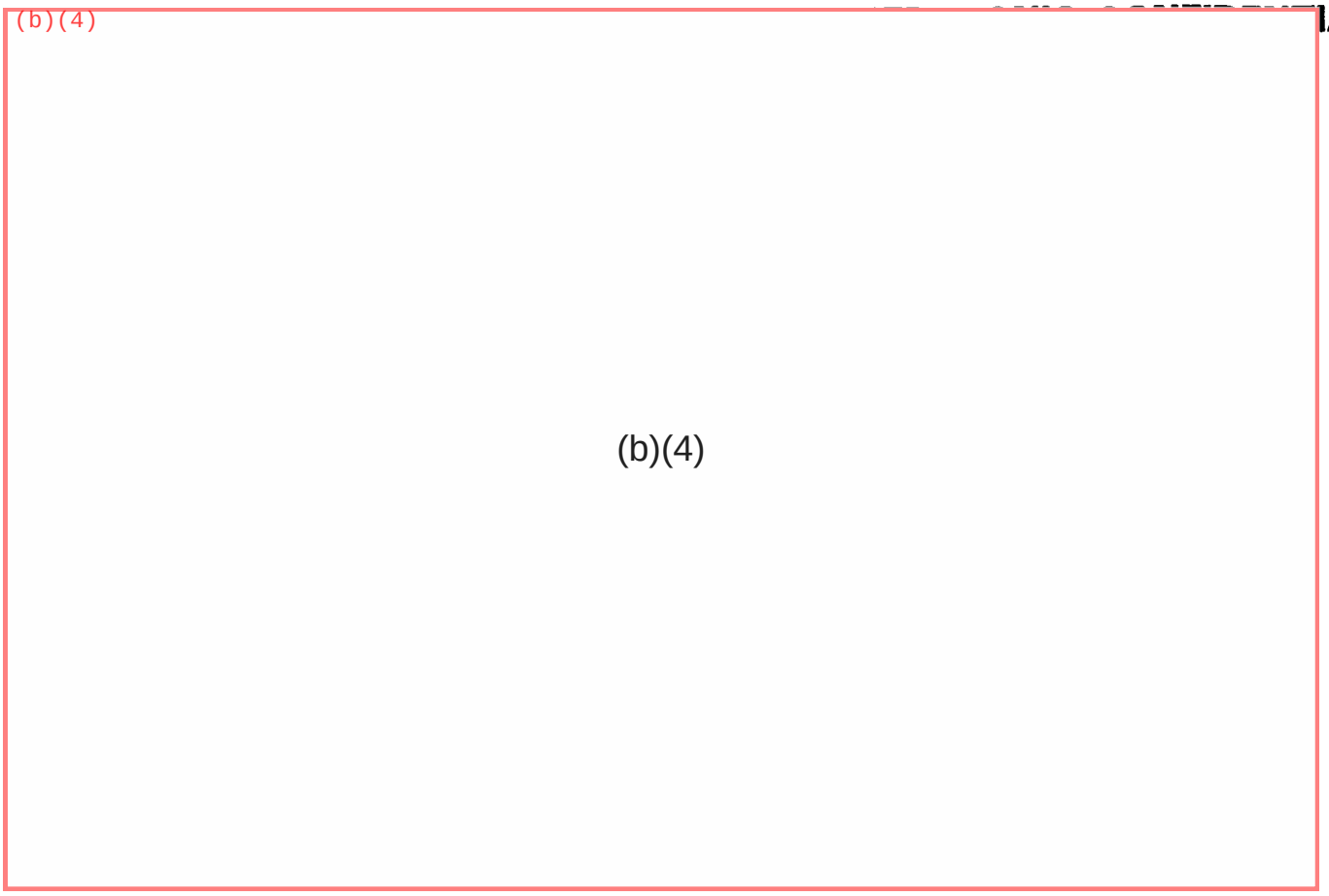
Table 15-2: PCD® Transvene™ System Spontaneous VT/VF Episode Efficacy

The physicians who are investigators in our study are all highly trained and are qualified by their education and experience to evaluate ICD performance. These physicians are the experts and leaders in their field and, as such, their interpretation of the data is considered the state of the art. Also, as the PCD is not designed nor intended to treat atrial arrhythmias, it is unlikely that the ventricular arrhythmia therapy from the PCD would terminate a ventricular arrhythmia. If an atrial arrhythmia was misinterpreted as a ventricular arrhythmia, the PCD therapy would likely be ineffective and this would, therefore, lower the reported percent success for PCD® therapies.

(b)(4)

(b)(4)

(b)(4)



10 Intervals Post LAST THERAPY Delivered

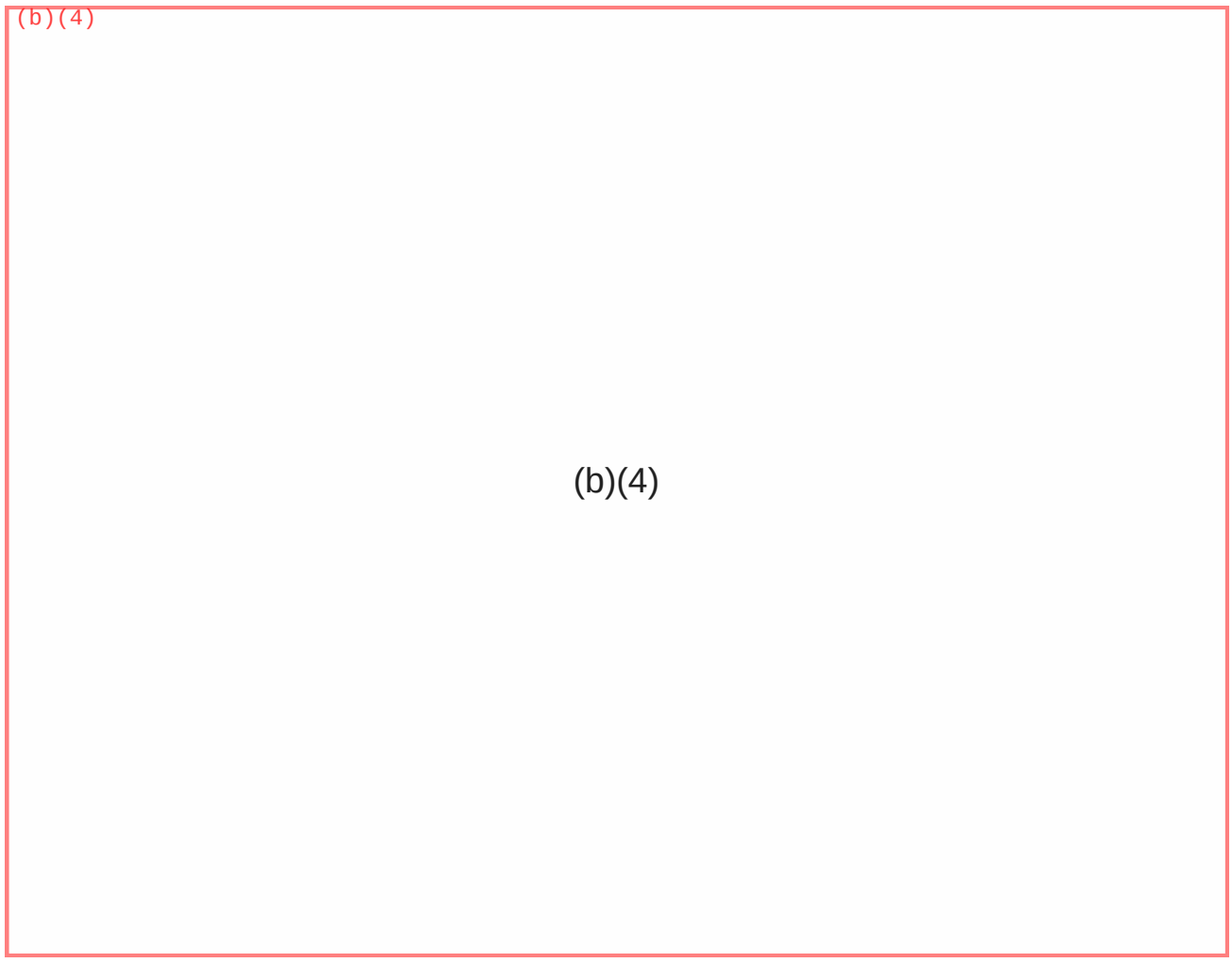
EVENTS AFTER LAST THERAPY:
+0. VT THERAPY #1 DELIVERED
+1. R-R INTERVAL- 1000 MS
+2. R-R INTERVAL- 1060 MS
+3. R-R INTERVAL- 670 MS
+4. R-R INTERVAL- 650 MS
+5. R-R INTERVAL- 660 MS
+6. R-R INTERVAL- 660 MS
+7. R-R INTERVAL- 670 MS
+8. R-R INTERVAL- 670 MS
+9. R-R INTERVAL- 650 MS
+10. R-R INTERVAL- 660 MS
+10. THERAPY WAS SUCCESSFUL

VF EPISODE TELEMETRY

(b)(4)

(b)(4)

(b)(4)



EVENTS AFTER LAST THERAPY:
+0. VF THERAPY #1 DELIVERED
+1. R-R INTERVAL- 1000 MS
+2. R-R INTERVAL- 1200 MS
+3. R-R INTERVAL- 1000 MS
+4. R-R INTERVAL- 700 MS
+5. R-R INTERVAL- 950 MS
+6. R-R INTERVAL- 1140 MS
+7. R-R INTERVAL- 1160 MS
+8. R-R INTERVAL- 1150 MS
+9. R-R INTERVAL- 1040 MS
+10. R-R INTERVAL- 860 MS
+10. THERAPY WAS SUCCESSFUL

■

10 Intervals After
LAST THERAPY DELIVERED

089

16. **Table IM-6, page 173 must be modified to include a column on inappropriate therapy or therapies delivered as the device was programmed so that the percentages add up to 100 percent.**

RESPONSE:

Table IM-6 has been modified to include rows for episodes that were unsuccessfully terminated but classified as Atrial Fibrillation or Sinus Tachycardia. Unsuccessful termination of an episode was defined as episodes in which the PCD® Device was ineffective in terminating a spontaneous episode despite delivery of all four programmed therapies.

PCD® Transvene™ System Performance Comparison		
Spontaneous VT Episodes		
	PCD® Transvene™ System	**PCD® Epicardial System**
Mean Follow-Up	5.6 months	9.7 months
Number of Episodes	5,430	13,706
% Overall Efficacy	5,362/5,430 98.7%	13,449/13,706 98.1%
% Unsuccessful Termination (VT)	27/5,430 0.4%	116/13,706 0.9%
% Unsuccessful Termination (AF,ST)	45/5,430 0.9%	141/13,706 1.0%
Spontaneous VF Episodes		
	PCD® Transvene System	**PCD® Epicardial System**
Mean Follow-Up	5.6 months	9.7 months
Number of Episodes	973	1,694
% Overall Efficacy	964/973 99.1%	1,671/1,694 98.6%
% Unsuccessful Termination (VT)	1/973 0.1%	9/1,694 0.5%
% Unsuccessful Termination (AF,ST)	8/923 0.8%	14/1,694 0.9%

Table IM-6: PCD® Transvene™ System: Comparison of Spontaneous VT/VF Episode Efficacy - 6/24/92

Thirty patients out of 757 in the Transvene™ population experienced 68 (68/5430 = 1.3%) episodes in which the PCD® Device was ineffective in terminating a spontaneous episode of VT despite delivery of all four programmed VT therapies. Twenty five patients experienced 45 (0.9%) episodes that were due to sinus tachycardia or atrial fibrillation/flutter (SVT) with a rapid ventricular response that had been detected as VT. These episodes were resolved with either modification of programmed parameters or of antiarrhythmic drug therapy. It should be noted that the PCD® Device responded appropriately based on the programmed detection parameters.

Seventy nine patients out of 742 in the Epicardial population experienced 257 (257/13,706 = 1.9%) episodes in which the PCD® was ineffective in terminating a spontaneous episode of VT despite delivery of all four programmed VT therapies. Of the ineffective episodes, 141 episodes (1.0%) were due to sinus tachycardia or atrial fibrillation with a rapid ventricular response that had been detected as VT. These episodes were resolved with either modification of programmed parameters or of antiarrhythmic drug therapy. It should be noted that the PCD® Device responded appropriately based on the programmed detection parameters.

Five patients in the Transvene™ population experienced 9 episodes (9/973 = 0.9%) in which the PCD® Device was ineffective in terminating a spontaneous episode of VF despite delivery of all four programmed VF therapies. Four patients had eight reported ineffective VF spontaneous episodes that were due to sinus tachycardia or atrial fibrillation with rapid ventricular response rather than VF. Reprogramming and pharmacologic intervention resolved these problems. It should be noted that the PCD® Device performance was appropriate based on the programmed detection parameters.

Thirteen patients in the Epicardial population experienced 23 episodes (23/1,694 = 1.4%) in which the PCD® Device was ineffective in terminating a spontaneous episode of VF despite delivery of all four programmed VF therapies. Fourteen of the ineffective episodes (0.9%) were due either to atrial fibrillation with a rapid ventricular response that had been detected as VF, sinus tachycardia or the device not being disabled at the time of explant allowing the PCD® Device to sense external noise as VF. The episodes due to atrial fibrillation and sinus tachycardia were resolved with either modification of antiarrhythmic drug therapy or programmed parameters. It should be noted that the PCD® Device performance was appropriate based on the programmed detection parameters.

17. **On page 162, Table IL-2 lists a category "Fail to Cardiovert/Defibrillate" as 0.8 percent. Please clarify. If a patient survives an episode of an inappropriate therapy, is it categorized as a success? Please discuss. The tables must include percentages with the representative numerical support.**

RESPONSE:

Table IL-2 references a side by side comparison of complication/ observation rates observed in the PCD® Transvene™ System and the AICD Epicardial System. The table is provided here for reference and the PCD® Transvene™ System reflects an update on the clinical experience with the 757 patients with a new cutoff date of 2/1/93. The incidence of "Fail to Cardiovert/Defibrillate" was 0.8% and is now 1.2% due to the increase in mean follow-up time from 5.6 months to 10.8 months.

PCD® Transvene™ System
Comparison of Complication/Observation Rates
PCD® versus AICD

Category	PCD%	AICD%
Fail to Cardiovert/Defibrillate	1.2% (9 pts)	4.1% (7 pts)
Inappropriate/Problematic VT/VF Therapy Delivery	9.6% (73 pts)	20% (55 pts)
Pocket Infection	2.9% (22 pts)	2.2% (6 pts)
Erosion	0.7% (5 pts)	0.7% (2 pts)

The AICD Epicardial System clinical experience data is from Winkle, et al. Long Term Outcome with Automatic Implantable Cardioverter-Defibrillator; JACC, May 1989; 13(6);135-161. This article was selected because it provides a detailed clinical complication experience on large patient population, 270 patients.

As described in the PCD® Transvene™ System PMA Application clinical experience report, Section X, Comparison to AICD System, the instances of failure to cardiovert and/or defibrillate in the PCD® Transvene™ System patient population were associated with increased defibrillation requirements during induced VF episodes, none of which resulted in patient death. The failures to cardiovert/defibrillate reported in Winkle et al, article were associated with patch dislodgement, patch crinkling, lead conductor fracture and elevated defibrillation thresholds due to changing patient conditions.

For purposes of this PCD® Transvene™ System clinical trial, spontaneous VT and VF episodes were defined as those episodes that **satisfied the programmed** VT and VF detection criteria. This includes all tachyarrhythmia episodes (i.e, VT, VF and supraventricular tachycardia) that meet the programmed detection criteria. It should be noted for all current ICD Systems, the possible delivery of inappropriate therapy for atrial fibrillation or sinus tachycardia is known risk of the therapy. There have been no patient deaths due to the delivery of inappropriate VT or VF therapy in the PCD® Transvene™ System population. Using the stored episode information available in the PCD® Device and evaluation of the patient's symptoms at the time of the episode, the physician can attempt to discern whether the therapy was delivered for spontaneous VT/VF episode or a nonventricular arrhythmia such as atrial fibrillation or sinus tachycardia.

18. There were 38 inactive patients reported in Table IH-1, however, 34 patients were reported to be no longer active. Please clarify.

RESPONSE:

The text accompanying Table IH-1: Inactive Patients, page 136 of the clinical summary provided in the September 18, 1992 amendment, contained an error. The text preceding the table should state "there are a total of 38 patients who had received a PCD system and are no longer active in the study as of 6/24/92." Note that the information in the table was correct.

As of 2/1/93 there are a total of 82 patients who had received a PCD system and are no longer active in the study. The distribution of these patients is presented below and also appears in the updated clinical summary report under "Inactive Patients."

Transvene Inactive Patients

Reason for inactivity	# of Patients
Patient deaths	51
Infection (explant)	22
Heart transplant	9
Total	82

19. Please discuss how the 1 year sudden cardiac death survival, as reported in Table IF-2, page 128, was calculated. The numbers and an explantation of patient classification must be included. Was every patient included who had a prior cardiac arrest regardless of the arrhythmia.

RESPONSE:

Sudden cardiac death is defined as a death that occurs within one hour of onset of symptoms or where the death is unwitnessed. The sudden cardiac death survival probability shown in Table IF-2 is calculated using a life-table survival analysis procedure. (b)(4) (b)(4)

(b)(4)

(b)(4)

Presentation of the number of patients does not allow calculation of the survival probability. Therefore, a dataset will be available upon request if you desire to verify the survival probability.

The sudden cardiac death survival probability estimates the likelihood that a patient enrolled in the study will survive to one year without dying a sudden cardiac death. All patients in the Transvene™ clinical study are included in the analysis regardless of the indication (VT,SCD or SCD/VT), arrhythmia (VT or VF), or prior cardiac arrest status.

20. On page 177, the number of patients must be provided so that the percentages and calculated p-values can be confirmed.

RESPONSE:

The percentages in Table IM-10 page 177 are calculated using the life-table survival estimate procedure.

PCD® Transvene™ System
Comparison of Actuarial Survival
PCD® Transvene™ System versus PCD® Epicardial System

One Year Survival	PCD® Transvene™ System	PCD® Epicardial System	(b)(4)
Number of Patients	757	742	
Sudden Cardiac	99.8%	98.7%	
Non-Sudden Cardiac	96.8%	95.7%	(b)(4)
All Cardiac	96.6%	94.4%	
Noncardiac*	99.4%	97.3%	
Overall*	95.3%	87.2%	

• (b)(4) (b)(4)

Table IM-10: Comparison of Actuarial Survival: PCD® Transvene™ System versus PCD Epicardial System - 6/24/92

The life-table procedure estimates the probability of survival for intervals. All patients for each population enter the model for estimation and are censored at their last known follow-up or counted as an event at time of death. The calculations were estimated using the commercial statistical software package (b)(4) Therefore, providing a number of patients would not aid in verification of percentages and p-values. For verification of percentages and p-values datasets are available upon request.

21. Table IV-C, page 649 of the original submission shows a comparison of patient variables for the three lead systems and provides p-values for the variables tested, but the hypothesis was not clearly stated. Please state the hypothesis and discuss the p-values obtained when reporting by primary indication, and the chi-square test of the data set and how it was computed.

RESPONSE:

For Table IV-C, page 649 of the original submission the null hypothesis was: the patient characteristics are equivalent for the three lead configurations; RV/SVC/SQ, RV/CS/SQ, and RV/CS/SVC.

PCD® Transvene™ System
RV/SVC/SQ vs RV/CS/SQ vs RV/CS/SVC

CATEGORY	RV/SVC/SQ	RV/CS/SQ	RV/CS/SVC	(b)(4)
Mean Age	57.9	60.7	56.3	
Number, % Male Number, % Female	170 82.9% 35 17.1%	71 83.5% 14 16.5%	19 70.4% 8 29.6%	
Mean Ejection Fraction	37.4%	35.5%	35.8%	
Primary Indication: SCD VT SCD & VT	 79 38.5% 92 44.9% 34 16.6%	 31 36.5% 41 48.2% 13 15.3%	 10 37.0% 12 44.5% 5 18.5%	
NYHA Classification: I/II III/IV	 163 81.1% 38 18.9%	 74 87.1% 11 12.9%	 23 85.2% 4 14.8%	
Coronary Artery Disease	73.2%	69.4%	74.1%	
Myocardial Infarction	68.3%	65.9%	66.7%	
Congestive Heart Failure	32.2%	25.9%	29.6%	
Cardiomyopathy	27 13.2%	14 16.5%	4 14.8%	

(b)(4)

Table IVC: Summary of Variables Tested on Lead Configurations - 11/27/92

(b)(4)

(b)(4)

differences between the observed and expected frequencies (b)(4) Users's Guide: Statistics, (b)(4) (b)(4)

There were no statistically significant differences at a (b)(4) significance level in patient characteristics between the lead configurations. Therefore, we accept the null hypothesis that the patient populations are equivalent.

22. For purposes of justification of data pooling and data analysis of Table IV-C, please discuss why the multiple statistical significant difference was not adjusted at a 0.05 significance level using a more widely accepted procedure such as the Hochberg procedure (Dunnett and Tarnhoue: A Step-up Multiple Test Procedure, Journal of the American Statistical Association, March, 1992, Vol 87: pp. 162-170).

RESPONSE:

The Hochberg procedure was not used to adjust for multiple inference in table IV-C of the original submission because the Dunnett and Tarnhoue article was not published and not known by us until the same month that the original submission was submitted, March 1992. Also procedures that adjust for multiple inference are used to adjust the p-value below 0.05 to correct for a type I error (rejecting the hypothesis of no difference between the populations when the hypothesis should be accepted). As shown in table IV-C below, none of the comparisons are significant at a 0.05 significance level so there is no reason to adjust the significance level below 0.05 to eliminate type I errors.

PCD® Transvene™ System RV/SVC/SQ vs RV/CS/SQ vs RV/CS/SVC				(b)(4)
CATEGORY	RV/SVC/SQ	RV/CS/SQ	RV/CS/SVC	
Mean Age	57.9	60.7	56.3	
Number, % Male Number, % Female	170 82.9% 35 17.1%	71 83.5% 14 16.5%	19 70.4% 8 29.6%	
Mean Ejection Fraction	37.4%	35.5%	35.8%	
Primary Indication: SCD VT SCD & VT	 79 38.5% 92 44.9% 34 16.6%	 31 36.5% 41 48.2% 13 15.3%	 10 37.0% 12 44.5% 5 18.5%	
NYHA Classification: I/II III/IV	 163 81.1% 38 18.9%	 74 87.1% 11 12.9%	 23 85.2% 4 14.8%	
Coronary Artery Disease	73.2%	69.4%	74.1%	
Myocardial Infarction	68.3%	65.9%	66.7%	
Congestive Heart Failure	32.2%	25.9%	29.6%	
Cardiomyopathy	27 13.2%	14 16.5%	4 14.8%	

Table IV-C: Summary of Variables Tested on Lead Configurations - 11/27/92

23. You claim that confidence interval analysis was performed to compare the overall mortality of the PCD® and AICD™ populations. What was the confidence interval?

RESPONSE:

The survival probability at one year for the Transvene™ population was 95.3%. From the analysis run, using the commercially available statistical software package (b)(4) the survival standard error was also calculated. The confidence interval was calculated by taking the survival probability (b)(4) survival standard error). The survival standard error was (b)(4) therefore the confidence interval for Transvene™ survival at 1 year is (b)(4) The overall survival probability reported for the Ventak-P was 90.8%. We do not have the data necessary to calculate the confidence interval around 90.8% for the Ventak-P. This probability is outside the lower range of the confidence interval for the Transvene™ survival probability at one year, therefore by using the best available information we conclude that there is a statistically significant difference between the survival probabilities.

24. Please clarify and/or discuss the following regarding Table XB-1, page 378, Volume 2:

a. the total number of patients in the Ventak P population (292) versus those reported by primary indication (291); and

RESPONSE:

b. a chi-square test of primary indication, using the (b)(4) computer software, yields a p-value of nearly 0. This is statistically significant, indicating the PCD® and Ventak P populations are significantly different.

RESPONSE:

As noted in the PCD® Transvene™ System PMA Application, for purposes of comparison the Ventak-P Epicardial System described in the Summary of Safety and Effectiveness Data (PMA Application Number P890061) dated May 2, 1991 was used. Therefore only that data which was presented in this summary is available via the Freedom of Information Act. The primary indication for one patient was not available in the Ventak P Epicardial System summary.

Analysis performed by Medtronic indicated that there was a statistical a difference in the category of patient indication between the two patient population groups. There were more patients that had Sudden Cardiac Death as their primary indication in the PCD® Transvene™ System population than the AICD Epicardial System population (b)(4)

Cox regression analysis was performed to see what effect gender, primary indication and system implanted (PCD® Transvene™ or PCD® Epicardial) had on survival outcome.

This analysis showed that for overall survival at one year the system implanted had an influence on the probability of survival but gender and primary indication had no influence.

Thus, since there is no impact on survival outcome based on primary indication, the PCD® Transvene™ System and AICD Epicardial System can be compared. There was a statistical difference (Confidence Interval Analysis) in one year overall survival between the PCD® Transvene™ (95.6%) and AICD Epicardial System (90.8%). This difference is due to the implanted defibrillation lead system.

25. **Please discuss the incidence of inappropriate therapies reported as observations in the Transvene™ study. It appears as if there has only been a slight improvement over the PCD® Epicardial study as it relates to programming and patient management (drug therapy). Please discuss the experience of both studies and how the labeling supports effective programming of the device parameters and the use of the Onset and Stability algorithms. How many patients in the Transvene™ study have the Onset and Stability algorithms programmed ON? At what interval during the study were the majority of patients programmed with the algorithms? Your experience in the treatment of induced and spontaneous episodes with use of the algorithms must be discussed.**

RESPONSE:

a. Inappropriate Therapies

Inappropriate therapy delivery is defined as the delivery of either VT or VF therapy for reasons other than a spontaneous VT or VF episode. This includes atrial fibrillation with a rapid ventricular response or sinus tachycardia that overlaps with the programmed detection criteria. Delivery of therapy for rhythms other than VT and VF is a known risk of ICD therapy which is clearly discussed in the device labeling.

Physicians initially program the PCD® based on the known cardiac arrhythmias and tend to program the device toward greatest sensitivity for VT and VF detection. When patients go home and recover from the implant procedure they will generally become more active and may experience increases in their sinus rate. If these increased sinus rates overlap the programmed VT detection rate criteria, the patient may experience an inappropriate VT therapy. Similarly atrial arrhythmias may develop as the patient's heart disease progresses. The philosophy behind Medtronic's labeling recommendations and the practice of PCD® investigators is to accept some overdetection of non-VT/VF rather than risk underdetection of a life threatening tachycardia. If the patient experiences inappropriate therapies due to either ventricular response to atrial fib/flutter or sinus tachycardia, the investigator will evaluate both device programming and other medical/surgical therapeutic options. Because of these patient management practices the incidence of inappropriate therapy delivery will never be zero. Physicians will likely always wait until inappropriate therapy delivery occurs before programming supplementary detection criteria.

The incidence of inappropriate/problematic VT/VF therapy delivery was lower in the PCD® clinical experience than the published experience with the AICD (Winkle, et al. Long-Term Outcome With the Automatic Implantable Cardioverter-Defibrillator; JACC, May, 1989; 13(6); 135-161.). Table XII F-2 on page 253 Transvene™ clinical update dated 9/18/92 shows 10.6% (N=742) of patients with the PCD® epicardial system and 8.2% (N=757) of patients with the Transvene™ system experienced inappropriate VT or VF therapies. The Winkle article reports a 20% rate of delivery of inappropriate therapies. The reduction in inappropriate therapies can be attributed to the incorporation of independently programmable detection algorithms for VT and VF.

The circumstances reported in the Winkle, et al article were nonsustained VT, recurrent stable VT, sinus tachycardia, atrial fibrillation with rapid ventricular response and pacemaker interaction. The patients with VT complained of receiving multiple shocks with limited or no symptoms. The incorporation of antitachycardia pacing in the PCD Device decreases the need for delivery of cardioversion shocks for the termination of stable VT and increases patient acceptance of ICD therapy.

The slight reduction of inappropriate therapies between the epicardial and the Transvene™ systems is likely due to the difference in the incidence of atrial fibrillation between the two systems. Atrial fibrillation, with a risk of inappropriate shocks and the potential need for concomitant antiarrhythmic drug therapy, is a recognized medical event in patients receiving an ICD System utilizing an epicardial defibrillation lead system. The occurrence of atrial fibrillation in these patients may be related to the thoracotomy procedure required for implant, manipulation of the atrium during the implant procedure or the positioning of the epicardial patch leads near or on the atrium resulting in irritation and induction of atrial fibrillation. The incidence of inappropriate therapy for atrial fibrillation in the PCD Epicardial System was 6.1% while that for that the PCD Transvene System was 4.9%. An decreased incidence of inappropriate therapy results in a decreased potential risk for acceleration on non VT/VF rhythms as well as increased patient acceptance of ICD therapy. Though the introduction of a transvenous lead system has not totally removed the risk of inappropriate therapy for atrial fibrillation, from this clinical experience it appears that the incidence has been decreased.

The Transvene™ clinical update dated September 18, 1992 reported forty nine patients with inappropriate VT therapy which

were all classified as observations and discussed this experience in detail. Inappropriate VT therapy was delivered for atrial fibrillation with a rapid ventricular response in 28 patients and due to sinus tachycardia in 21 patients. This observation was resolved by reprogramming of the VT detection parameters in 21 patients, with modification of drug therapy in 26 patients and no action was required in one patient. One patient with atrial fibrillation underwent successful AV Node ablation. Post this procedure, appropriate PCD Device function was documented.

In two patients in whom inappropriate VT therapy was delivered for sinus tachycardia, the ONSET algorithm was enabled to improve discrimination between VT and sinus tachycardia. The use of this algorithm resulted in no further delivery of inappropriate therapy for sinus tachycardia.

In three patients in whom inappropriate VT therapy was delivered for atrial fibrillation, the STABILITY algorithm was enabled to improve discrimination between VT and atrial fibrillation. The use of this algorithm resulted in no further delivery of inappropriate therapy for atrial fibrillation.

The Transvene™ clinical update also reported thirteen patients who experienced an episode of inappropriate VF therapy, all of which were classified as observations. In nine cases, inappropriate VF therapy was delivered for atrial fibrillation that had a rapid ventricular response that met the programmed VF detection criteria. In two cases, inappropriate VF therapy was delivered secondary to sinus tachycardia that was detected as ventricular fibrillation. Modification of the programmed VF detection criteria or the patient's antiarrhythmic drug therapy corrected these two clinical observations.

One patient received inappropriate VF therapy secondary to the sensing of T waves during sinus rhythm with the PCD device programmed to a sensitivity of (b)(4) This was resolved with reprogramming of the sensitivity to (b)(4) Appropriate VF sensing was documented at this programmed setting.

The final patient received inappropriate VF therapy secondary to nonsustained ventricular tachycardia. In the PCD Device, once "VF" is detected the device is committed to the delivery of defibrillation therapy. This observation was resolved by reprogramming of the FDI and VF NID.

b. Labeling

The PCD® technical manual contains specific recommendations for programming both VT and VF detection. For VT detection, specific statements are made for programming the Tachycardia Detection Interval (TDI), the Number of Intervals to Detect (VT NID), as well as the Onset and Stability Criteria. For VF detection recommendations are made for Sensitivity, Fibrillation Detection Interval (FDI) and Number of Intervals to Detect (VF NID).

The recommendations specify initial programming recommendations for each parameter as well as appropriate warnings for potential programming problems.

The programming recommendations for the Onset Criterion in the PCD® technical manual are:

> Onset Criterion is indicated if inappropriate detection of sinus tachycardia resulting in inappropriate VT therapy delivery has occurred. Treadmill testing, beginning at 81% Onset, is suggested to evaluate the appropriate function of this algorithm.
>
> This algorithm was used safely in 8.5% of 434 patients in the clinical study. Its use has demonstrated its safety and effectiveness.
>
> If the Onset Criterion is ON and is not met at the beginning of a spontaneous ventricular tachycardia, the VT episode could remain "undetected", such as with an exercise-induced VT. If VT Detection uses the Onset Criterion and detection is enabled after the start of a VT, the VT may not be detected.
>
> A low programmed onset percentage value will increase the specificity of the Onset Criterion to detect the targeted tachycardia, but will also decrease the sensitivity of the overall VT detection algorithm.

The programming recommendations for the Stability Criterion in the PCD® technical manual are:

> Stability Criterion is indicated if atrial fibrillation or atrial flutter with a rapid ventricular response has caused inappropriate detection and therapy delivery. A stability value of 60ms is suggested initially.
>
> This algorithm was used safely in 17.9% of 434 patients in the clinical study. Its use has demonstrated its safety and effectiveness.
>
> Decreasing the programmed interval stability value increases the specificity of the Interval Stability Criterion to detect the targeted stable tachycardia, but may also decrease the sensitivity of the detection algorithm.

The labeling directed at programming these two algorithms is necessary and appropriate in that it clearly states that while specificity for VT detection is enhanced, sensitivity for VT detection is reduced. For this reason the recommendations clearly state that these supplementary detection criteria should be used after the need for this increase in specificity has been clearly demonstrated, that is, inappropriate therapies form either sinus tachycardia or atrial fib/flutter have occurred.

The values recommended for initial programming of both of these features was made through analysis of the clinical data base. In both cases the values chosen were the most widely used values.

c. Transvene™ Experience

As of February 1, 1993 thirty-three (33) of the 757 Transvene™ patients in the clinical report had the Onset Criterion enabled and 55 patients had the Stability Criterion enabled. Eleven of these patients had both the Onset and the Stability Criteria programmed ON. The most widely used programmed value for the Onset Criterion was 81% (54.5% of patients with Onset programmed ON). The most widely used programmed value for the Stability Criterion was (b)(4) (45.4% of patients with Stability programmed ON).

Table 25c-1 shows a distribution of the time from implant to the first programming of the Onset and the Stability Criteria. Almost half (48.5% 16/33) of the patients with the Onset Criterion programmed ON did so within the first 30 days following implant. The greatest time from implant to the first programming of the Onset Criterion is 345 days. More than half (63.6% 35/55) of the patients with the Stability Criterion programmed ON did so within the first 30 days. Like the Onset Criterion many patients had the Stability Criterion programmed on for the first time very late in the follow-up period, the greatest being 622 days.

PCD® Transvene™ System Time to Program Onset and Stability Criterions ON		
Days Post Implant	**Onset Criterion (# of Patients Programmed ON)**	**Stability Criterion (# of Patients Programmed ON)**
0 - 10 days	13	29
10 - 30 days	3	6
30 - 100 days	7	9
101 - 200 days	3	3
201 - 300 days	4	4
301 - 400 days	3	1
401+ days	0	3
Total	33	55

Table 25c-1: Time to Program Onset and Stability Criterions ON

While most of the patients requiring these supplementary detection algorithms do so relatively early following implant, some patients require this feature much later. This is an example of the dynamic nature of patient's underlying heart disease and the need to have these programmable features available for use long after implant, as the patient's cardiac condition changes.

At the time of programming either of these supplementary VT detection criteria ON, many patients had arrhythmias induced to assure appropriate detection of VT/VF. Table 25c-2 shows the number of episodes of VT and VF induced during the follow-up evaluation where the criterion was programmed ON. Fifty percent (11/22) of the patients with the Onset Criterion only programmed ON were induced into a tachyarrhythmia at the follow-up evaluation where the programming occurred. Over half (61.3% 27/44) of the patients with the Stability Criterion only programmed ON and 72.7% (8/11) of those patients with both supplementary criteria programmed ON were induced at the follow-up where the programming occurred. In all cases the PCD® system performed appropriately.

PCD® Transvene™ System Induced Episodes When Onset or Stability Were Programmed ON			
	VT	V-Flutter	VF
Onset Only ON (11 of 22 Patients)	18 Episodes 10 Patients	-- --	14 Episodes 8 Patients
Stability Only ON (27 of 44 Patients)	78 Episodes 19 Patients	4 Episodes 2 Patients	41 Episodes 21 Patients
Both ON (6 of 11 Patients)	31 Episodes 6 Patients	-- --	18 Episodes 5 Patients

Table 25c-2: Induced Episodes When Onset or Stability Were Programmed ON

Table 25c-3 shows the spontaneous episode experience in the patients with these two detection criteria programmed ON. Three-hundred-nine (309) episodes occurred in 30 of the patients with the Stability Criterion programmed ON. Two-hundred-ninety-three (293) were successfully terminated by the PCD® Transvene™ system. The remaining episodes were due to ventricular response to atrial fib/flutter that met the programmed Stability Criterion value. Twelve (12) of the "Failed" episodes were in one patient who was hospitalized for titration of medical therapies. Eleven patients with the Onset Criterion experienced 493 VT episodes which were terminated with an efficacy of 99.2%. Ventricular fibrillation was terminated 100% of the time in this patient group.

PCD® Transvene™ System Spontaneous Episodes When Onset or Stability Were Programmed ON		
	VT	VF
Stability Criterion Only # Patients # Episodes Efficacy	 30 309 94.8%	 18 125 100.0%
Onset Criterion Only # Patients # Episodes Efficacy	 11 493 99.2%	 7 17 100.0%
Both Criteria # Patients # Episodes Efficacy	 10 364 97.0%	 4 39 100.0%

Table 25c-3: Spontaneous Episodes When Onset or Stability Were Programmed ON

d. Conclusion

The Onset and the Stability Criteria for VT detection are the same algorithms that were demonstrated to be safe and effective with the market released PCD® Epicardial System. They remain a useful tool in a subset of patients requiring discrimination between ventricular tachycardia and the rapid ventricular response to atrial fib/flutter or sinus tachycardia in the PCD® Transvene™ System.

26. Please discuss the "device related" complications reported for the Transvene™ and the PCD® Epicardial System.

RESPONSE:

As described in the PCD® Transvene™ System PMA Application, "Device Related" complications includes patients in whom the device was explanted for reasons other than patient death, infection or transplant.

In the case of the PCD® Transvene™ System, these patients were discussed in detail in the Clinical Experience Report, Section XII, Complications and Observations and detailed information on each patient was provided in Volume 3, Clinical Appendices, Appendix C. There were four patients (0.5%) in whom the PCD® Device was explanted due to reasons other than death, infection or heart transplant. Reasons for explant included, **(1)** lower than expected battery voltage for time in service due to leakage at the input to one of the integrated circuits (1 unit), **(2)** failure to appropriately synchronize and deliver cardioversion therapy for an induced VT episode (1 unit); **(3)** Power on Reset (POR) condition that was not related to the delivery of external defibrillation or cautery (1 unit); and, **(4)** inappropriate delivery of VF therapy during a manual capacitor charge time (1 unit). In all cases, the devices were safely replaced with no adverse patient consequences. The attached information from the PCD® Transvene™ System Application provides a summary of these patients.

In the case of the PCD® Epicardial System, there were seven patients (0.9%) in whom the PCD® Device was explanted due to reasons other than death, infection or heart transplant. The reason for explant for all seven devices was lower than expected battery voltage for time in service. The identified causes for low battery voltage were (1) failure in an integrated circuit which increases the current drain and results in reduced battery longevity (3 units); (2) leakage at the input of one of the integrated circuits where voltage measurement is taken (1 unit); and (3) leakage at tantalum capacitors (3 units). Information on these identified causes for low battery voltage have been previously provided the agency. In all cases, the devices were safely replaced with no adverse patient consequences.

Early Device Explant

There were four patients in whom the PCD Device was explanted due to reasons other than death, infection or heart transplant. In all cases these medical events were classified as complications.

In the first patient the PCD Device was explanted for lower than expected battery voltage measurement for time in service. Analysis indicated the decreased battery voltage measurement was due to leakage at the input to one of the integrated circuits. This lead to a voltage drop across a resistor where the voltage measurement was taken. Analysis indicated the battery to be performing to specifications and the leakage to be a random event.

The second patient received inappropriate VF therapy during reformation of the device capacitors. Analysis of the explanted unit indicated that arcing occurred between the conductors in the high power hybrid. As a result, high voltage was momentarily applied to the low power circuitry, including the low power hybrid. This low power hybrid lost function including the capability to pace and transmit telemetry due to the excessive voltage applied.

Since this is the only device that exhibited this type of failure in the field and the hybrid manufacturing process has demonstrated that it will screen out infant mortality, this was determined to be a random component failure.

In the third patient, during the pre-hospital discharge electrophysiology study, VT was induced and cardioversion therapy failed to appropriately synchronize and deliver therapy for this induced episode. The PCD Device was explanted and the patient received a second device without difficulties. Analysis of the explanted PCD Device indicated a random device failure in the microprocessor and low power hybrid. The manufacturing process was modified to incorporate a screening process to identify any further devices which may exhibit this behavior.

In the final patient, the PCD Device exhibited a Power On Reset (POR) condition that could not be related to use of electrocautery or external defibrillation. The device was explanted and returned to Medtronic for analysis. Final results on the analysis are not available at the time of this submission but will be submitted to the FDA when they are available.

27. Please describe in detail the complications reported in the patients followed for a year.

RESPONSE:

Complications and Observations in the patients followed for 1 year or more

The use of a multiprogrammable implantable cardioverter defibrillator (ICD) device allows the physician to resolve most relevant medical events by noninvasively changing programmed parameters thus, avoiding invasive procedures. However, there will continue to be certain relevant medical events which will require invasive procedures for resolution.

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following definitions:

COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

As of February 1, 1993, of the 393 patients with implant durations of greater than or equal to one year, there have been a total of 89 complications reported in 76 patients and 122 observations reported in 99 patients in the PCD™ Transvene™ System patient population. Thus, 19.3% (76/393) of the patients had a clinical event which was categorized as a complication and 25.2% (99/393) of the patients had a clinical event which was categorized as an observation. These percentages are consistent with the percentages of patients with complications, 19.4% (147/157) and observations 23.8% (180/757) in the original PMA patient population.

Table 27-1 summarizes the reported PCD® Transvene™ System complications and observations by category. The reported complications and observations are recognized clinical events that may occur with **any** of the current ICD devices. These complications and observations are discussed in the PCD® device and Transvene™ manual. **None of the reported complications or observations have resulted in a patient death.**

PCD® Transvene System Reported Complications/Observations in Patients followed for 1 Year or more : By Category (n=393)		
Category	**Complications**	**Observations**
	Num (% of Pts)	Num (% of Pts)
Increased Defibrillation Requirements	3 (0.8%)	2 (0.5%)
Inappropriate VF Therapy Delivery	-	10 (2.5%)
Inappropriate VT Therapy Delivery	-	40 (10.2%)
Loss of Capture	2 (0.5%)	6 (1.5%)
Oversensing	-	29 (7.4%)
Undersensing	-	-
Skin Erosion	2 (0.5%)	1 (0.3%)
Pocket Infection	5 (1.3%)	7 (1.8%)
Seroma	1 (0.3%)	9 (2.3%)
Hematoma	1 (0.3%)	7 (1.8%)
Pneumothorax	2 (0.5%)	1 (0.3%)
Pacemaker Syndrome	-	1 (0.3%)
Perforation	1 (0.3%)	-
Subclavian Vein Thrombosis	-	1 (0.3%)
Lead Fracture	6 (1.5%)	-
Subcutaneous Patch Crinkling	5 (1.3%)	3 (0.8%)
Early Device Explant	3 (0.8%)	-
Total Lead Dislodgement	56 (14.2%)	6 (1.5%)
Total	**89**	**122**

Table 27-1: PCD Transvene System: Reported Complications and Observations - 2/1/93

Table 27-2 contains a description of the lead dislodgements that have occurred in less than 30 days and in greater than 30 days.

PCD® Transvene System Reported Complications/Observations in Patients followed ≥1 Year Lead Dislodgements <30 days and >30 days (N=393)			
Complications		Observations	
Num (% of Pts)		Num (% of Pts)	
<30 days	>30 days	<30 days	>30 days
27 (6.9%)	29 (7.4%)	0 (0)	6 (1.5%)

Table 27-2: PCD Transvene System: Lead Dislodgements <30/>30 days - 2/1/93

There have been a total of 29 lead dislodgements reported in patients at greater than 30 days. None of the lead dislodgements resulted in an ineffective therapy for a spontaneous VT of VF episode or patient death. Lead dislodgements were documented by fluoroscopic examination during electrophysiologic evaluation, chest x-ray obtained during routine follow-up, or during pacing/sensing threshold evaluation during routine follow-up. In all 29 cases, reoperation was required to reposition the lead and reestablish an effective defibrillation lead system.

Lead dislodgements are not specific to the PCD® Transvene™ System and have been reported with dual chamber pacemakers and the current market released implantable cardioverter defibrillator (ICD) system. The early history of dual chamber pacemakers witnessed a high lead dislodgement rate of at least 20% (Smyth, PND, et al. Permanent perivenous atrial sensing and pacing with a new J-shaped lead. J Thoracic Cardiovascular Surgery. 1976;72:565-570). Winkle, et al reported that the incidence of dislodgement of the superior vena cava spring leads with the current market release ICD system to be 6.3%. (Winkle, et al. Automatic Implantable Cardioverter-Defibrillator: Efficacy, Complications, and Survival in Patients with Malignant Ventricular Arrhythmias. JACC. June 1988; Vol.11, No.6:1278-86).

28. **There was a substantial increase in the number of infections reported in the Transvene™ study. Even though you discussed why there was an increase, based on your experience, how will your labeling address the procedures for reduction in the number if infections? Please validate these procedures.**

RESPONSE:

In the current update of our database, we report in Table IM-7 (a copy is attached for your convenience) that there is a 2.9% incidence of infection leading to explant of the PCD® in the 757 Transvene™ patients and 2.3% for the 742 Epicardial patients. These two rates are not substantially different nor are they different from the 2.4% rate reported in the Ventak-P Summary of Safety and Effectiveness Data, PMA Application P890061, May 2, 1991. Therefore, it is our assertion that there is not a substantial increase in infections and the current labeling is appropriate.

29. A discussion of your experience in the use of the different entry sites for the placement of the Transvene™ leads, and how your labeling assists in the selection of an entry site, must be provided.

RESPONSE:

Transvene leads are placed via several approaches; either through the subclavian, cephalic or jugular veins. The specific site is determined by the implanting physician. Analysis of Transvene data shows that the left subclavian vein is the most frequently used entry site regardless of the type of lead or intended lead location, i.e., RV or CS/SVC lead. A presentation of entry sites is presented below. The total number of RV lead entry sites is greater than the total number of patients included in this report because of patients with multiple lead evaluation sessions. This information was also presented in the clinical experience report provided in the September 1992 PMA amendment.

PCD™ Transvene™ System Venous Entry Site			
	RV Leads Model 6884/6966/SP2100	CS/SVC Leads Model 6881/6963	All Transvene™ Leads
Left Subclavian	483	583	1066
Right Subclavian	40	47	87
Left Cephalic	213	180	393
Right Cephalic	8	7	15
Left Internal Jugular	7	9	16
Right Internal Jugular	11	9	20
Other	5	4	9
Total	767	839	2097

Venous Entry Site - 6/24/92

There have been two reports of fractures of the Model 6884 right ventricular lead associated with clamping of the lead body between the clavicle and first rib. Both of these leads were placed via a right subclavian approach. These patients are discussed in detail in the complications section of the clinical summary. There were no reports of ineffective therapy for a spontaneous VT/VF episode due to a right ventricular lead fracture.

Technical manuals for both the Model 6966 RV lead and Model 6963 CS/SVC lead provide a detailed discussion of selection of a lead entry site. This is addressed under, "Suggested Implantation Procedure" in each of the technical manuals. Copies of the applicable pages of the technical manual for each lead are provided following this response. Note that this information was also provided in the original Transvene PMA application dated March 31, 1992.

TECHNICAL MANUAL

TRANSVENE™-SVC Unipolar, Endocardial, Coronary Sinus or Superior Vena Cava Lead for Cardioversion and Defibrillation

MODEL 6963

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POTENTIAL COMPLICATIONS

The potential complications related to the use of transvenous leads include, but are not limited to, the following patient-related conditions that can occur during and following lead insertion: fibrillation or other arrhythmias, conduction disturbances, loss of contractility, air embolism, cardiac perforation, heart wall rupture, cardiac tamponade, infection, and tissue necrosis.

Other potential complications related to the lead include, but are not limited to, the following: lead dislodgement, lead conductor fracture, and insulation failure.

ENSURING PRODUCT INTEGRITY

Carefully inspect the package before opening. It is not recommended that you use the product after its expiration date.

If the integrity of the package has been compromised prior to the product expiration date, place the contents in a gas-permeable bag and resterilize it with ethylene oxide as described below.

CAUTION: Use ethylene oxide only.

The process should not exceed temperatures of 55° C (125° F). Allow proper aeration of ethylene oxide residues prior to implantation. Use some acceptable method to determine sterilizer effectiveness, such as a biological indicator.

Due to the variability between sterilizers, precise sterilization instructions cannot be provided. Contact your sterilizer manufacturer for more information regarding sterilization procedures.

SUGGESTED IMPLANTATION PROCEDURE

General Instructions

The implantation procedure generally includes using a stylet guide, stylets, and vein lifter; selecting an insertion site; positioning the lead; taking electrical and defibrillation efficacy measurements; anchoring the lead; and connecting the lead to the pulse generator.

Some implantation techniques vary according to physician preference and the patient's anatomy or physical condition. The techniques for selecting an insertion site, using a stylet guide or a stylet, positioning a lead, and anchoring a lead,

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described below suggest one or two possible versions, while more may exist.

Opening the Package

While lifting the lead out of the package, make sure that the anchoring sleeve does not slide off the distal end of the lead.

Using the Stylet Guide and Stylets

The lead is packaged with the stylet guide attached to the connector pin and a stylet already inserted. If the stylet guide has been removed, replace it by gently pushing it as far as possible onto the connector pin (Figure 1).

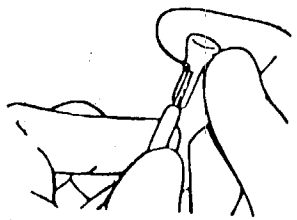

Figure 1. Stylet guide attachment.

A stylet provides additional stiffness and controlled flexibility for maneuvering the lead into position. Stylets vary in stiffness for different lead and stylet flexibility. Each stylet knob is etched with the stylet diameter and length.

If a stylet is not already in the lead, insert a stylet through the stylet guide and into the lead body. If a slight curve is needed for the stylet, refer to instructions in the section titled "Positioning a Lead in the Coronary Sinus or Superior Vena Cava."

CAUTION: To avoid damage to the lead or body tissue, do not use excessive force or surgical instruments to insert a stylet into the lead. When handling a stylet, avoid overbending, kinking, or blood contact.

CAUTION: Repeated insertions of a stylet increase the chance that blood may accumulate on it, which may cause difficulty in passing the stylet through the lead and may cause damage to the lead.

Selecting an Insertion Site

The lead may be inserted by venotomy through several different venous routes, including the right or left cephalic vein or the external or internal jugular vein. In general, a left venous entry site will aid in maneuvering the lead into the coronary sinus orifice.

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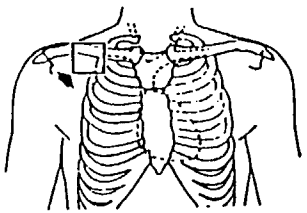
CAUTION: If insertion is done via a subclavian approach, the lead should be positined far laterally to avoid clamping the lead body between the clavicle and the first rib. Clamping the lead may eventually cause the conductor to fracture, may cause damage to the insulation, or may cause other damage to the lead. This may result in complications such as loss of detection, loss of pacing therapies, or loss of cardioversion./defibrillation therapy. Certain anatomical abnormalities, such as thoracic outlet syndrome, may also precipitate pinching andf subsequent fracture of the lead. If significant resistance is encountered during a subclavian stick implant procedure, do not force the lead by adjusting patient's posture (i.e., raising the arm or putting a towel behind the person's back) to facilitate the passage of the lead. In such cases it is recommended that an alternate venous entry site be used.

Use fluoroscopy to facilitate accurate lead placement.



Using a Vein Lifter

A vein lifter facilitates lead introduction. Insert its tapered end into the incised vein and gently push the lead tip underneath and into the vein (Figure 2). During insertion of the lead into the vein, make sure the anchoring sleeve does not slide off the distal end of the lead.

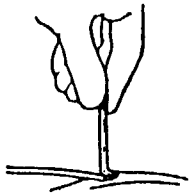


Figure 2. Using the vein lifter.

CAUTION: Avoid placing the lead under extreme tension or angulation to prevent lead dislodgement and possible lead fracture. **Do not grip the lead with surgical instruments.**

Positioning a Lead in the Coronary Sinus or Superior Vena Cava

For added control in maneuvering the lead tip, the distal end of the lead may be slightly curved by inserting a gently curved stylet as shown in Figure 3. A possible angle of curvature is illustrated in Figures 4 and 5.

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TECHNICAL MANUAL

The TRANSVENE™-RV Tripolar, Endocardial, Screw-in Lead for Ventricular Pacing, Sensing, Cardioversion and Defibrillation

MODEL 6966

CAUTION: Investigational Device. Limited by U.S. Law to Investigational Use.

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ENSURING PRODUCT INTEGRITY

Carefully inspect the package before opening. It is not recommended that you use the product after its expiration date.

If the integrity of the package has been compromised prior to the product expiration date, place the contents in a gas-permeable package and resterilize it with ethylene oxide as described below.

CAUTION: Use ethylene oxide only.

The process should not exceed temperatures of 55° C (125° F). Allow proper aeration of ethylene oxide residues prior to implantation. Use some acceptable method to determine sterilizer effectiveness, such as a biological indicator.

Due to the variability between sterilizers, precise sterilization instructions cannot be provided. Contact your sterilizer manufacturer for more information regarding sterilization procedures.

SUGGESTED IMPLANTATION PROCEDURE

The implantation procedure generally includes checking the mechanical functioning of the lead electrode before it is inserted; using a stylet guide, stylets, and vein lifter; selecting an insertion site; positioning the lead; securing the lead; taking electrical and defibrillation efficacy measurements; anchoring the lead; and connecting the lead to the pulse generator.

Some implantation techniques vary according to physician preference and the patient's anatomy or physical condition. As described below, the techniques for selecting an insertion site, using a stylet guide or a stylet, positioning a lead, and anchoring a lead suggest one or two possible versions, while more may exist.

Verifying the Mechanical Functioning of the Helix Electrode

Before implantation, verify the mechanical functioning of the electrode, as described below.

1. Within the sterile field, remove the lead and the accompanying stylets from the sterile packaging. The lead is packaged with a stylet guide attached and a stylet already inserted. The connector pin that accepts the stylet controls the helix mechanism.

2. To attach the fixation tool, first remove the stylet guide. Press both legs of the fixation tool together and place the most distal hole of the fixation tool on the connector pin that accepts the stylet (Figure 2).

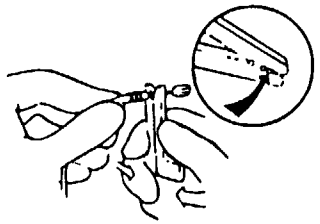

Figure 2. Attachment of the fixation tool to the connector pin.

3. Rotate the tool clockwise until the coiled electrode is completely exposed (Figure 3). Maximum electrode exposure reveals 2 coils.

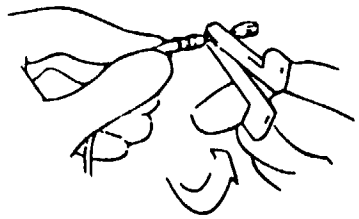

Figure 3. Rotating the fixation tool.

The maximum number of revolutions of the fixation tool needed to extend or retract the helix is 20.

CAUTION: Exceeding the maximum number of revolutions may damage the lead.

4. Disconnect the fixation tool from the connector pin and release the proximal end of the lead body. Allow several seconds for the lead and its conductor coil to unwind.
5. After allowing the lead and its conductor coil to unwind, reattach the fixation tool and turn it counterclockwise until the helix tip is retracted in the sheath.

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Using the Stylet Guide and Stylets

The lead is packaged with a stylet guide attached and a stylet already inserted. The connector pin with the stylet in it controls the helix mechanism. Use of the stylet guide is optional. An attached stylet guide may be removed by gently pulling it off. To attach a stylet guide, gently push it as far as possible onto the connector pin that accepts the stylet (Figure 4).

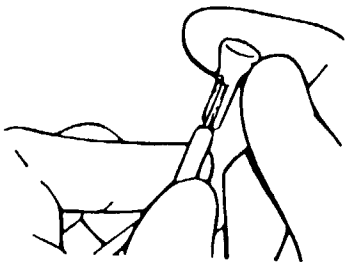

Figure 4. Stylet guide attachment.

A stylet provides additional stiffness and controlled flexibility for maneuvering the lead into position. Stylets vary in stiffness to accommodate a physician's preference for lead and stylet flexibility.

CAUTION: To avoid damage to the lead or body tissue, do not use excessive force or surgical instruments to insert a stylet into the lead. When handling a stylet, avoid overbending, kinking, or blood contact.

CAUTION: Repeated insertions of a stylet increase the chance that blood may accumulate on it, which may cause difficulty in passing the stylet through the lead and may cause damage to the lead.

After the stylet is inserted, gently remove the stylet guide so that it rests alongside the stylet knob.

Selecting an Insertion Site

The lead may be inserted by venotomy through several different venous routes, including the right or left cephalic vein or the external or internal jugular vein.

CAUTION: If insertion is done via a subclavian approach, the lead should be positioned far laterally to avoid clamping the lead body between the clavicle and the first rib. Clamping the lead may eventually cause the conductor to fractur, may cause damage to the insulation, or may cause other damage to the lead. This may result in complications such as loss of detection, loss of pacing therapies, or loss of cardioversion/defibrillation therapy. Certain anatomical abnormalities, such as thoracic outlet syndrome, may also precipitate pinching and subsequent fracture of the lead. If significant resis-

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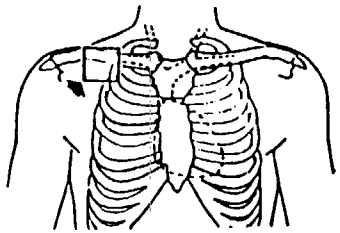
tance is encountered during a subclavian stick implant procedure, do not force the lead by adjucting patient's posture (i.e., raising the arm or putting a towel behind the person's back) to facilitate the passage of the lead. In such cases it is recommended that an alternate venous entry site be used.

Use fluoroscopy to facilitate accurate lead placement.



Using the Vein Lifter

A vein lifter facilitates lead introduction. Insert its tapered end into the incised vein and gently push the lead tip underneath and into the vein (Figure 5).

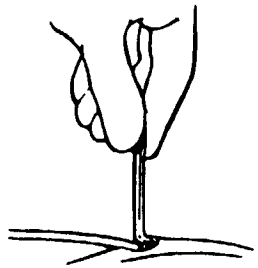


Figure 5. Using the vein lifter.

CAUTION: Avoid placing the lead under extreme tension or angulation to prevent lead dislodgement and possible lead fracture. **Do not grip the lead with surgical instruments.**

Positioning a Ventricular Lead

Advance the lead into the right atrium. For added control in maneuvering the lead tip through the tricuspid valve, the distal end of the lead may be slightly curved by inserting a gently curved stylet (Figure 6). After the lead tip is passed into the ventricle, the curved stylet may be replaced with a straight stylet. Then the lead tip may be advanced to the right ventricular apex while taking care to avoid perforation of the ventricular wall.

CAUTION: To avoid damage to the stylet, do not use a sharp object to impart a curve to the distal end (Figure 6).

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30. Of the 22 deaths, 15 systems were explanted and returned for analysis. The results of the analyses (PCD® and Transvene™ leads) must be provided. What did device interrogation reveal? How many of the 41 Transvene™ lead systems which were explanted were returned and analyzed? How long were the leads implanted? A description of the protocol for analysis and the results of the analyses on all leads and devices must be provided. The PMA application must document how your study has addressed the need for the return and analysis of all Transvene™ leads and the PCD®.

RESPONSE:

In the 762 implants in 757 patients, a total of 41 units (5.4%) were explanted secondary to patient deaths, infection, heart transplant, low battery voltage measurement and PCD® Device performance issues. This information was provided in the PCD® Transvene™ System PMA Application, Clinical Experience Report, Section IX, System Performance. For convenience, Table 30-1 provides an overview of the units explanted, and returned to Medtronic for analysis and reason for explant.

PCD® Transvene™ System Reasons for PCD® Device Explant	
Reason	**All Models**
Number of Implants	762
Patient Death	15
Infection	17
Cardiac Transplant	5
Low Battery Voltage Measurement	1
PCD® Device Performance Issues	3
Total	41

Table 30-1: Reasons for PCD® Device Explant

There were 22 reported patient deaths and 15 devices were explanted and returned to Medtronic for analysis. In the remaining 7 deaths, either the family refused to allow the PCD® Transvene™ System to be explanted or the patient expired and was buried prior to notification of the primary investigator.

Of the fifteen devices which were explanted due to patient death, ten (10) have been analyzed and found to be performing within normal specifications. The remaining five (5) PCD® Devices are pending final analysis, however, none of the deaths were classified as being PCD® Transvene™ System related, and initial analysis has not indicated that these devices were performing outside normal specifications. Results of analysis performed on the 41 explanted devices is presented in Table 30-2.

PCD® Transvene™ System Final Analysis on Explanted PCD® Devices (N = 762)	
Within Normal Specifications	20
Hermetic Leakage at IC	1
Random Component Failure	2
Shorted on Pulse 2 Output	1
Analysis Pending	17
Total	41

Table 30-2: Final Analysis on Explanted PCD® Devices

Of the 41 devices explanted, final analysis on 19 units indicated that the devices were functioning within normal specifications. Final analysis is not available on 17 units which have been explanted. The reason for explant in these units includes patient death (5), infection (10) and cardiac transplant (2). It should be noted that none of these devices were explanted secondary to concern over the function of the implanted PCD® Transvene™ System.

Four PCD® Devices were explanted for the following device performance issues:

- explanted due to a Power On Reset (POR) condition that was not related to the delivery of external defibrillation or cautery (N = 1);
- explanted for lower than expected battery voltage for time in service (N = 1);
- explanted secondary to failure to appropriately synchronize and deliver cardioversion therapy for an induced VT episode (N = 1); and
- explanted post inappropriate delivery of VF therapy during a manual capacitor charge time (N = 1).

Of the 41 lead systems previously discussed, 21 lead systems, or portions of systems, were returned. Of those 21 only one 6966 lead was damaged, specifically, the helix. The remaining leads were found to be within specification.

The investigational plan requests that if the PCD® Transvene™ System is explanted during the course for any reason (i.e., patient death, infection, cardiac transplant or PCD® Device performance issues) that the PCD® device be returned to Medtronic for analysis. In addition, the patient informed consent also indicates that the patient allows permission of explant of the PCD® Transvene™ System at the possible time of his/her death.

The PCD® Transvene™ System clinical dataform specifically requests information on whether the system has been explanted and justification for not explanting the system.

A description of the protocol for PCD device and Transvene lead analysis is presented below.

Failure Analysis Procedure: PCD Device and Transvene Leads

(b)(4)

(b)(4)

PCD Device

(b)(4)

(b)(4)

Specialized testing may include:

(b)(4)

(b)(4)

Destructive testing may include:

(b)(4)

(b)(4)

Specialized battery depletion testing may include:

(b)(4)

(b)(4)

Transvene Leads

(b)(4)

(b)(4)

Specialized testing may include:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

M.4 Incidence of Complications/Observations

A comparison of the reported complications and observations was made between the PCD™ Transvene™ System and the PCD™ Epicardial System. The PCD™ Epicardial System patient population used for comparison included clinical experience as of January 5, 1992 with 742 patients and a mean implant duration of 16.3 months. These two patient groups are similar in the patient demographics and indication for implant of the PCD™ System. In the PCD™ Transvene™ System patient population, 19.4% of the patients experienced a clinical complication and 23.8% of the patients experienced a clinical observation. In the PCD™ Epicardial System, 14.2% of the patients experienced a clinical complication and 32.9% of the patients experienced a clinical observation.

Table IM-7 and IM-8 provide a comparison of the reported complications/observations and their incidence in the two patient populations.

PCD™ Transvene System
PCD™ Transvene System versus PCD™ Epicardial System Reported Complications

Reported Complications	PCD™ Transvene™ System (N = 757)	PCD™ Epicardial System (N = 742)
Increased Defibrillation Requirements	1.2%	0.5%
Inappropriate Therapy	-	2.2%
Pace/Sense Related	0.8%	3.5%
Infection Related - Explant	2.9%	2.3%
Lead Related	9.5%	2.8%
Device Related	0.5%	0.9%

Table IM-7: Reported Complications: PCD™ Transvene™ System versus PCD™ Epicardial System - 2/1/93

31. Please discuss the circumstances surrounding the death of the patient who died (b)(4) months post implant. What did interrogation of the device reveal?

RESPONSE:

The circumstances of this patient death (Patient ID (b)(4) were provided in PMA Amendment (9/18/92), Volume 3 page 543-545. A copy of the patient death summary is provided here for convenience.

In summary, the patient had been admitted for worsening symptoms of congestive heart failure, renal decompensation and increased frequency of spontaneous VT and VF episodes. In addition the patient had digitalis toxicity. The patient's condition worsened and the family members elected not to use heroic measures in the treatment of the patient. The patient eventually expired secondary to progressive cardiac failure due to left ventricular pump dysfunction. The patient death was classified as non-sudden cardiac and not related to the PCD® Transvene™ System. Final interrogation of the PCD® Device, at the time of explant, indicated normal battery voltage and charge time and the patient had experienced no new episodes of VT or VF since the last follow-up visit. The PCD® Device was explanted and analysis found the device to be performing within specifications.

115

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant:
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

136

(b)(4), (b)(6)

(b)(4), (b)(6)

116

as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	440 ms
VT NID	12
VT Rx #1	Burst
VT Rx #2	CV/10J/SIM
VT Rx #3	CV/20J/SIM
VT Rx #4	CV/34J/SIM
FDI	330 ms
VF NID	18
VF Rx #1	34J/SIM
VF Rx #2	34J/SIM
VF Rx #3	34J/SIM
VF Rx #4	34J/SIM

(b)(4), (b)(6)

(b)(4), (b)(6)

137

(b)(4), (b)(6)

117

(b)(4), (b)(6)

The investigator classified this patient death as non-sudden cardiac and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

1380

32. Of the perioperative deaths, how many devices were programmed OFF? Please discuss the circumstances surrounding each death. The number of perioperative deaths must be reported in a table and be identified as sudden cardiac, non-sudden cardiac or non-cardiac. Were there other deaths when the device was programmed OFF? 118

RESPONSE:

As of February 1, 1993, there have been a total of 51 reported patients deaths in the 757 patients who received a PCD® Transvene™ System. There have been five (5) reported perioperative patient deaths with a resultant perioperative mortality of 0.7%. The patient death in which the PCD® Device was programmed OFF (Patient ID (b)(6) was classified as non-sudden cardiac and was not related to a ventricular tachyarrhythmia episode. Table 32-1 summarizes these perioperative patient deaths.

PCD® Transvene™ System Perioperative Patient Deaths	
Death Classification	**Number of Patients**
Sudden Cardiac	2
Non-Sudden Cardiac	2
Noncardiac	1
TOTAL	5 (0.7%)
PCD® Device OFF	1

Table 32-1: PCD® Transvene™ System Perioperative Death Classifications

The circumstances of these patient deaths were provided in PMA Amendment (9/18/92), Volume 3 page 503-580. A copy of the patient death summaries is provided here for convenience.

In the total patient death group of 51 patients, there were seven (7) deaths were the device was programmed OFF. In none of these cases did the primary investigator indicate that the patient death was related to the implanted PCD® Transvene™ System. There was one sudden cardiac death in which the PCD® Device was programmed OFF. One month post implant of the PCD® Transvene™ System, this patient experienced fourteen (14) episodes of VF which were all successfully terminated by the PCD® Device. The patient was admitted for evaluation and during this hospitalization requested that the PCD® Device be programmed OFF. Approximately 30 minutes later the patient experienced an episode of ventricular tachycardia and expired. The death classifications for those patient deaths where the PCD® Device was programmed OFF are provided in Table 32-2.

PCD® Transvene™ System PCD® Device OFF Death Classification	
Death Classification	**Number of Patients**
Sudden Cardiac	1
Non-Sudden Cardiac	4
Noncardiac	2
TOTAL	7
Perioperative	1

Table 32-2: PCD® Transvene™ System - PCD® Device OFF Death Classifications

120

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant:
Date of Death:
Death Classification: **Noncardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

C3 141

Parameter	Value
Sensitivity	0.3 mV
TDI	450 ms
VT NID	20
VT Rx #1	CV/34J/SEQ
VT Rx #2	CV/34J/SEQ
VT Rx #3	CV/34J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	380 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified the patient death as perioperative, noncardiac and not related to the implanted PCD Transvene System. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

Patient (b)(6)

122

PCD Serial Number: (b)(6), (b)(4)
Date of Implant:
Date of Death:
Death Classification: **Sudden Cardiac**

(b)(4), (b)(6)

143

(b)(4), (b)(6)

(b)(4), (b)(6)

123

Parameter	Value
Sensitivity	0.3 mV
TDI	490 ms
VT NID	12
VT Rx #1	Burst
VT Rx #2	CV/5J/SIM
VT Rx #3	CV/34J/SIM
VT Rx #4	CV/34J/SIM
FDI	320 ms
VF NID	18
VF Rx #1	18J/SIM
VF Rx #2	34J/SIM
VF Rx #3	34J/SIM
VF Rx #4	34J/SIM

(b)(4), (b)(6)

(b)(4), (b)(6)

144

The investigator classified this patient death as perioperative and sudden cardiac. The relationship of the death to the implanted PCD Transvene System was classified as unknown. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification. 124

135

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant:
Date of Death:
Death Classification: Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

successfully reprogrammed and VF inductions were performed.

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(b)(4), (b)(6)

(b)(4), (b)(6)

programmed status was as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	450 ms
VT NID	12
VT Rx #1	Ramp
VT Rx #2	CV/34J/SINGLE
VT Rx #3	CV/34J/SINGLE
VT Rx #4	CV/34J/SINGLE
FDI	300 ms
VF NID	12
VF Rx #1	34J/SINGLE
VF Rx #2	34J/SINGLE
VF Rx #3	34J/SINGLE
VF Rx #4	34J/SINGLE

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4)

(b)(4)

The investigator classified this patient death as perioperative, sudden cardiac and not related to the implanted PCD Transvene System. The investigator felt that the patient's death was related to her severe left ventricular dysfunction. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

129

Patient (b)(6)

PCD Serial Number:
Date of Implant:
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(6), (b)(4)

(b)(4)

(b)(4)

150

(b)(4)

130

(b)(4)

The investigator classified this patient death as periopertive, non-sudden cardiac and related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and felt that the death was related to the implant procedure and not the implanted PCD Transvene System.

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Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant:
Date of Death:
Death Classification: **Non-Sudden Cardiac**

(b)(4)

132

Parameter	Value
Sensitivity	0.3 mV
TDI	OFF
VT NID	OFF
VT Rx #1	OFF
VT Rx #2	OFF
VT Rx #3	OFF
VT Rx #4	OFF
FDI	320 ms
VF NID	24
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4)

(b)(4)

The cause of death was reported as perioperative, non-sudden cardiac secondary to end stage heart failure by the investigator and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of the patient death and agreed with the investigator's classification.

153

33. (b)(4)

(b)(4)

17. **Please discuss your clinical experience (treatment efficacy, lead orientation, complications and survival rates) of the patients who have been followed for 1 year and more.** 134

RESPONSE:

A summary table of this experience and relevant discussion is provided below.

PCD™ Transvene™ System Data Summary		
	All Patients (3 Electrode Systems)	Patients with 12 months of Follow-up
Number of Patients	757	115
Device Months Follow-up	4246.4 mo	1835.5 mo
Mean Follow-up Time	5.6 mo	15.7 mo
Maximum Follow-up Time	28.6 mo	28.6 mo
Number, % Male Number, % Female	610 80.6% 147 19.4%	91 79.1% 24 20.9%
Mean Age	59.4 yrs	57.0 yrs
Primary Indication: SCD VT SCD/VT	 281 37.1% 377 49.8% 99 13.1%	 45 39.1% 56 48.7% 14 12.2%
Coronary Artery Disease	561 74.1%	85 73.9%
Mean Ejection Fraction	35.6% (n=688)	40.5% (n=104)
Lead Orientation: RV-CS-SQ RV-SQ-SVC RV-CS-SVC	 222 29.3% 496 65.5% 39 5.2%	 33 28.7% 73 63.5% 9 7.8%
Mean LED	16.0 (n=702)	15.2 (n=105)
Mean DFT	14.8 (n=316)	13.8 (n=62)
Spontaneous VT: Number of Patients Number of Episodes % Success	 226 5430 98.7%	 60 1770 98.9%
Spontaneous VF: Number of Patients Number of Episodes % Success	 198 973 99.1%	 37 248 98.8%
One Year Overall Survival One Year SCD Survival	95.3% 99.8%	100.0% 100.0%
Patients with complications	138 18.2%	24 20.9%

The patients population (n=115) with 12 months or more of follow-up is predominantly male (79.1%) with a mean age of 57.0 years. In the majority of patients (48.7%), the primary indication for implant was recurrent, sustained ventricular tachycardia without an episode of sudden cardiac death. The treatment efficacy for this patient population was 98.9% for spontaneous VT episodes, and 98.8% for VF episodes, which is equivalent to the overall patient population with 98.7% and 99.1% respectively. Overall and sudden cardiac death one year survival for this patient population is 100.0% since all patients have been followed for one year or greater. In the patients followed for 12 months or more there has been one death which is classified as non-sudden cardiac. This death occurred 684 days (22.5 months) post implant. Twenty-four (20.9%) of the patients followed for 12 months had a complication.

Based on the data above, the PCD™ has performed safely and reliably for patients followed for 12 months or greater.

18

34. Please provide an engineering drawing of each Transvene™ lead model which identifies the segments of the lead and a description of the tests that each segment and the full lead body underwent. 136

RESPONSE:

The table below lists the tests which each Transvene™ lead underwent as indicated by the "x". The segments are labeled on the engineering drawings that follow. For consistency, each lead has been labeled as follows:

(b)(4)

(b)(4)

Test Method	Segment A	B	C	D
(b)(4)				

(b)(4)

(b)(4)

Test Method	Safety Issue
(b)(4)	

(b)(4)

Test Description

Lead System Test

(b)(4)

(b)(4)

DC Resistance

(b)(4)

(b)(4)

Leak Test

(b)(4)

(b)(4)

Lead Stiffness

(b)(4)

(b)(4)

Anchor Sleeve Sliding

(b)(4)

(b)(4)

Flex Testing

(b)(4)

(b)(4)

(b)(4)

(b)(4)

.41

Tensile Strength

(b)(4)

(b)(4)

Crimp/Weld Strength

(b)(4)

(b)(4)

Crush Test

(b)(4)

(b)(4)

Biostability

(b)(4)

(b)(4)

Biocompatibility

(b)(4)

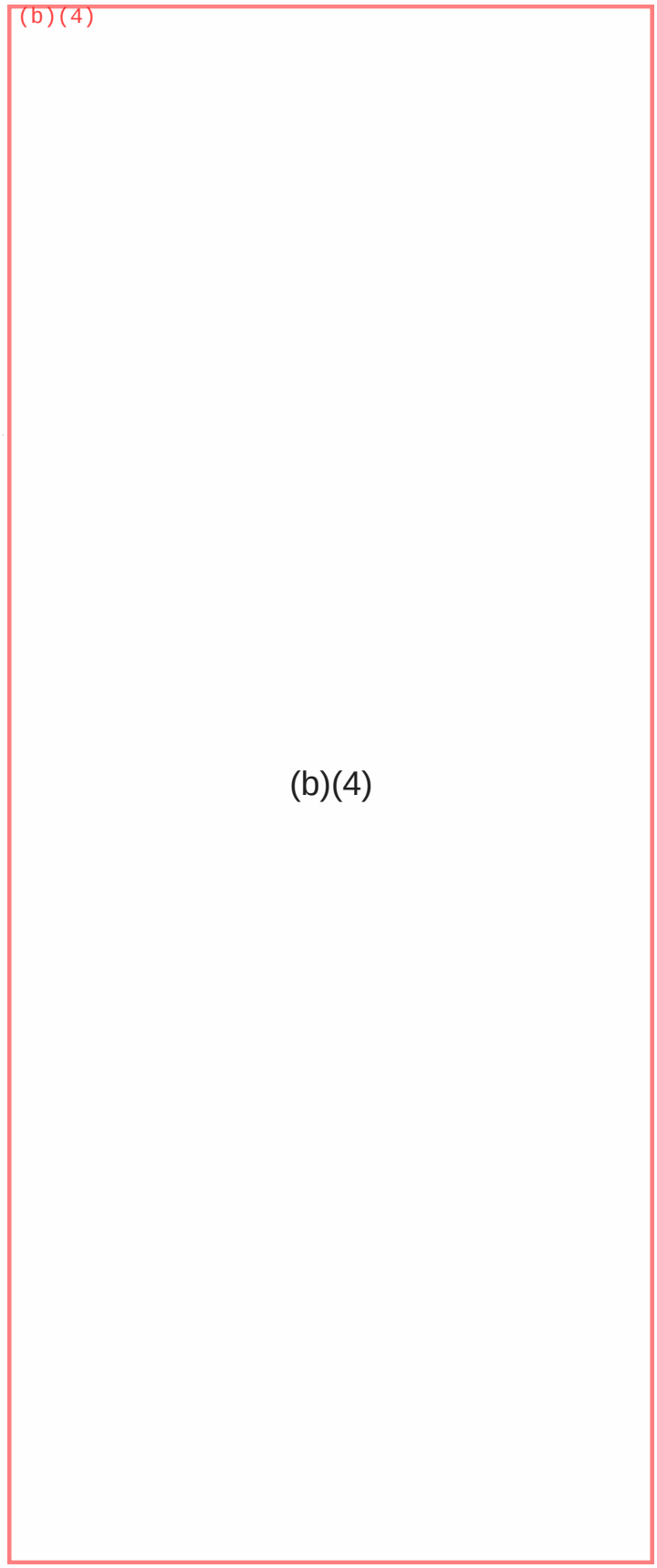
(b)(4)

(b)(4)

(b)(4)

MODEL 6963 CS / SVC LEAD

(b)(4)



MODEL 6963 CS / SVC LEAD

(b)(4)

(b)(4)

MODEL 6963 CS / SVC LEAD

(b)(4)

(b)(4)

MODEL 6963 CS / SVC LEAD

(b)(4)

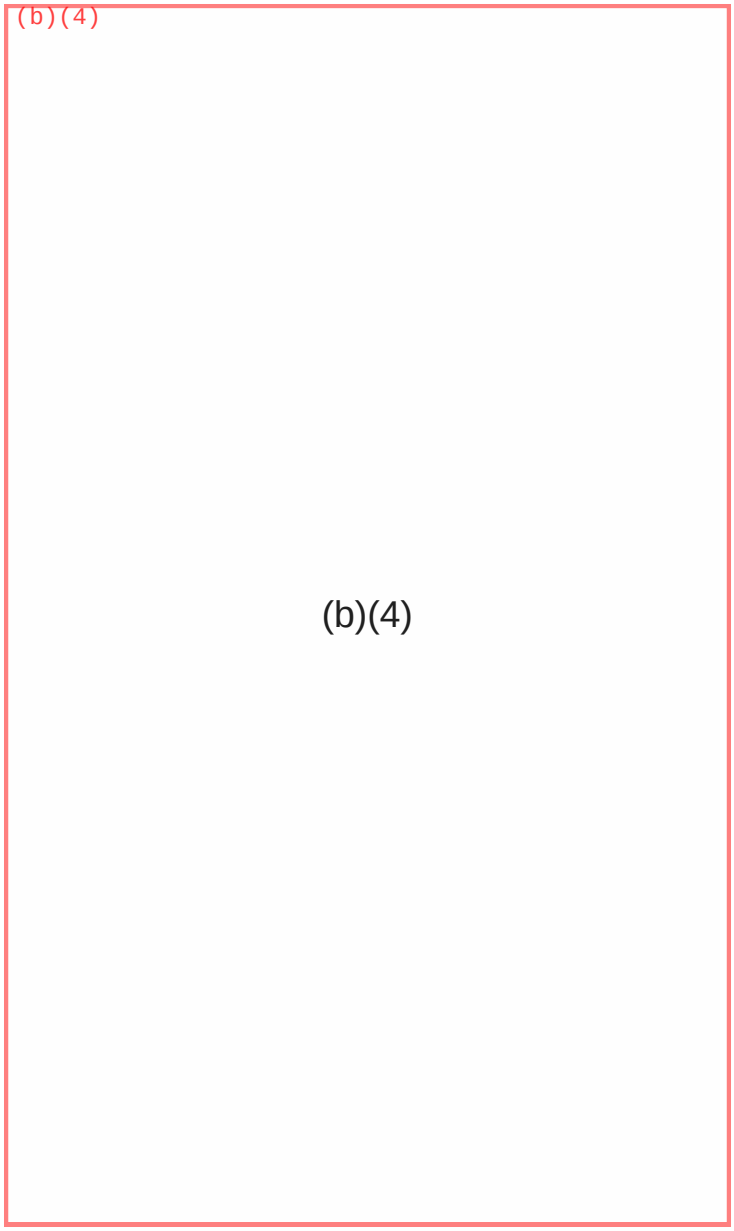
MODEL 6966 RIGHT VENTRICULAR LEAD

(b)(4)

(b)(4)

MODEL 6966 RIGHT VENTRICULAR LEAD

(b)(4)



MODEL 6966 RIGHT VENTRICULAR LEAD

(b)(4)

(b)(4)

MO

(b)(4)

(b)(4)

DEL 6966 RIGHT VENTRICULAR LEAD

(b)(4)

FIDENTIAL

151

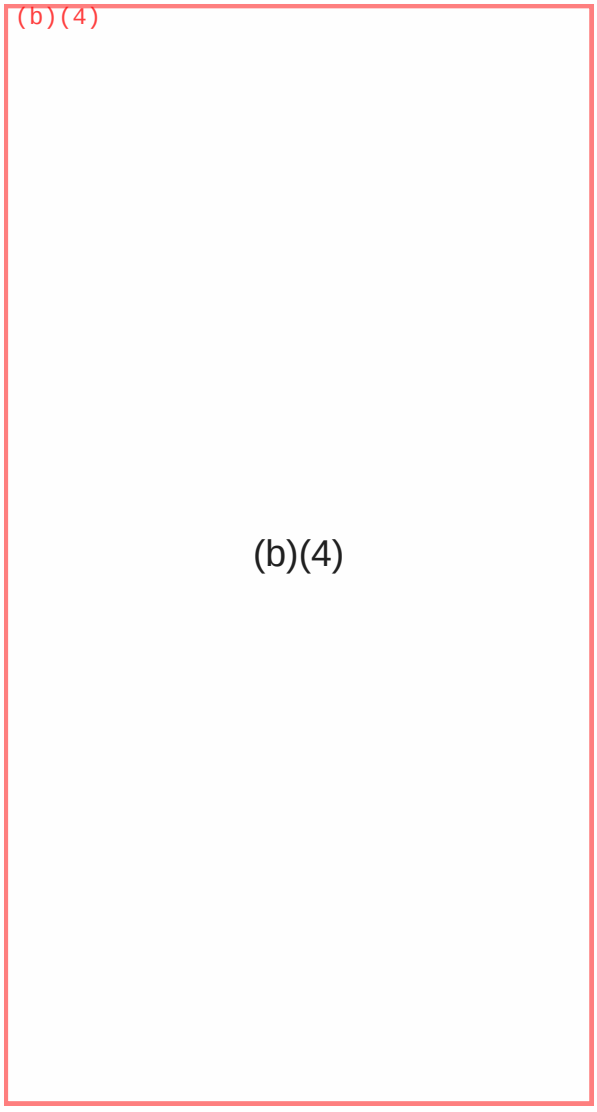
(b)(4)

MODEL 6999 SUBCUTANEOUS PATCH LEAD

173

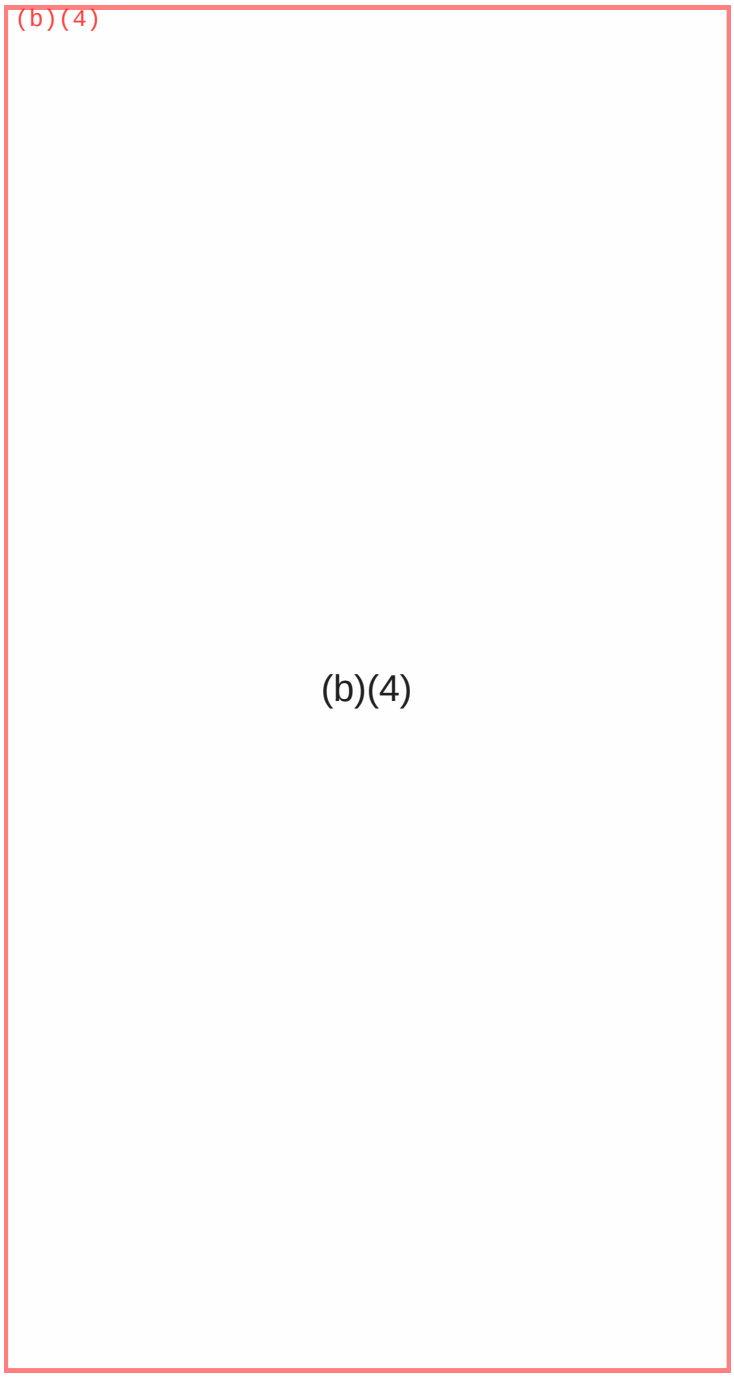
(b)(4)

(b)(4)



MODEL 6999 SUBCUTANEOUS PATCH LEAD

(b)(4)



MODEL 6999 SUBCUTANEOUS PATCH LEAD

35. Since flex testing exerts a considerable amount of stress on the lead, and is essential to life testing, why was it considered that (b)(4) cycles at a bend radius of (b)(4) inch per lead model over a (b)(4) month period would be sufficient? Describe how the full lead and different segments were flexed. Did you do a finite element stress analysis to validate the flex testing stress?

RESPONSE:

Flex testing is considered an important factor in assessing lead flex life longevity. The Medtronic flex standard minimum requirement is a (b)(4) (b)(4) of (b)(4) cycles at a (b)(4) inch radius. This flex standard was applied to the design of the (b)(4) Lead System Test sequence. Initially each lead was inspected and tested for DC resistance. In the (b)(4) test protocol, each lead went through the following sequence of tests (b)(4)

(b)(4)

(b)(4)

At the end of the Lead System Testing, each lead was visually reinspected, had the DC resistance measured and intermittency tested. In conclusion, all the leads met all test requirements without failure and therefore demonstrate an acceptable assurance of safety and reliability in lead design.

Each lead had a section marked to identify were to flex the lead body. This was done to assure that each lead had the same section of the lead body flexed for each of (b)(4) test cycles. By assuring the same location, each lead body was subjected to a total of (b)(4) cycles of flexing. The marked section was in the same region identified as "Lead Body" in the answer to question 34 for each lead Model. The Lead Body flex test set-up is illustrated below:

FLEX TEST FIXTURE

(b)(4)

(b)(4)

Each lead was flexed at the rate of (b)(4) cycles (b)(4) over a radius of (b)(4) inch at (b)(4) until reaching the required number of cycles per the Lead System Testing protocol.

The Model 6999, a unipolar, subcutaneous patch, was subjected to a flex test of the (b)(4) that could be a result of patient body motion. The patch flex set-up is illustrated below:

(b)(4)

(b)(4)

TEST FIXTURE FOR FLEX OF PATCH BODY

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

36. In light of the failure of your platinum sputtered polyurethane bradycardia pacing leads, and since the Transvene™ lead Model 6966 is also a platinum sputtered polyurethane lead, please provide documentation regarding the failure mechanism of the pacing leads and all relevant information pertaining to these cases. How can we be assured that the failure may be restricted to the bradycardia pacing leads? Based on your testing to date regarding the pacing leads and the testing of the Model 6966 lead, discuss the potential and the probability of failure of the Model 6966 lead. A side by side comparison of the Model 6966 and the 4,000 series bradycardia pacing leads must be provided. The comparison must include material, design, dimensions, function, tests performed and a schematic drawing.

RESPONSE:

Background on Brady Pacing Lead Experiences

Medtronic utilizes two systems to monitor performance of its brady pacing leads. The analysis of returned product is used to identify lead failure mechanisms. However, it cannot be used to estimate clinical performance since all leads/lead segments are not explanted or returned. Clinical performance is monitored through our (b)(4) (b)(4) a multi-center study currently involving eleven representative U.S. Clinical centers and over (b)(4) leads. Lead performance in the (b)(4) is presented as actuarial survival from clinical complications resulting in lead explants or abandonment. Specific complication criteria have been established (reference Medtronic Product Performance Report, February 1993, in Appendix C). Since all leads are not explanted it is not always possible to relate a clinical complication to a specific failure mechanism and not all complications are associated with lead failure.

The primary failure mechanisms for brady pacing leads are conductor fracture and insulation failure. Conductor fractures are primarily associated with the widely accepted "Subclavian Stick" implant procedure using percutaneous lead introducers. Leads implanted by this procedure can be clamped and crushed between the first rib and clavicle, leading to fracture of the conductor, and sometimes, insulation failures as well. Bipolar leads are more susceptible to this failure mechanism than unipolar leads because of their larger lead body diameter. Crush fractures tend to occur primarily during the first two years post implant.

For leads with polyurethane insulation, the primary insulation failure mechanisms are Environmental Stress Cracking (ESC) and Metal Ion

Oxidation (MIO); both tend to occur starting about 2 years post implant. Bipolar leads tend to be more susceptible to insulation failure than unipolar leads.

ESC is associated with stress on the lead either induced during manufacture or via implant procedure. Newer generation Medtronic leads have greater ESC resistance due to improvements in design, manufacturing processes and materials.

MIO is an oxidative degradation of polyurethane insulation. The reaction is catalyzed by metal ions released by the corrosion of the conductor coils. To reduce the potential for MIO, newer Medtronic lead designs have applied a sputtered coating of platinum to the conductor coils. Also, (b)(4) polyurethane tends to be more resistant to MIO than (b)(4) Medtronic has used an accelerated oxidation environment, (b)(4) to evaluate MIO and potential factors that can minimize its occurrence.

A table depicting the frequency of these failure mechanisms (conductor fractures, MIO and ESC) for brady leads, Models 4004/M and 4058/M, follows this response. As shown, conductor fracture due to crush is the predominate failure mode. See table, Failure Mechanisms, following this response.

The Model 4004/M is a bipolar lead incorporating (b)(4) polyurethane and platinum coating. As of February 28, 1993, survival probability of the Models 4004/4004M is (b)(4) months (reference the February 1993 Product Performance Report in Appendix C). Crush fracture is the primary source of lead failures to date, with rates comparable to that of earlier bipolar lead designs.

Over the past several months Medtronic and FDA have had numerous discussions about the occurrences of failure associated with MIO in the Model 4004/M lead. As of February 28, 1993, Returned Product Analyses has identified (b)(4) failures out of approximately (b)(4) leads implanted (b)(4) MIO failures in previous lead designs tend to predominate (b)(4) areas: proximally in the pacemaker pocket, medially in the clavicular region, and distally near the ring electrode. With Models 4004/M, platinum sputter coating appears to reduce the occurrence of MIO proximally and medially. The majority of the MIO failures (b)(4) occurred distally. Distal failure occurs between the ring electrode and the AV valve and appear to be related to flexing of the lead associated with ventricular contractions.

Initial (b)(4) testing was conducted under static conditions and gave no indication of this failure mechanism. Currently testing is underway to develop a dynamic (b)(4) test to study factors affecting this

failure mechanism and potential corrective actions. To date, we have been able to induce failures and are conducting experiments to understand contributing factors.

In order to illustrate the similarities and differences between the brady and tachy leads, a side-by-side comparison of the Model 6966 to the 4,000 series brady leads is presented in a table following this response. Note that only bipolar, polyurethane, brady leads from the 4,000 series are presented (includes Models 4016A, 4058/M, 4024, 4004/M and 4012/4082). This is due to their similarity of design characteristics to the 6966, and also because these brady leads are being, or were, widely used in the field, and therefore present with comprehensive data from the (b)(4) (b)(4) and Medtronic's returned product analysis. Tests performed to qualify the brady leads were the same as those used for the tachy leads (except for high voltage system and crush testing). All tests are consistent with Medtronic standards and requirements for implantable cardiac leads (reference response to #34). Drawings of these brady leads are also presented following the comparative tables.

Some common features to all the leads in the table are the (b)(4) conductor coil, coaxial coil design, polyurethane insulation (b)(4) and/or (b)(4) and platinum alloy electrode material. Like the 6966 lead, the Models 4016A, 4058/M and 4024 also have platinum coating on the conductor coil and (b)(4) as the inner insulation. Individual lead differences include the electrode fixation mechanisms, i.e., screw-in helix versus tines and the (b)(4) versus (b)(4) insulation usage. Using (b)(4) insulation provides more stiffness, and greater resistance to insulation failure, whereas (b)(4) provides for greater ease of handling.

As presented in the lead comparison table, the brady lead most similar to the 6966 lead is the 4016A. Both have (b)(4) polyurethane as the inner(most) insulation, (b)(4) for the middle/outer insulations, distal screw-in fixation mechanisms, similar French (introduction) sizes and virtually identical insulation dimensions. Only the coil dimensions vary slightly. Note that the 4058/M lead is also very similar to the 4016A; the only substantive change is the introduction size, (b)(4) Model 4016A and 4058/M leads have shown excellent clinical performance; for the 4016A actuarial survival is 98.2% at three years (b)(4) implants) and for the 4058/M actuarial survival is 99.7% at three years (b)(4) implants), reference the CLS and returned product analysis as presented in the Medtronic Product Performance Report, Appendix C.

As previously presented, the 6966 lead has a larger body diameter than the brady leads. This is to be expected given the tripolar coaxial design of the lead. Given the larger French size of the 6966, it is more susceptible to crush between the clavicle and rib than the smaller French

leads. Lead fracture due to crush in this area is, however, a recognized failure mechanism for all transvenous leads implanted via subclavian insertion, (brady or tachy leads). This is vigorously addressed in product labeling (lead technical manuals) and includes appropriate cautions about the use of the procedure.

Also, the larger diameter of the 6966 lead body and presence of a defibrillation coil electrode proximal to the distal pace/sense ring of the 6966 lead imparts more stiffness to it than the brady leads. Hence, there is less lead body movement below the valve when the 6966 is implanted in the right ventricle as compared to a brady lead. This was clearly evident in the videotape comparing the in-vivo flexing of both a brady and tachy lead (presented in FDA/Medtronic meeting of February 18, 1993). Decreased flexing of the 6966 lead below the valve is our basis for expecting flex-related MIO will not be a significant failure mechanism of the 6966 lead.

Analysis of Transvene Model 6966 Lead and Clinical Presentation

The Model 6966 tripolar tachy lead is comparatively less flexible than brady leads. Therefore, distal MIO as evident in a very small percent (b)(4) of brady 4004/4004M leads is not necessarily indicative of a similar occurrence in the 6966 lead. A videotape illustrating the clinical flex performance differences between brady and tachy leads was presented during the FDA/Medtronic meeting on February 18.

Analysis of the Model 6966 lead, as it relates to the potential for MIO, indicates that it would be more likely to occur on the middle versus the outer or innermost insulations. Lead failure due to MIO typically is found on the inner insulation on returned bipolar brady leads. Therefore, this failure mechanism is not expected to significantly affect the (b)(4) outer insulation of the 6966 lead. Should MIO occur on the outer insulation of the 6966 lead, the net effect would be an increased defibrillation electrode surface area. This would not be expected to significantly affect system performance. Additionally, the more resistant properties of (b)(4) (to MIO), of the 6966 innermost insulation, are expected to further reduce the potential for MIO (99.7% survival Model 4058/M at three years, see Product Performance Report, Appendix C).

For the Model 6966 lead, should the middle (b)(4) insulation fail, it would likely present initially as an intermittent short (as is more typical with brady leads) and can progress over time if not identified and treated, to a hard (direct) short. These could manifest initially as oversensing, and ultimately as integrated bipolar sensing, respectively (intermittent versus hard short). In the case of a hard short of the middle insulation, specifically, shorting the pacing tip to the common

defibrillation electrode, an integrated bipolar sensing system is created. In this type of system, sensing occurs between the unipolar pacing tip and the common defibrillation electrode (versus standard bipolar sensing between the pace/sense tip and the ring electrodes). This type of sensing system is identical to the (b)(4) (b)(4) currently in clinical trials, and also to Medtronic's historic Transvene RV lead, the Model SP2100 lead. These type of integrated systems have been shown to be clinically acceptable. Note that fifteen Model SP2100 leads were implanted at the start of the Transvene clinical study. There have been no observations or reported problems related to the SP2100 lead performance. (Data from the SP2100 lead have been incorporated in the clinical experience analysis reported in this PMA application.)

Intermittent sensing could result in oversensing, if the detection criteria are also met, and this could result in delivery of inappropriate, i.e., not needed, therapies. This can be considered a "safe failure" given the system would "err" by oversensing (versus undersensing) and the patient could receive an unnecessary therapy. Also, patients are instructed to report therapies to their physicians; this facilitates identification of any inappropriate therapy.

Recently, a Model 6884[1] lead was explanted after 27 months when the patient received a heart transplant. The lead was fully functional at explant, however, returned product analysis has indicated the presence of some MIO in the clavicular region. Transvene leads, like brady leads, are implanted by subclavian insertion and are susceptible to being crushed between the clavicle and first rib. As indicated above, with brady leads this can result in conductor fractures, insulation failures or both. Analysis of the specific Model 6884 lead is ongoing and a more detailed report will be provided in approximately 30 days.

It should be noted that MIO is only one potential failure mechanism of implantable leads. As discussed, others include fracture due to crush in the area of subclavian insertion, environmental stress cracking due to stresses the in-vivo environment may impart to the lead and lead dislodgement.

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[1] The Model 6884 lead is the earlier version of the Model 6966 lead and differs only in the connector pin configuration; the 6884 has a (b)(4) high voltage connector pin and the 6966 has a (b)(4) high voltage connector pin. Otherwise the leads are the same.

Transvene Clinical Assessment Experience

Given over 2000 worldwide Transvene patients implanted to date, ranging from zero to forty months implant duration, there have been no reports of undersensing, insulation failures, or oversensing that could not be managed via reprogramming. Furthermore, the benefits of Transvene implantation are dramatically apparent from the perspective of perioperative mortality, 0.7 percent for Transvene versus 5.3 percent for epicardial implants. Transvene survival from SCD is 99.5 percent and overall survival is 93.3 percent at one year. Additionally, Transvene implants, on average, require 8 days in hospital versus 11 days for an epicardial system; a significant cost savings. In summary, the benefits of the Transvene system performance clearly surpass the potential for MIO, or other potential failure mechanisms, in the 6966 lead.

Conclusions

Although Medtronic cannot assure that MIO or other lead failure mechanisms will not occur in the Model 6966 lead, the actual benefits of the Transvene system, as previously discussed, would appear to exceed the potential risk due to MIO. Analysis shows that the potential for MIO to occur in the 6966 lead would result in a "safe failure." Note that preclinical and animal testing cannot completely simulate the long-term implant environment, thereby eliminating all potential for lead failures in-vivo. This was recognized by Congress in implementing the Postmarket surveillance provision in the Safe Medical Device Act of 1990. It is clear that postmarket surveillance mechanisms, e.g., returned product analysis and chronic lead monitoring, are more appropriate mechanisms for evaluating and managing potential failure mechanisms of implantable cardiac leads.

FAILURE MECHANISMS

(CLINICAL/ELECTRICAL FAILURES FROM RETURN PRODUCT ANALYSIS)

MECHANISM	MODEL 4004/4004M	MODEL 4058/4058M
(b)(4)	(b)(4)	

TACHY/BRADY LEAD COMPARISON

Parameter	Model 6966	Model 4016A	Model 4058/M1
(b)(4)			

4004M, 4058M and 4082 are the IS-1 versions of the respective leads.

TACHY/BRADY LEAD COMPARISON (CONTINUED)

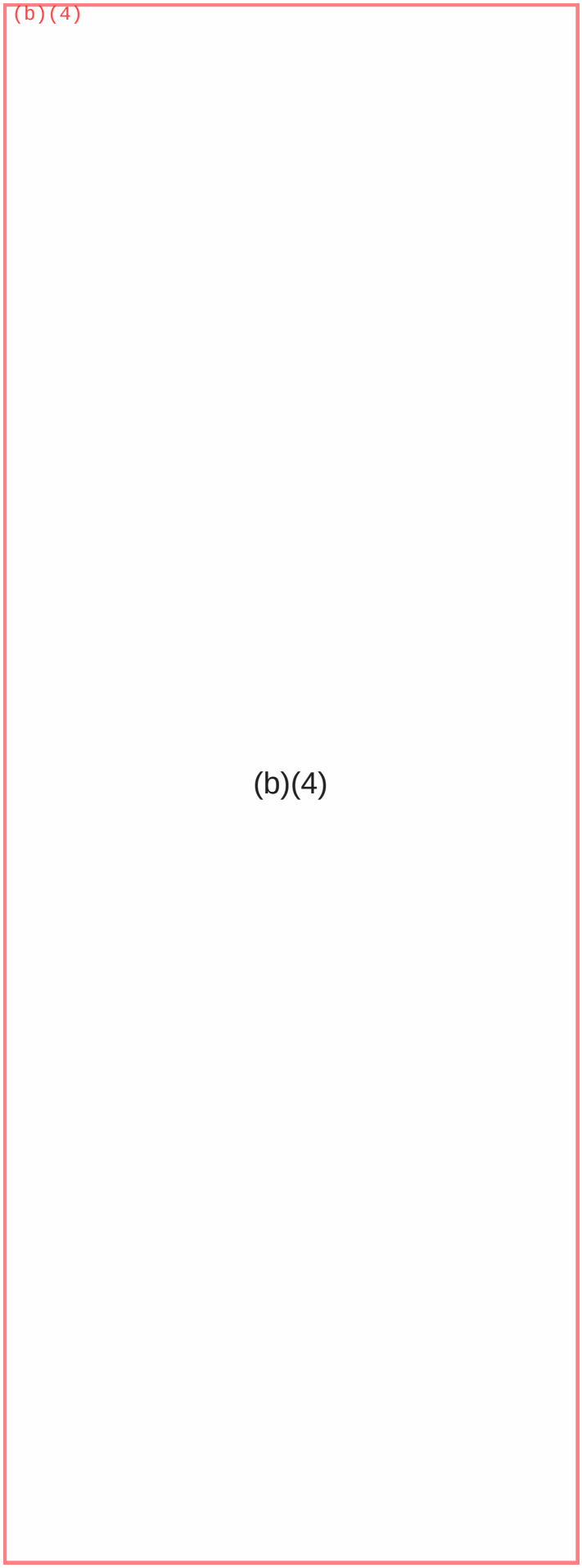
Parameter	Model 4024	Model 4004/M[1]	Model 4012/4082[1]

(b)(4)

(b)(4)

[1] 4004M, 4058M and 4082 are the IS-1 versions of the respective leads.

(b)(4)



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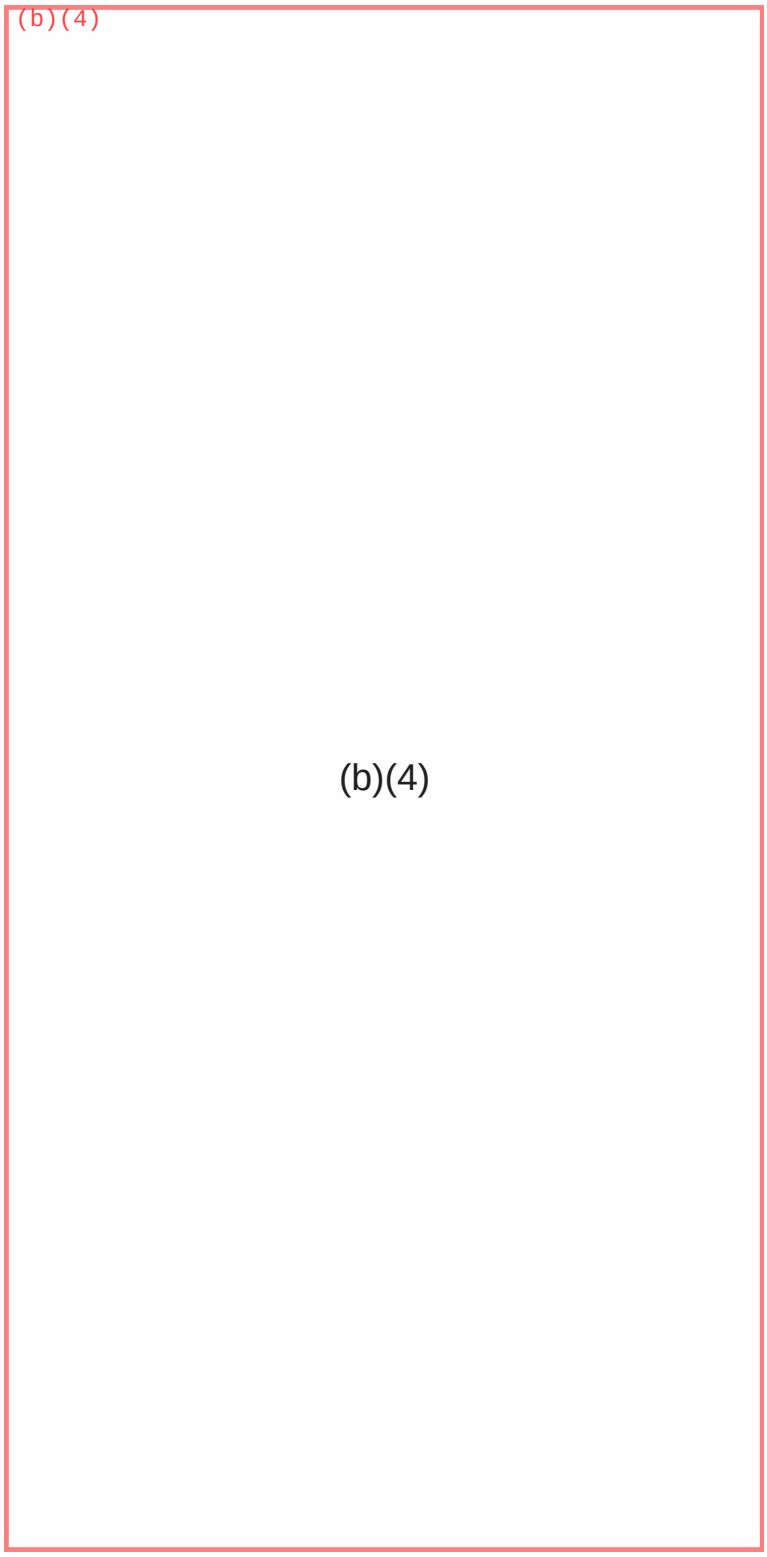

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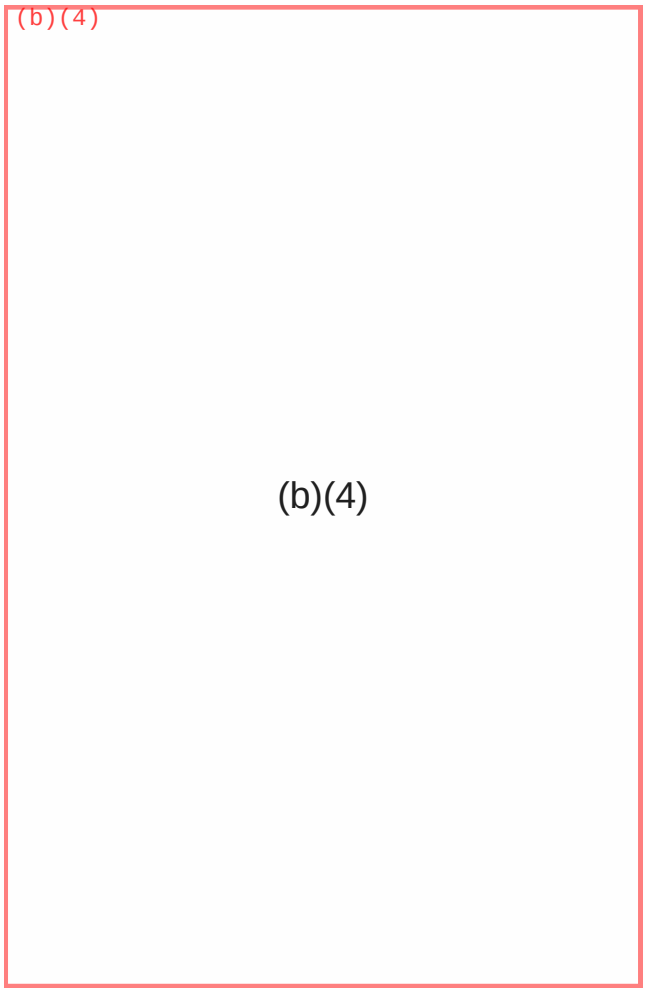
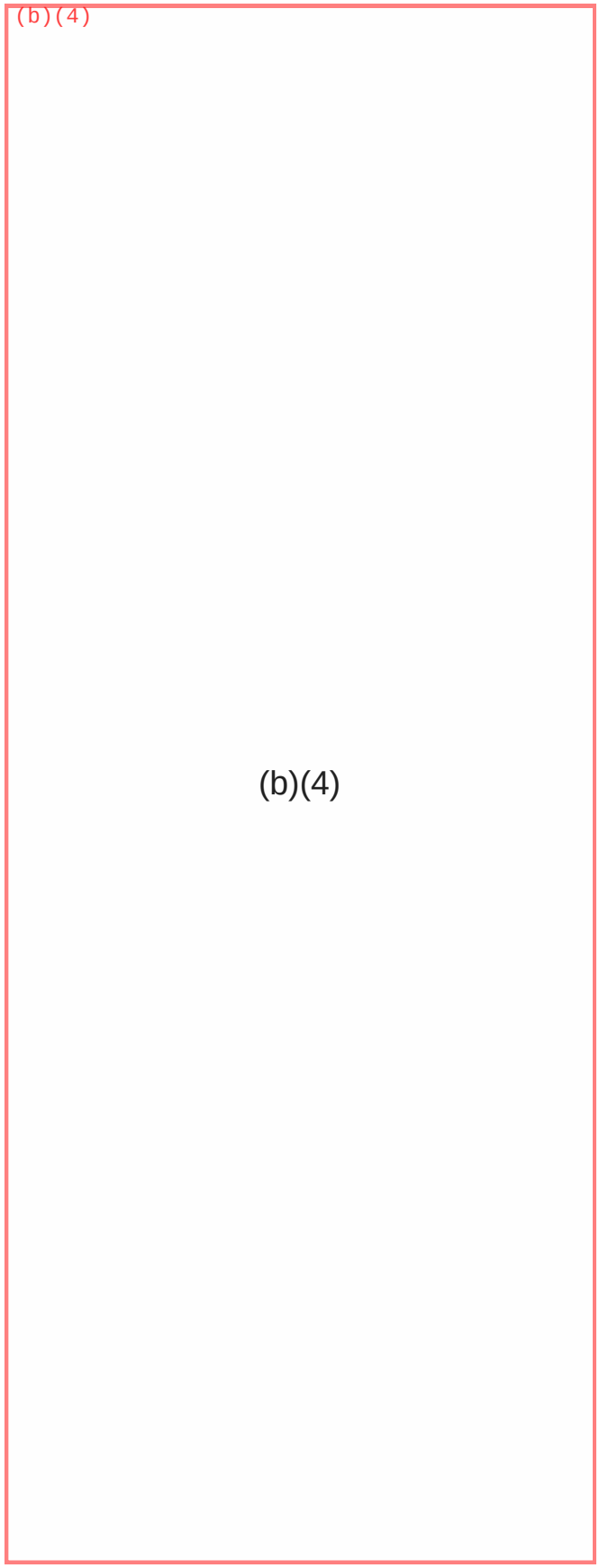


MODEL 4016A

(b)(4)

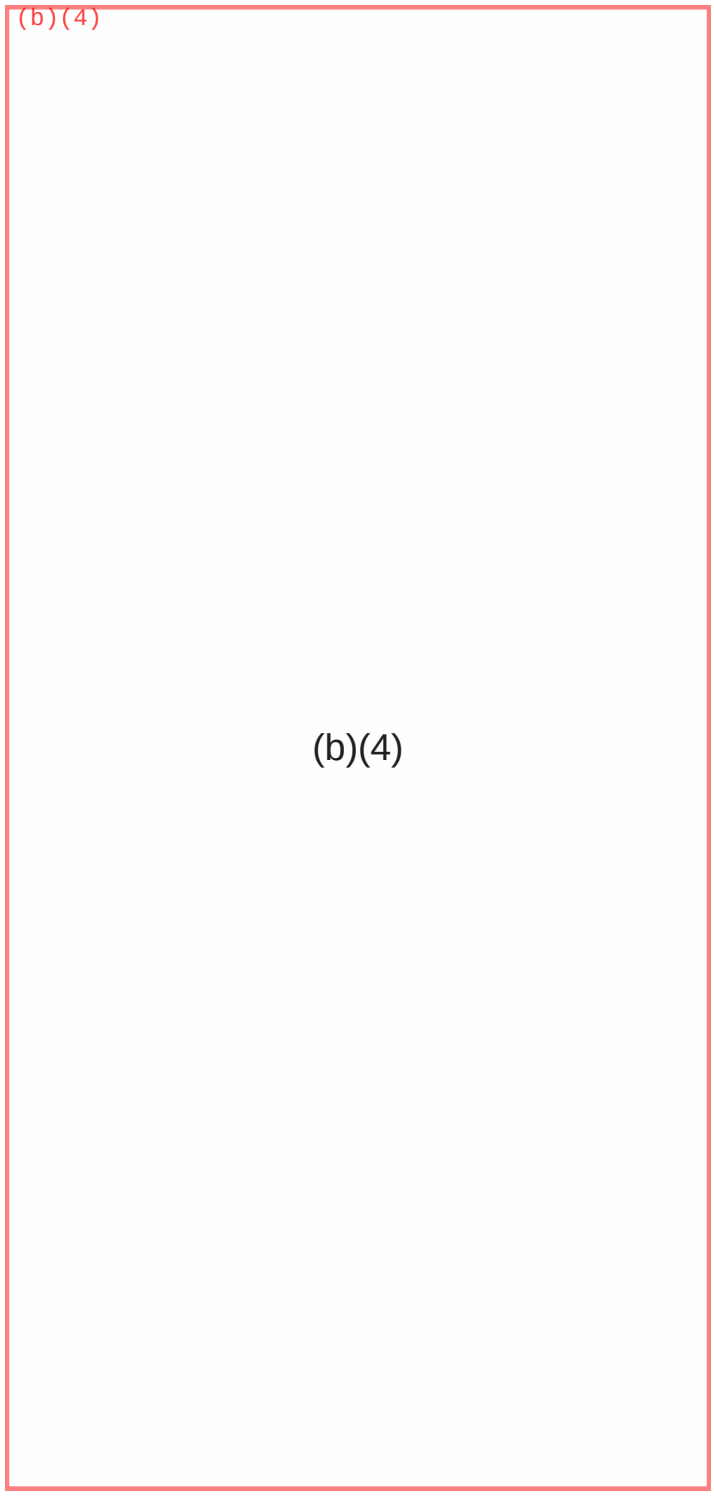
MODEL 4016A

(b)(4)

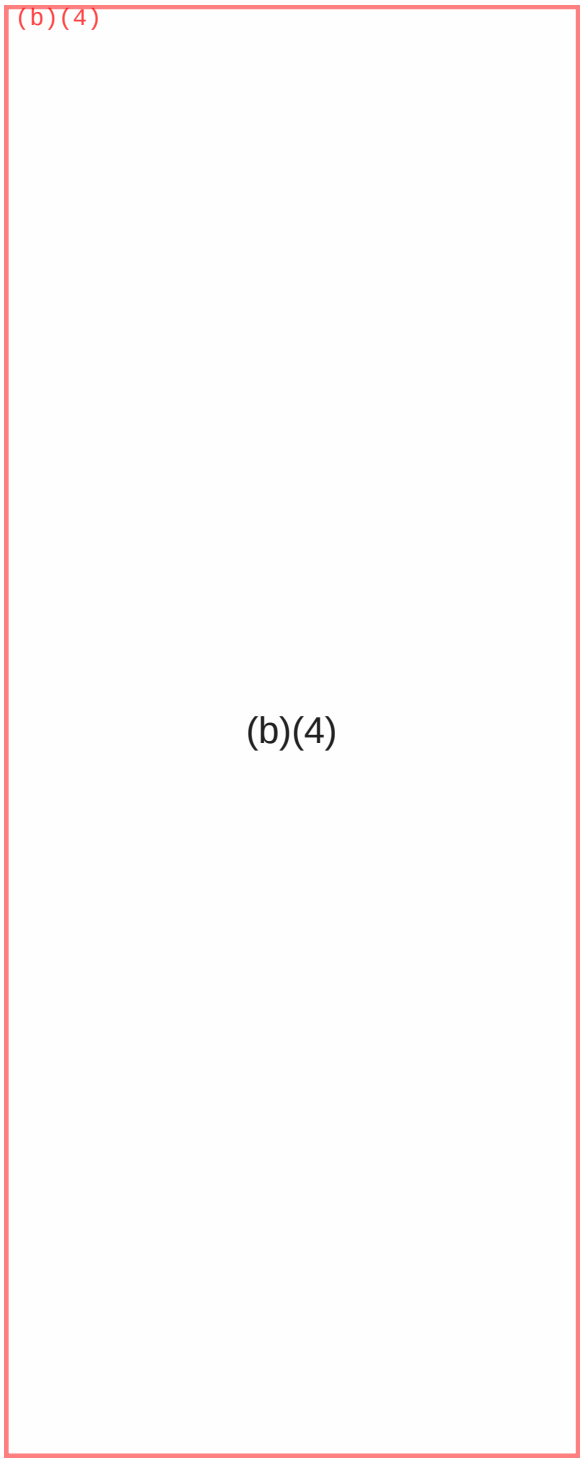


MODEL 4058/M

(b)(4)



(b)(4)



MODEL 4058/M

(b)(4)

(b)(4)

MODEL 4058/M

MODEL 4024

(b)(4)

ASSEMBLY

(b)(4)

MODEL 4024

(b)(4)

TIP AND CONNECTOR ASSEMBLIES

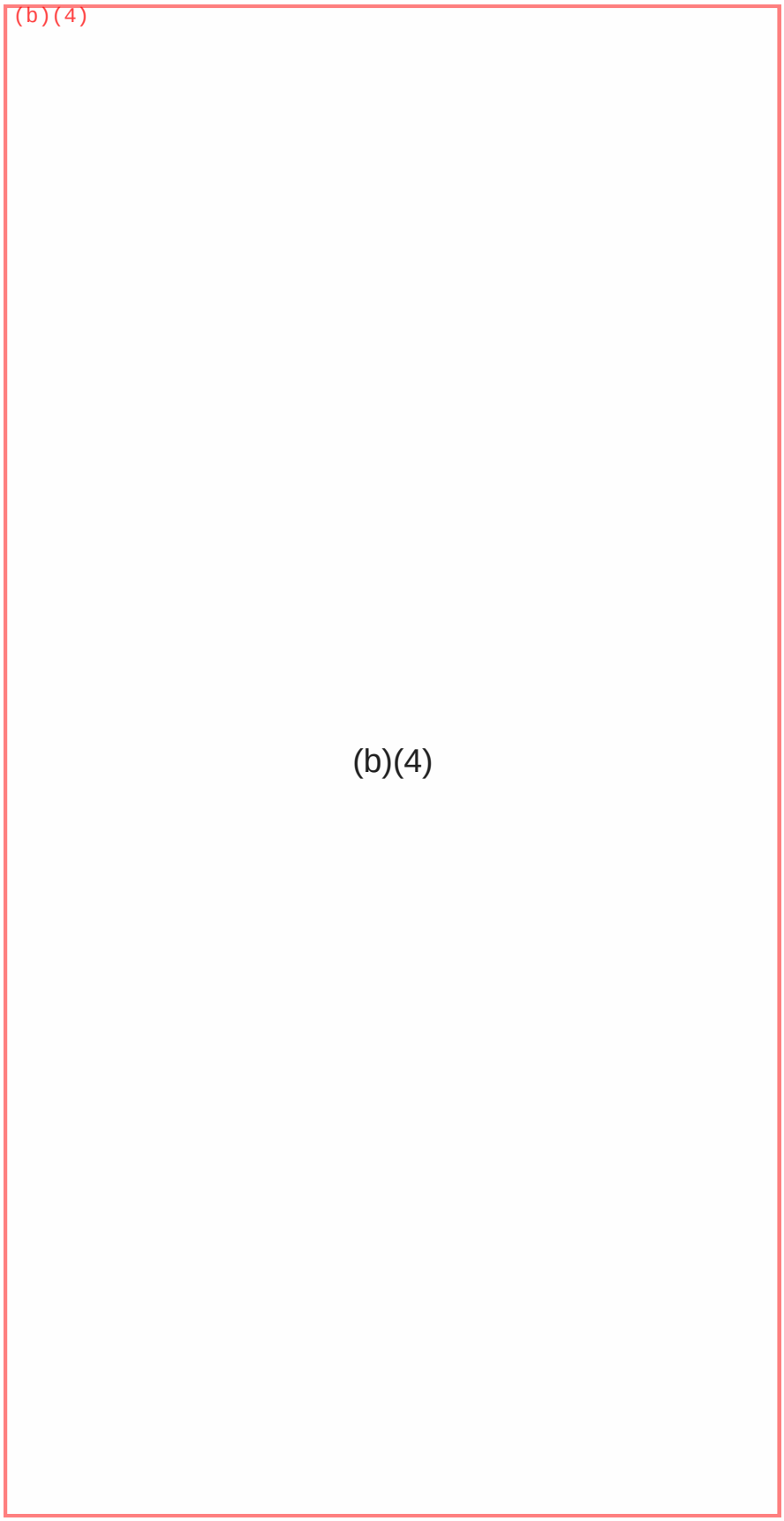
(b)(4)

MODEL 4004M

(b)(4)

CONNECTOR ASSEMBLY

(b)(4)



MODEL 4004M

DISTAL ASSEMBLY

63

(b)(4)

MODEL 4082

(b)(4)

CONNECTOR ASSEMBLY

37. A copy of the Summary of Safety and Effectiveness which includes the updated data must be provided.

RESPONSE:

See Attachment 3.

3

Summary of Safety and Effectiveness (March 26, 1993)

A. Indications For Use

The Medtronic PCD Model 7217B Multiprogrammable Tachyarrhythmia Control System with Nonthoracotomy Cardioversion and Defibrillation Electrodes (hereafter referred to as the PCD Transvene System) is intended to treat patients at risk of sudden cardiac death due to ventricular tachyarrhythmias. Indications for use include:

- Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or
- Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.
- Patients undergoing replacement of a previously implanted implantable cardioverter defibrillator.

The patients who meet the above patient selection criteria should have also undergone a complete cardiological evaluation that includes electrophysiological testing. Electrophysiologic evaluation and testing of the safety and efficacy of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the PCD Transvene System.

The PCD Transvene System components, except for the defibrillation lead system, are identical to the PCD Epicardial System which was unanimously recommended for approval by the FDA Advisory Panel on February 3, 1992 and FDA approved on February 11, 1993.

Market approval **is not** being sought for use of the PCD Device with other manufacturers transvenous defibrillation lead systems. In addition, market approval **is not** being sought for the use of the PCD Transvene lead system with other manufacturers implantable cardioverter defibrillators.

B. Description of the Transvene Lead/PCD System

The Medtronic Tachyarrhythmia Control System consists of two fundamental configurations: (1) the implantable configuration and (2) the external configuration. Both configurations use the Transvene lead system. See Figure III B-1

The implantable configuration is composed of a Pacer-Cardioverter-Defibrillator (PCD) device, implantable leads, and a programmer. The PCD device is an implantable, multiprogrammable, automatic tachyarrhythmia control device.

The external configuration is composed of an External Tachyarrhythmia Control Device (ETCD), a patient cable, implantable leads, and a programmer. The ETCD is an externally-operated, multiprogrammable, tachyarrhythmia control device.

Intended Uses - Transvene Leads

Model 6963 Lead

The Medtronic Transvene Model 6963 Unipolar, Coronary Sinus or Superior Vena Cava, Transvenous Lead features an electrode for the delivery of cardioversion and defibrillation therapies. It is intended for long-term use in the coronary sinus or superior vena cava and is designed to be used with an implantable tachyarrhythmia control device along with at least one other lead, such as the Model 6966 Tripolar, Right Ventricular, Transvenous Lead.

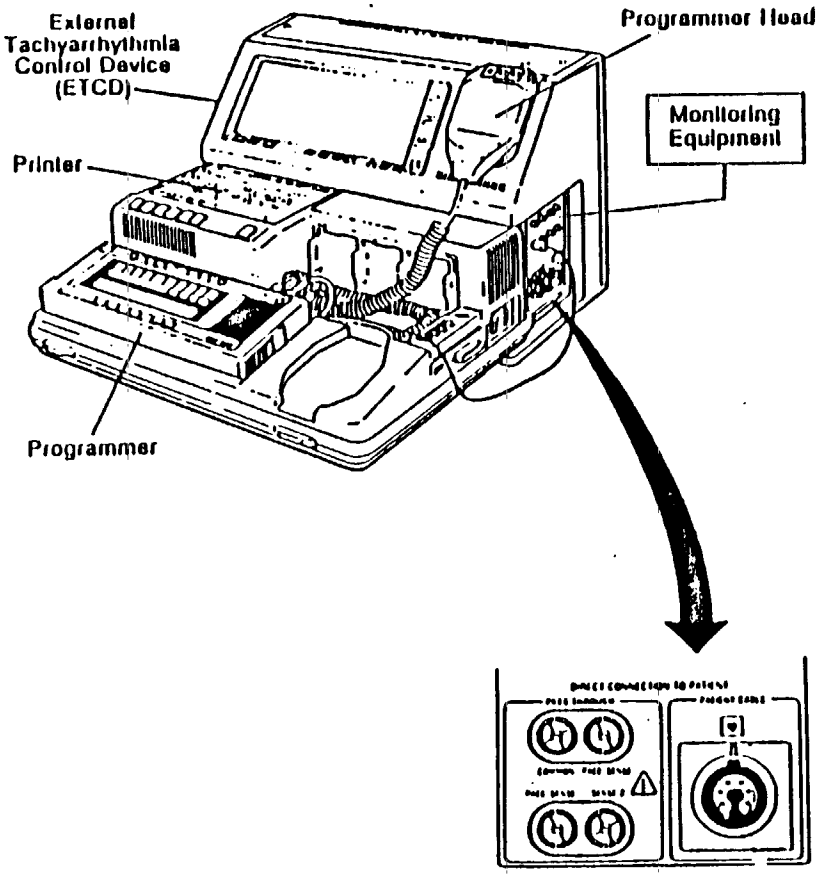
The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

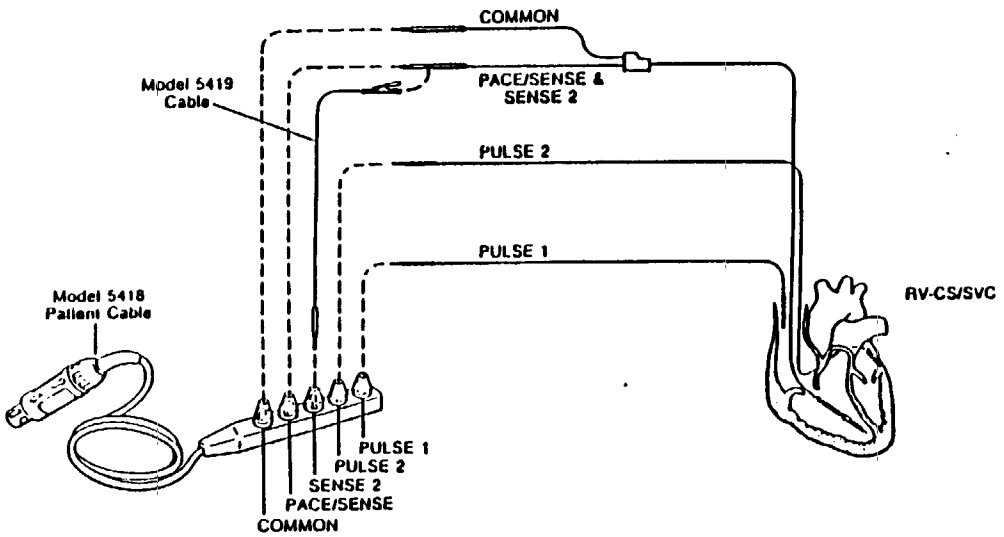
Model 6966 Lead

The Medtronic Transvene Model 6966 Tripolar, Endocardial, Screw-In Lead is designed for pacing, sensing, and delivering cardioversion and defibrillation pulses in the ventricle. The lead has application where implantable tachyarrhythmia control systems are indicated.

The Model 6966 lead has a helical electrode made of platinum alloy that can be actively fixed in the endocardium. The helix can be extended or retracted by rotating the lead connector pin with a special fixation tool.

Active fixation leads are particularly beneficial for patients who have smooth or hypertrophic hearts where lead dislodgement may be potential a problem.





Connections to Model 5418 Patient Cable for
Typical Simultaneous or Sequential Pathway (RV-CS/SVC).

FIGURE III B-1

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The three electrodes of this lead are the coil, ring, and helix:

The defibrillating **coil electrode** is most proximal to the pulse generator and connects electrically to the connector pin of the unipolar leg of the bifurcation. This unipolar leg will not accept a stylet.

The **ring electrode** is proximal to the helix and connects electrically to the connector ring of the bipolar leg of the bifurcation.

The **helix tip electrode** is most distal to the pulse generator and provides active fixation in the endocardium. It can be extended or retracted by rotating the lead connector pin with a special fixation tool. The helix electrode connects electrically to the connector PIN of the bipolar leg of the bifurcation. This bipolar leg is the only one that will accept a stylet.

The helix tip electrode and the ring electrode may be used for bipolar pacing and sensing; the coil electrode is intended to be used for delivery of cardioversion and defibrillation pulses.

The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

Model 6999 Lead

The Medtronic Model 6999 Unipolar, Subcutaneous, Oval, Patch Lead features an electrode for the delivery of cardioversion and defibrillation therapies. It is intended for long-term use and is designed to be used with an implantable tachyarrhythmia control device along with at least one complementary defibrillating electrode and a pacing/sensing lead; a third defibrillating electrode may also be used.

The lead has application for patients in whom implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

Intended Uses - PCD Device

The Model 7217B PCD device is intended for use in patients who are at high risk of sudden death due to ventricular tachyarrhythmia.

Current medical research indicates that such patients should:

- have survived at least one episode of a cardiac arrest, presumably due to a ventricular tachyarrhythmia as evidenced by resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; or

- in the absence of a prior cardiac arrest, have recurrent, sustained ventricular tachycardia that occur spontaneously or can be induced, despite the most efficacious antiarrhythmic drug therapy that can be tolerated chronically.

Extensive electrophysiologic evaluation and testing of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the Model 7217B PCD device. Before permanently programming the PCD device to the automatic detection and delivery of the VT and/or VF therapies, the patient should have demonstrated a satisfactory response to the proposed therapy.

Intended Uses - ETCD

The Model 5355 External Tachyarrhythmia Control Device is intended for use in conjunction with an antitachycardia/defibrillation lead system during diagnostic studies for implanting the Model 7217B PCD device.

Indications for use of the ETCD include:

- Patients experiencing recurrent episodes of ventricular tachyarrhythmia,

- Patients who survived a cardiac arrest due to a ventricular tachyarrhythmia and are at risk for repeated episodes,

- Patients who are undergoing an assessment of the efficacy of antitachycardia pacing, cardioversion, or defibrillation therapies in anticipation of an implantable cardioverter-defibrillator.

Components of the System

A list of components used in the system is given below. It is separated into a listing of those components for which market approval is sought and those components that are now commercially available. Market approval is not being sought for use of the PCD Device with other manufacturers transvenous defibrillation lead systems or for the use of the PCD Transvene lead system with other manufacturers implantable cardioverter defibrillators.

Seeking Approval:

Transvene Leads
- Model 6963
- Model 6966
- Model 6999

Pacer-Cardioverter-Defibrillator (PCD) Device
- Model 7217B

External Tachyarrhythmia Control Device (ETCD)
- Model 5355 ETCD
- Model 5418 Patient Cable
- Model 5419 Patient Cable
- Model 5414 Test Load
- Model 5417 EGM Cable

Programmer Software Cartridge
- Model 9788 - Memory Module for 7217B PCD Device and 5355 ETCD Devices

Lead Accessories
- Model 6701 Lead End Cap

Commercially Available:

Programmers Model 9710 and accessories

Printers Model 9751/9712

Components Used in the Implantable Configuration

The implantable configuration is composed of a PCD Device, lead system, and a 9710 Programmer with applicable software cartridge. The implantable device is a Model 7217B PCD Device. The PCD device requires an appropriate lead system consisting of up to three cardioversion/defibrillation electrodes. See Figure III B-2. The Transvene leads used with the Model 7217B PCD Device are the Models 6963, 6966, and 6999.

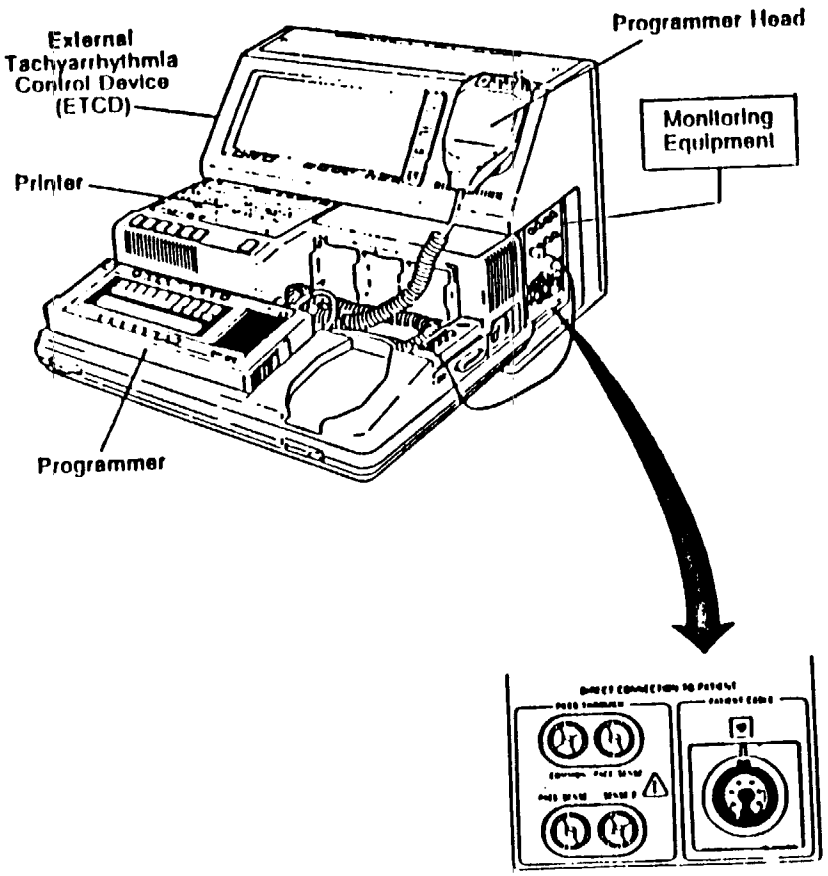
The Model 9710 Programmer is commercially available. Two printers are also commercially available. When higher printing speeds are desired, it is recommended that the programmer be used with the faster printer, the Model 9751. If slower printing speeds are acceptable, as may be the case in some follow-up situations, the Model 9710 Programmer can be used with the battery-powered Model 9712 Printer.

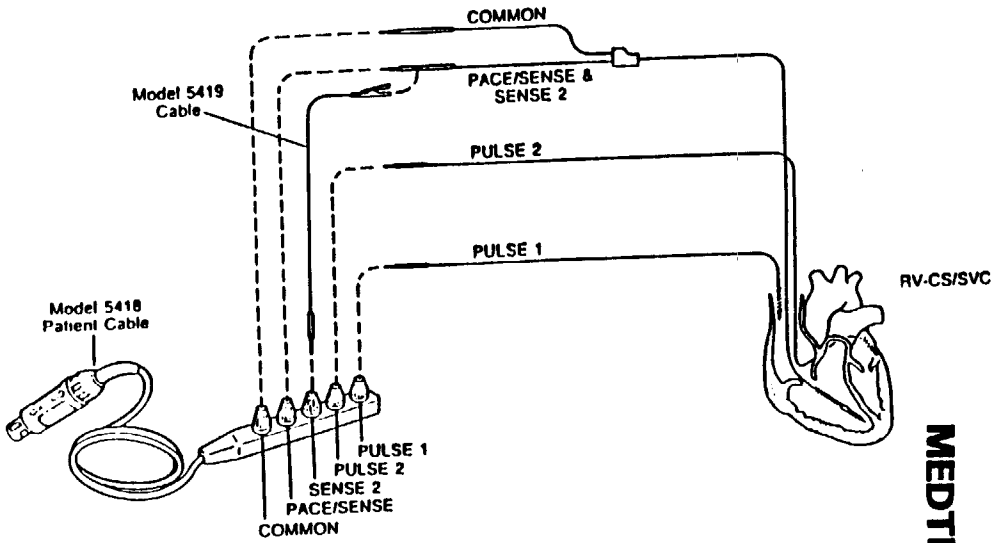
Components used in the External Configuration

The external tachyarrhythmia control system is composed of the Model 5355 ETCD, a Model 5418 Patient Cable, a Model 5419 cable, lead system, and a Model 9710 Programmer with applicable software cartridge, see Figures IV-A-3, 4. The ETCD uses replaceable batteries as its power source. The Model 5418 Patient Cable and Model 5419 Cable are designed to connect the Transvene leads to the ETCD. Like the implantable system, the ETCD uses the same Transvene leads (Models 6963, 6966, and 6999).

Figure II-B-2

Non-Thoracotomy Lead System for PCD





Connections to Model 5418 Patient Cable for
Typical Simultaneous or Sequential Pathway (RV-CS/SVC).

Figure IV-A-3

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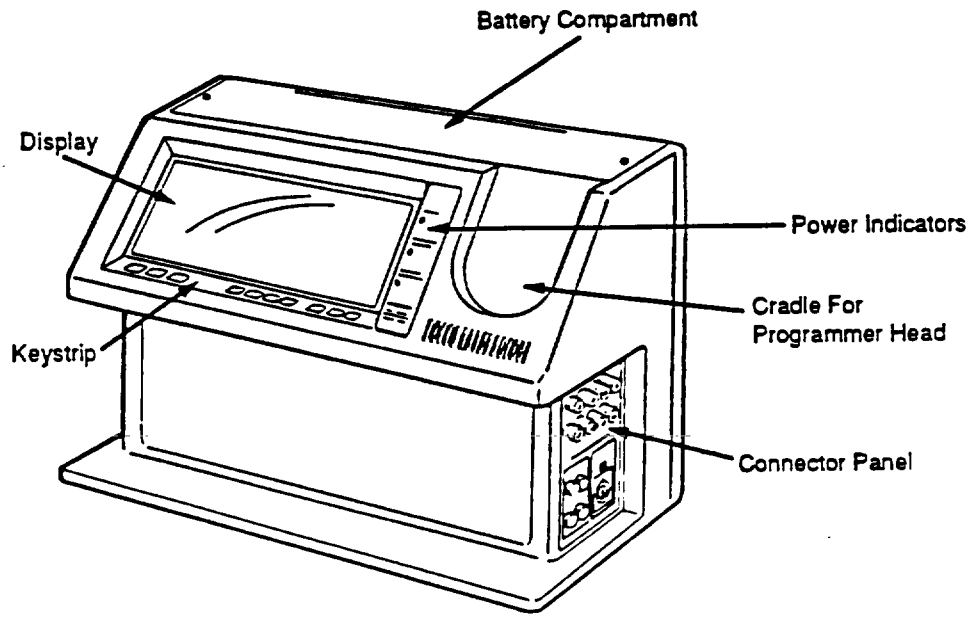

Figure IV-A-4. Model 5355 External Tachyarrhythmia Control Device

Purpose of the System

PCD System Configuration

The PCD Device is an implantable device designed to detect episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF), and upon detection, automatically deliver the appropriate therapy or a progression of therapies programmed by the physician for each patient. The available therapy types that can be programmed are overdrive pacing, cardioversion, and defibrillation. The PCD Device also has bradycardia pacing capability. The Transvene leads allow the PCD device to deliver these therapies to the heart.

ETCD System Configuration

The ETCD is an external tachyarrhythmia control device designed to deliver overdrive pacing, cardioversion, defibrillation, and bradycardia therapies in the same fashion as the PCD device. The ETCD can be programmed to automatically deliver overdrive pacing therapy upon detection of VT. When used as a component of a system that includes the appropriate Medtronic programmer and applicable software cartridge, the ETCD can deliver manually-initiated VT pacing, cardioversion, and defibrillation therapies. The ETCD allows the assessment of the Transvene lead system characteristics and aids in the assessment of lead system pacing and sensing characteristics.

Overview of System Features

General

The PCD device is designed to automatically detect episodes of VT or VF and, upon detection, deliver the appropriate programmed pacing, cardioversion, or defibrillation therapies. The device has two independently programmable detection and therapy procedures, one for VT and a second for VF.

When used as a component of a system that includes the appropriate Medtronic programmer and dedicated software, the ETCD is designed to deliver manually initiated cardioversion and defibrillation therapies. The ETCD is also designed to detect episodes of VT and VF. It can automatically deliver VT overdrive therapies (burst and ramp) upon detection of a VT.

VT Detection and Therapy

Both the PCD device and ETCD use a VT detection algorithm which can use up to three separately programmable criteria as it monitors the cardiac cycle length to identify the presence of a tachycardia. Upon detection, the devices deliver their first programmed VT therapy. If the VT episode persists and is again detected, up to three additional independently programmable VT therapies may be delivered to restore the patient's normal cardiac rhythm. This progression of four VT therapies can be tailored to each patient's need. For the PCD device the therapies may be selected from two methods of overdrive pacing (burst and ramp) and synchronized cardioversion.

For the ETCD the same overdrive pacing therapies can be automatically delivered, with cardioversion therapy being available as a manual therapy.

VF Detection and Therapy

The VF Detection algorithm monitors the cardiac cycle length to identify a VF episode. Upon detection, the PCD device provides a programmable high energy defibrillation pulse for VF therapy. Up to a maximum of four VF therapies may be delivered for ongoing detected VF episodes. Each defibrillation therapy consists of one (single pulse) or two (simultaneous or sequential) high voltage pulses designed to restore the normal cardiac rhythm.

For the ETCD, each cardioversion or defibrillation therapy, which must be initiated manually via the programmer, also consists of one high-voltage pulse or two (simultaneous or sequential) high-voltage pulses in the same fashion as the PCD devices.

Bradycardia Therapy

For both the ETCD and PCD devices, bradycardia pacing is delivered in the VVI mode. Asynchronous, (VOO), pacing is not available, and is avoided even with magnet application since this type of pacing has increased potential to initiate ventricular arrhythmias in patients receiving this system.

Lead Systems

The PCD Device and the ETCD perform pacing, sensing, cardioversion, and defibrillation through multiple electrodes in the lead system. Listed below are the electrodes and their function:

- The PACE/SENSE electrodes are incorporated in the right ventricular defibrillation lead. These electrodes function as the sensing circuit and deliver pacing pulses. The PACE/SENSE electrodes are used for sensing in conjunction with the SENSE2 electrode.
- The COMMON electrode is an electrode coil that serves as the cathode for cardioversion, defibrillation, and pacing.
- The PULSE2 electrode is an electrode coil that serves as the anode for cardioversion and defibrillation.
- The PULSE1 electrode is an optional electrode coil that serves as an additional anode for sequential and simultaneous cardioversion and defibrillation.

Cardioversion and defibrillation current pathways are between the PULSE2 and COMMON electrode coils and, if the additional lead is implanted, between the PULSE1 and COMMON electrode coils.

Other Capabilities

The physician may use the ETCD or the PCD devices to conduct noninvasive electrophysiologic studies (EPS) via the programmer with the appropriate software cartridge. The physician can also manually deliver various therapies via the programmer to manage an induced or spontaneous tachyarrhythmia.

The PCD device will provide the physician with information, via the Programmer, about its present programmed status and data on its operation accumulated between office visits. This information may be printed and retained in the patient's file.

The PCD Device and ETCD can also transmit an electrogram to the programmer. The electrogram is the electrical signal sensed on the leads.

A programmer-generated set of symbols, termed Marker Channel™, allows real-time visualization of sensing, pacing, detection, and therapy events occurring within the device.

In addition, the ETCD provides a display of measurements and other information related to delivered cardioversion and defibrillation pulses.

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With this information and other features, the ETCD can be used to assess the suitability of the lead system and its placement for individual patients.

PCD Battery Longevity Expectations

The longevity of the Model 7217B PCD Device depends upon several factors, including programmed bradycardia pacing parameters, the percentage of paced to sensed events, the pacing load, and on the frequency of high voltage capacitor charging. The longevity projections found in Table IV-A-1 apply under the following conditions:

- 65 ppm pacing rate,
- 5.4 V pacing pulse amplitude,
- 0.49 ms pacing pulse width, and
- 500 ohm pacing lead.

Projected Longevity[1]
Table IV-A-1

Pacing/Sensing	34 Joule Charging Frequency	Average Longevity Model 7217B
100% Sensing	Quarterly	5.0 years
15% Pacing	Monthly	4.2 years
100% Pacing	Monthly	3.4 years

The longevity of the device decreases with the following:

- An increase in pacing rate,
- An increase in pacing amplitude,
- A decrease in pacing impedance,
- An increase in pacing pulse width,
- An increase in the percentage of bradycardia paced to sensed events, or
- An increase in the charging frequency.

Each 34 Joule charging cycle will typically decrease the longevity of the device by approximately six days.

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[1] These preliminary longevity projections are based upon accelerated battery data and device modeling. They include an estimate of five months between time of manufacture of a PCD device and its implant. If a device was stored for the full twelve-month shelf life, the average longevity would be reduced an estimated 4.3 to 5.9 months, depending on device use. With the stated condition, 100% pacing and monthly 34 Joule charging cycles, the minimum longevity of the device will be 2.5 years (7217B). Average refers to the projected mean longevity of the modeled run of PCD devices at the stated conditions. Minimum longevity means that virtually all (i.e., 99.9%) of all modeled production run of PCD devices will attain the value given.

C. Alternative Practices and Procedures

The use of implantable defibrillators in patients with drug refractory ventricular tachycardia/ fibrillation (VT/VF) and in survivors of sudden cardiac death has reduced the arrhythmic mortality in these patients. Other treatments available to treat ventricular tachyarrhythmias include antiarrhythmic drug therapy, ventricular tachycardia surgery, transthoracic defibrillation and other market released implantable defibrillators with epicardial defibrillation lead systems.

D. Marketing History

All of the Medtronic Transvene Tachyarrhythmia Control System device components which have been implanted in the U.S. to date have been part of the IDE clinical study and have followed the FDA approved investigational protocol. In November 1991, the Medtronic PCD Transvene System, and respective components described in this submission, were market released in Europe. In March 1991, the Medtronic PCD Epicardial System, and respective components, were market released in Europe. And in February 1993, the FDA approved the Medtronic PCD Epicardial System.

E. Adverse Effects

Potential adverse effects which may be associated with the use of the PCD Device include but are not limited to: failure to detect ventricular tachycardia or ventricular fibrillation; failure to terminate ventricular tachycardia or ventricular fibrillation; delivery of pacing or shock therapy when no ventricular tachyarrhythmia is present, which would precipitate an episode of ventricular tachycardia or ventricular fibrillation; acceleration of a ventricular arrhythmia; failure to capture after a shock delivery; discomfort or pain during or following the delivery of electrical shock; or infection.

The following additional, potential adverse effects associated with all pacemaker systems include loss of normal pacemaker function due to battery failure or other component failure, inability to program a pacemaker pulse generator because of programmer failure, infection, erosion, undesired muscle or nerve stimulation, and inadequate sensing or pacing. Any demand pulse generator can be affected by magnetic, electrical and electromagnetic signals of sufficient strength or with characteristics which mimic cardiac function. Possible effects of electrical interference on pulse generator operation include reversion to asynchronous pacing, inhibition of output pulses and rapid synchronous pacing. Certain environmental sources can couple sufficient energy into a cardiac pacing system to damage the pulse generator or cardiac tissue adjacent to the electrodes.

Failure of the pulse generator system to function properly may result in the patient experiencing the symptoms for which the pulse generator was originally indicated.

The potential complications related to the use of the PCD Transvene Lead System include, but are not limited to, the following patient-related conditions: fibrillation, air embolism, cardiac perforation, heart wall rupture, cardiac tamponade, pericardial rub, infection, myocarditis, constrictive pericarditis, pneumothorax and hemothorax. Other potential complications related to the lead system include, but are not limited to, the following: lead dislodgement, lead conductor fracture, and insulation failure.

The above referenced information is provided in the labelling of the PCD Transvene System.

F. Summary of Studies

To validate the performance of the Medtronic Tachyarrhythmia Control System nonclinical laboratory (bench) testing, animal studies and human clinical trials were performed. All of the nonclinical bench and animal testing demonstrated that the devices are safe and performed according to design intent.

The nonclinical laboratory (bench) testing provides information relative to the Model 6966, Model 6963 and Model 6999 Transvene Leads, Model 7217B PCD, Model 5355 ETCD, and Model 9788 Memory Module.

The animal studies were performed to evaluate acute and chronic performance PCD Transvene System and to validate that the PCD and ETCD System are safe for human use.

Finally, human clinical trials were performed to evaluate the safety and effectiveness of the PCD Transvene System in treating patients with life-threatening ventricular arrhythmias.

All of the studies have demonstrated that the PCD Transvene System functions safely and is appropriate for human use.

The following summaries are provided in this section.

1. Model 6966, Model 6963 and Model 6999 Nonclinical Testing

2. Non-clinical Testing of the Related Components of the Transvene Lead system: Models 7217B PCD, Model 5355 ETCD and Model 9788 MemoryMod Model 7217B PCD Nonclinical Testing

3. Animal Testing

4. Clinical Study of the PCD Transvene System

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1. Model 6966, Model 6963 and Model 6999 Defibrillation Leads: Summary of Nonclinical Testing

To validate the performance of the Medtronic Tachyarrhythmia Control System nonclinical laboratory (bench) testing, animal studies and human clinical trials were performed. All of the nonclinical bench and animal testing demonstrated that the devices are safe and performed according to design intent.

The nonclinical laboratory (bench) testing provides information relative to the Model 6963 CS/SVC lead, Model 6966 RV lead, Model 6999 SQ patch lead, and related system components.

a. Electrical Testing

Electrical D.C. resistance testing was performed to ensure proper functioning of the Model 6963, 6966 and 6999 leads.

Seventeen Model 6963, thirty-five Model 6966 and eighteen Model 6999 leads were submitted for testing. Electrical resistance was measured utilizing a milliammeter under ambient room conditions. All samples measured were within the individual design specifications.

b. Environmental Analysis Testing

The purpose of the testing was to subject the lead to temperature extremes to determine the lead's resistance to the thermal stresses when transported from extremes of climate.

Thermal Shock

Fifteen Model 6963 and thirty-five Model 6966 leads were subjected to five cycles from -45°C to 70°C with a soak time of thirty minutes at each temperature extreme with a transfer time of one minute. Thirty-five Model 6999 leads were subjected to five cycles from -40°C to 66°C with a soak time of thirty minutes at each temperature extreme with a transfer time of one minute.

After the thermal shock testing was completed visual inspection and electrical resistance measurements were performed. There were no visual defects and the electrical D.C. resistance of all the samples met the design specification.

c. Mechanical Testing

The purpose of the mechanical testing was to determine the mechanical integrity of the leads to ensure that the devices are safe, reliable, and suitable for their intended use and conform to design specifications. The leads and/or assemblies were subjected to the following:

- flex testing
- composite pull strength testing
- crimp/weld pull strength testing
- insertion/withdrawal force testing
- A.C. impedance/leakage testing

Flex Testing

The flex testing consisted of mounting the insulated conductor coils and uninsulated electrode coils of the Models 6963, 6966 and 6999 in a lead flex test fixture. The insulated conductor coils and uninsulated electrode coils were flexed under ambient room conditions at a specified radius. Eleven samples were used in each test. Samples exceeded specifications and therefore are considered to be satisfactory for their intended use.

Lead Joint Tensile Strengths

Pull testing of the various lead joints is conducted to ensure that the integrity of the joint meets the design specification and is, therefore, adequate for its intended application. The testing conducted consists of a composite pull test which evaluates the overall pull strength of the lead and crimp pull testing that evaluates the crimped connections of the leads to assure specification conformance.

Composite Pull Strength

Leads were boiled in Ringer's solution or soaked in normal saline and pull tested, while wet (the lead is usually cut in half to facilitate fixturing limitations) utilizing a tensile testing machine. The samples were pulled until failure at a rate of five inches per minute. The initial failures were then analyzed statistically for the confidence level in meeting the specification for the composite lead which is 1.0 lb. minimum.

Model 6963 data demonstrates that with a 95% confidence at least 97% (distal) and 99.9% (proximal) of the leads will meet or exceed the specification.

Model 6966 data demonstrate that with a 99% confidence at least 99.9% of the leads will meet or exceed the specification.

Model 6999 data demonstrate that with a 99% confidence at least 99.9% of the leads will meet or exceed the specification.

Therefore, Models 6963, 6966 and 6999 leads, with respect to composite pull strength, are adequate for their intended use.

Crimp/Weld Pull Strengths

Crimp and weld pull strength tests were conducted to evaluate the strength of the connections to ensure that they meet the design specification and are, therefore, adequate for their intended application. The connections tested are:

- Distal crimp sleeve to conductor coil crimp (6963)
- Double crimp core to conductor coil crimp (6963)
- Electrode coil to double crimp core weld (6963)
- Electrode coil to distal crimp sleeve weld (6963)
- Tip crimp sleeve to conductor coil crimp (6963)
- Connector pin to conductor coil crimp (6963 and 6999)
- Helix electrode to inner conductor coil crimp (6966)
- Electrode ring to middle conductor coil crimp (6966)
- Transition sleeve to electrode coil weld (6966)
- Transition sleeve to outer conductor coil crimp (6966)
- Fixed connector pin to outer conductor coil crimp (6966)
- Connector ring to middle conductor coil crimp (6966)
- Rotating connector pin to inner conductor coil crimp (6966)
- Manifold crimp sleeve to conductor coil crimp (6999)
- Manifold crimp sleeve to electrode coil (b)(4) crimp (6999)
- Manifold crimp sleeve to electrode coil (b)(4) crimp (6999)

Subassemblies were submitted for testing and pull tested by using a tensile testing machine. The samples were pulled until failure at a rate of four inches per minute.

Pull strength testing consisted of a minimum of 15 subassemblies of each crimp connection and a minimum of

7 subassemblies of each weld connection All samples tested exceeded the individual specification. The test results indicated that with a 95% confidence, at least 95% of the leads will have crimp and weld strengths that exceed the specification.

Therefore, the Model 6963, 6966 and 6999 leads, with respect to crimp and weld connection pull strengths, are adequate for their intended use.

Insertion/Withdrawal Forces

Insertion/withdrawal forces are measured to ensure compatibility with the implantable device without causing damage to the lead. Twenty five each of the lead Models 6963, 6966 and 6999 were tested with the Model 7217B PCD Device connector modules. There were no physical changes and all measurements met the design specification.

A.C Impedance/Leakage Testing

Fluid leakage tests are conducted on the lead assemblies/implantable device connector to determine leakage. Ten of each lead model Models 6963, 6966 and 6999 were tested with the Model 7217B connector modules. A.C. impedance was measured from the PCD device case to the lead connections while immersed in fluid. All samples met the design specification.

d. Biocompatibility Testing

The materials used in the Models 6963, 6966 and 6999 that are directly exposed to body tissue are:

- Polyurethane
- Silicone rubber (methylvinylpolysiloxane)
- Silicone rubber/titanium dioxide
- Platinum/Iridium

These materials have been shown to be biocompatible through many years of use in Medtronic permanent implantable endocardial/myocardial permanent pacing leads. In addition to extensive implant experience with these materials, standard biocompatibility tests have been performed to verify the biocompatibility of the above-listed materials. Testing has demonstrated that all materials are nonhemolytic, nonpyrogenic, nontoxic, nonmutagenic and

biocompatible. Therefore, the materials passed the tests and are considered suitable for human implant. The materials used in the Models 6963, 6966 and 6999 are identical to those used in other commercially available Medtronic pacing leads.

e. Lead System (Life) Testing

In addition to the aforementioned tests, the Transvene leads were subjected to system, or life, testing. Further testing also evaluated the leads with respect to crush resistance. Testing included subjecting the leads to soaking, flexing and high-voltage pulsing. A separate test evaluated crush performance. The purpose of these tests was to subject the leads to severe conditions and assess the overall integrity of the system.

D.C. resistance values and intermittance data measured before and after being subjected to soaking, multiple flexing and high voltage pulsing, as well as crushing, demonstrated the non-thoracotomy leads satisfied requirements and are therefore acceptable for their intended use.

2. Non-clinical Testing of the Related Components of the Transvene Lead system: Models 7217B PCD, Model 5355 ETCD and Model 9788 MemoryMod

Non-clinical testing of these components was provided Volume 4 of the original PMA application (P900061) dated September 27, 1990, Volume 3 of the amendment dated March 8, 1991, and Volume 2 of the amendment dated August 30, 1991. A summary of the test results for each of the components is provided.

Model 7217B PCD: Summary of Nonclinical Testing

Testing of the Model 7217B pulse generators and the peripheral devices that comprise the system, i.e., the Pacing System Analyzers, the Model 9710 Programmer utilizing the Model 9788 MemoryMod and the Model 9751 Printer have been tested and found to be acceptable. All aspects of system interaction and operation are in accordance with the Model 7217B PCD Device and Model 9788 technical manuals and system specifications. Therefore, the Medtronic Tachyarrhythmia Control System, in its entirety, is acceptable for its intended use.

Model 9788 Memory Module: Summary of Nonclinical Testing

The Medtronic Model 9788 MemoryMod Cartridge was designed for insertion into the commercially available Model 9710 Programmer. When inserted, it becomes an integral part of the non-invasive programming system for the implantable PCD devices to establish pacing, ventricular tachycardia (VT) detection and therapy, ventricular fibrillation (VF) detection and therapy, and electrophysiological study (EPS) capabilities of an implanted pacemaker/ cardioverter/defibrillator (PCD). Both the Model 7217B PCD device and the Model 5355 ETCD are programmed with the Model 9788 MemoryMod cartridge when used with the Model 9710 Programmer.

Testing of the Model 9788 MemoryMod cartridge has demonstrated conformance to specification requirements. Therefore, the Model 9788 MemoryMod is acceptable for its intended use with the Model 7217B PCD Devices and the Model 5355 ETCD Device.

Model 5355 ETCD: Summary of Nonclinical Testing

Testing of the Model 5355 ETCD and respective accessories has shown conformance to specification requirements. Therefore, the Model 5355 ETCD Device/accessories are acceptable for their intended use.

3. Animal Testing

The information presented in this section is an accumulation of several studies, some of which FDA has previously reviewed in IDE submissions (G870102). These studies demonstrate the safety of the Transvene lead Models 6963, 6966 and 6999.

A variety of non-thoracotomy leads were evaluated in a series of four canine studies. Descriptions of the leads, as well as the study number(s) (1, 2, 3 or 4) in which they were evaluated, are presented below.

Description: Non-thoracotomy Leads

CORONARY SINUS/SUPERIOR VENA CAVA LEADS

Model 6963, evaluated in Study No. 4, is a silicone, unipolar, coronary sinus or superior vena cava lead with a 6.5 mm connector and platinum alloy electrode for delivery of cardioversion and defibrillation therapies.

Model 6881, evaluated in Study Nos. 2, 3 and 4 is functionally equivalent to the Model 6963 except the 6881 has a 3.2 mm connector.

Model 10285, evaluated in Study No. 1, is the temporary version of the Model 6963/6881.

RIGHT VENTRICULAR LEADS

Model 6966, evaluated in Study No. 4, is a polyurethane, tripolar, extendable/retractable, screw-in lead with a 6.5 mm connector and platinum alloy electrode for delivery of cardioversion and defibrillation therapies. Additionally, the 6966 has a 3.2 mm connector for pacing and sensing.

Model 6884, evaluated in Study Nos. 2 and 3, is functionally equivalent to the Model 6966 except the 6884 has a 3.2 mm connector in place of the 6.5 mm connector for the cardioversion-defibrillation electrode.

Model 10284, evaluated in Study No. 1, is the temporary version of the Model 6966/6884.

SUBCUTANEOUS PATCH LEADS

Model 6999, evaluated in Study No. 4, is a silicone, unipolar, oval, subcutaneous patch with a 6.5 mm connector and platinum alloy electrode coils that are partially embedded in the silicone patch for delivery of cardioversion and defibrillation therapies. Additionally, the patch is embedded with (b)(4) (b)(4)

Model 6895, evaluated in Study Nos. 2 and 3, is functionally equivalent to the Model 6999 except the 6895 has a 3.2 mm connector and is covered with (b)(4) (b)(4)

Model 10317, evaluated in Study No. 3, is functionally equivalent to the 6895 except it is embedded on the outer edge with (b)(4) (b)(4)

Although model numbers differ, all leads in each of the three groups are functionally equivalent. The various model numbers reflect an evolution of temporary to transvenous lead development, as well as minor changes, such as the connector pin modification from 3.2 mm to 6.5 mm.

Additional devices were used to evaluate the non-thoracotomy lead studies in canines. These are described below.

External Devices for Implant Support

Model 5355 External Tachyarrhythmia Control Device (ETCD)

The Model 5355 ETCD provides the same detection capabilities as the implantable Model 7217B PCD Device. Therapies are identical except that the maximum output energy is 40 joules (J) and automatic defibrillation and cardioversion are not available in the Model 5355. The Model 5355 ETCD provides measurement and display of output waveform parameters and ETCD status, an isolated electrogram signal, and passthrough connections of pacing and sensing electrodes to external instrumentation.

Model 2394 External Cardioverter/Defibrillator (ECVD)

The Model 2394 ECVD instrument can deliver: (1) a single stimulation pulse on one output channel, or (2) a pair of pulses, delivered individually on the two different output channels. Monophasic and biphasic pulses are provided, output capacitance can be varied between 10 and 150 microFarads (mf) depending on which external capacitor modules are used, and pulse width

can be specified as a fixed duration (0.1-19.9 ms) or "tilt" (10-90%). Pulse output voltages can range between 50 and 1090 volts and may be delivered asynchronously (upon manual command) or synchronized with an intrinsic sensed event.

Model 2376 External Cardioverter/Defibrillator (ECVD)

The output stimulation parameters of the Model 2376 are very similar to those of the Model 2394 except for the following modifications:

- All pulses are monophasic, truncated, exponential waveforms.
- Output capacitance is fixed at 50 microFarads and pulse width is determined by a fixed pulse duration only.
- Pulse output voltages can range between 50 and 1090 volts and may be delivered asynchronously (upon manual command) or synchronized with an intrinsic sensed event.

Study Methods

All canine studies were conducted according to the 1966 and 1970 Animal Welfare Acts, 1985 NIH Laboratory Animal Use and Care Guidelines and GLP regulations. Adult mongrel canines were used for all studies. The dogs weighed 20 kg or more.

Specific details of each study are presented in the following "Animal Studies/Results" section.

Each study is briefly described below. Both acute and chronic studies were performed to assess the toxicity of the non-thoracotomy lead system as well as its stability over time.

Study #1: Acute Toxicity Testing of Non-thoracotomy Leads

The objective of this study was to quantify the amount and nature of shock-induced damage to the myocardial tissue resulting from multiple, high energy defibrillation shocks delivered through transvenous defibrillation leads and a subcutaneous patch. This information has previously been submitted to the agency in the Non-Thoracotomy IDE, reference Document Control Number G870102/S23; FDA Approved October 4, 1990. Lead models evaluated in this study are functionally equivalent to the Models 6963, 6966 and 6999. Results of these studies revealed only minimal shock-induced necrosis (<0.1-0.5 percent by weight), which did not result in functional impairment of the cardiac tissue. Therefore, the use of the Model 6963, 6966 and 6999 leads did not result in significant myocardial damage in canines and could be safely implanted in humans.

Study #2: Model 6881, 6884 and 6895 Chronic Lead Evaluation

The objective of this study was to evaluate the suitability of the lead system for human clinical use. Lead models evaluated in this study are functionally equivalent to the Models 6963, 6966 and 6999. Study results demonstrate that the performance of the non-thoracotomy lead system when used with the PCD and ETCD devices is in conformance with system design and expected operation.

One canine in this study has presented with two mastocytomas; a common type of skin tumor in middle-aged canines. This observation is not related to the PCD system, nor is it relevant to the clinical application of the PCD system. The tumors were excised and the animal remains in good health.

Study #3: Model 6881, 6884 and 6895 Chronic Lead Defibrillation Study

This study is an evaluation of the chronic stability of the non-thoracotomy lead system via the monitoring of defibrillation and pacing thresholds. In addition, histopathological examinations have been performed to assess the amount and nature of shock-induced damage to the myocardial tissue resulting from defibrillation shocks. Lead models evaluated in this study are functionally equivalent to the Models 6963, 6966 and 6999. Results demonstrate stable pacing, sensing and defibrillation thresholds over time. Additionally, histopathology analysis shows no cardiac tissue damage due to delivery of defibrillation shocks.

Study #4: Model 6963, 6966 and 6999 Chronic Lead Defibrillation Study

This study is an ongoing evaluation of the non-thoracotomy lead system to assess chronic defibrillation threshold stability, pacing thresholds, intracardiac sensing capabilities and tissue damage. Results indicate the lead system performs as intended; DFTs and pacing thresholds have remained stable throughout the study (60 weeks) and intracardiac sensing is appropriate. Additionally, pathology data, to date, indicates minimal localized trauma to the cardiac tissue (<0.05 percent by weight).

Conclusion

All of these canine studies have demonstrated that the non-thoracotomy lead system, which includes the Model 6963 CS/SVC lead, 6966 RV lead and 6999 SQ patch lead, functions safely and is therefore appropriate for human use.

4. Summary of Clinical Experience

A. Introduction

The efficacy and safety of implantable cardioverter defibrillator (ICD) therapy for recurrent ventricular tachycardia (VT) and ventricular fibrillation (VF) has been well established. The current market released device (Medtronic Model 7217B with Epicardial Cardioversion/Defibrillation Leads) incorporates multiprogrammability, multiple detection and therapeutic options for the treatment of ventricular tachycardia and fibrillation. The current system, while providing lifesaving treatment of ventricular arrhythmias, requires a significant surgical procedure (thoracotomy, median sternotomy, etc.) for the placement of the epicardial lead system. The need to reduce the surgical mortality and morbidity associated with epicardial cardioversion/defibrillation lead systems has lead to the development of the PCD® Transvene™ System.

This report represents a full report of Medtronic's clinical experience with the Medtronic PCD® Model 7217B Multiprogrammable Tachyarrhythmia Control System with Transvene™ Cardioversion and Defibrillation Electrodes (Reference IDE G870102). The data included in this analysis is all data that was received by Medtronic and entered onto the clinical database as of **February 1, 1993.**

The PCD® Model 7217B Multiprogrammable Tachyarrhythmia Control System described in this submission is identical to the system which was recommended for approval by the FDA advisory panel on February 3, 1992, with the addition of Transvene™ leads.

The data analysis is organized in functional rather than chronological categories in order to present a complete picture of each of the PCD® Device's various functions. The sections included in this summary are:

- Indicated Patient Population/Therapeutic Options
- PCD Therapy Applications
- Indicated Patient Population
- Study Objectives and Protocol Summary
- Overview of Clinical Experience
  - Implant Data
  - Spontaneous VT/VF Episode Experience

Overall Success Rate
- Complications and Observations
- Inactive Patients
- Patient Deaths
- Clinical Experience by Primary Indication
- Patients not Meeting Implant Criteria
- Comparison to AICD Clinical Experience
- Comparison to PCD® Epicardial Clinical Experience
- PCD® Transvene™ System Performance

This summary provides an overview of the clinical experience which verifies that the PCD® Transvene™ System is safe and effective in the indicated patient population.

B. Indicated Patient Population

B.1 Patient Population

The PCD® Transvene™ System is intended to treat patients at risk of sudden cardiac death due to ventricular tachyarrhythmias which have been shown to be reliably terminated, and in the case of VF, terminated at an energy level below the maximum output of the PCD® Device.

Results provided in this application will support Medtronic's request for market release of the PCD® System for use in the following patient population:

- Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or

- Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

Malignant ventricular tachyarrhythmias remain a major unsolved problem in the management and prevention of coronary artery disease. It is estimated that 450,000 people experience sudden cardiac death annually, and 80%-90% of these events are caused by ventricular fibrillation. (Gillum RF. Sudden coronary death in the United States. Circulation 1989; 79:756-765.)

Survivors of out-of-hospital cardiac arrest not associated with acute myocardial infarction are at risk for recurrent cardiac arrest as reported by Wilber, et al.(Wilber, et al. Out-of-Hospital Cardiac Arrest - Use of Electrophysiologic Testing in the Prediction of Long-Term Outcome. NEJM 1988; Vol.318:19-24.). In this study group of 166 survivors of out-of-hospital cardiac arrest, ventricular arrhythmias were inducible in 131 patients (79%) and were suppressed by antiarrhythmic drug therapy or surgery (or both) in 91 patients (72%). During a median follow-up of 21 months, cardiac arrest recurred in 29 patients: 11 in whom inducible arrhythmias had been suppressed, 12 in whom inducible arrhythmias persisted and 6 in whom arrhythmias could not be induced at initial electrophysiologic study.

C. PCD® Transvene System Therapy Applications

The PCD® System is intended to treat patients at risk of sudden cardiac death due to ventricular tachyarrhythmias and/or recurrent ventricular tachycardia.

For this patient population, the primary benefits from the use of the PCD® System center on the detection and termination of life-threatening ventricular arrhythmias. The use of the PCD® Transvene™ system allows for the application of identical therapies as an epicardial system without requiring an open chest procedure for implantation of the lead system. This less invasive surgical approach allows the system to be applied in patients who may not be able to undergo an open chest procedure. The use of pacing therapies for the treatment of ventricular tachycardia reduces patient trauma associated with higher energy cardioversion pulses and extends the longevity of the PCD® pulse generator.

The PCD® System allows the titration of therapies for patients with ventricular tachycardia while providing critical defibrillation backup. Multiple detection algorithms are designed to allow the device to distinguish ventricular tachycardia from sinus tachycardia and atrial fibrillation. In addition, independent detection algorithms for VT and VF allow the delivery of different types of therapy for each of these two arrhythmias. The incorporation of antitachycardia pacing algorithms allows the use of pacing for the termination of well tolerated ventricular tachycardia. These algorithms, which are rate adaptive, can adapt

to changes in the ventricular tachycardia and successfully terminate the episode. Defibrillation therapy is important in the event that an episode of VT accelerates to VF whether spontaneously or as a result of a delivered therapy. The incorporation of multiple cardioversion and defibrillation pathways (SINGLE, SEQUENTIAL and SIMULTANEOUS) allows the physician to provide an adequate cardioversion/defibrillation efficacy safety margin for all patients. The capacity to provide programmable extrastimuli pacing allows noninvasive electrophysiologic studies to be performed. The potential benefits from permanent cardiac pacing provide support for chronic and transient episodes of bradycardia.

Finally, the benefits of programmability of tachyarrhythmia detection and therapy parameters, VVI parameters, and stored telemetry data on the delivery of therapy may avert the need for reoperation in the event of changing patient conditions or complications.

D. Study Objectives and Protocol Summary

The clinical study was designed to evaluate the operation, safety and effectiveness of the PCD® System components in detecting and treating episodes of ventricular tachycardia and ventricular fibrillation.

The analysis focuses on data supporting the safety and effectiveness of the PCD® system, including the implantable pulse generator and associated transvenous lead system and its therapy in this patient population. The analysis includes the clinical experience with the PCD® system, pace/sense, detection and therapy functions in both the acute and chronic implant settings. In addition, data is provided on clinical observations, clinical complications and deaths in this patient population. The analysis will also provide data demonstrating the safety and effectiveness of the Model 5355 ETCD.

This summary presents safety and efficacy evaluation performed on 757 patients, 657 of which have implant durations equal to or greater than six months.

Clinical data was collected at the following study points to support the safety and efficacy of the PCD® System:

Pre-implant Patient Assessment
Lead System Testing at Implant
Implantable Pulse Generator Testing at Implant
Pre-hospital Discharge Testing
Follow-up Evaluation 1 and 3 months post implant then at 3 month intervals

Patients were evaluated prior to hospital discharge and/or one (1) month post implant, three months post-implant and then at intervals of every three months. In some cases additional testing was performed at physician discretion to evaluate spontaneous events and/or potential clinical complications.

Medtronic collected all clinical data on the PCD® System and its components under the clinical protocol outlined in the Investigational Plan. A common protocol was used on all study patients on a worldwide basis.

International centers were subject to the appropriate requirements (e.g., the Declaration of Helsinki) in order that the data met the statutory requirements of the FDA. All clinical data, U.S. and International, obtained with the PCD® System with Transvene™ Leads is included in this report.

E. Overview of Clinical Experience

This report covers a total of 762 implants in 757 patients of the PCD® Device with the Transvene™ Defibrillation Lead System. A total of 78 investigative centers participated in the clinical trial with 35 centers in the U.S. and 43 Internationally. The first implant occurred internationally on October 20, 1989, and the first implant in the U.S. occurred on October 16, 1990. Table E-1 shows the distribution of Model 7216A and Model 7217B patients between U.S. and International investigators.

PCD® Transvene™ System
Implant Distribution

	Total	U.S.	Int'l
7216A	18 (2.4%)	3 (0.7%)	15 (4.8%)
7217B	744 (97.6%)	444 (99.3%)	300 (95.2%)

Table E-1: PCD® Transvene™ System - Implant Distributions - 2/1/93

The mean documented implant duration for this patient population is 11.7 months and ranged from implant to 37.4 months. The cumulative implant duration is 8894.8 months. There are 657 patients with implant durations equal to or greater than six months. Table E-2 provides the distribution of follow-up quantity of patients by data form type.

PCD® Transvene™ System
Follow-Up Quantity
by Data Form Type

(b)(4)

(b)(4)

Table E-2: PCD® Transvene™ System - Follow-Up Quantity - 2/1/93

The patient population enrolled in the clinical trial was predominately male (80.6%) with a mean age of 59.4 years. In half of the patients (49.8%), the primary indication for implant was recurrent, sustained ventricular tachycardia without an episode of sudden cardiac death. Sudden Cardiac Death was the primary indication for 37.1% of the patients and SCD in combination with recurrent, sustained VT was the primary

indication in 13.1%. Coronary artery disease was the primary heart disease in 74.1% of the patient population with a mean reported ejection fraction of 35.6% Table E-3 provides a data summary on these patients. Also included is the data summary of the patients with 6 months and 12 months of follow-up.

PCD® Transvene™ System Data Summary			
	All Patients (3 Electrode Systems)	Patients with 6 months of Follow-up	Patients with 12 months of Follow-up
Number of Patients	757	657	393
Device Months Follow-up	8894.8	8602.6	6454.6
Mean Follow-up Time	11.7 mo	13.0 mo	16.3 mo
Maximum Follow-up Time	37.4 mo	37.4 mo	37.4 mo
Number, % Male **Number, % Female**	610 80.6% 147 19.4%	527 80.2% 130 19.8%	310 78.9% 83 21.1%
Mean Age	59.4 yrs	59.1 yrs	58.8 yrs
Primary Indication: **SCD** **VT** **SCD/VT**	 281 37.1% 377 49.8% 99 13.1%	 249 37.9% 326 49.6% 82 12.5%	 150 38.2% 191 48.6% 52 13.2%
Coronary Artery Disease	561 74.1%	483 73.5%	272 69.2%
Mean Ejection Fraction	688 35.6%	595 36.6%	357 38.0%
Defibrillation Pathway: **Sequential** **Simultaneous** **Single**	 574 75.3% 178 23.4% 10 1.3%	 496 74.9% 156 23.6% 10 1.5%	 296 74.9% 93 23.6% 6 1.5%
Mean LED	16.0J (N=702)	16.0J (N=609)	15.6J (N=365)
Mean DFT	14.8J (N=316)	14.8J (N=277)	14.3J (N=184)
Spontaneous VT: **Number of Patients** **Number of Episodes** **% Success**	 316 10027 98.4%	 288 8820 98.3%	 186 6338 99.0%
Spontaneous VF: **Number of Patients** **Number of Episodes** **% Success**	 317 1982 98.4%	 292 1742 98.3%	 176 1105 98.6%
One Year SCD Survival	99.5%	99.7%	100.0%

Table IF-2: PCD® System Data Summary - All Transvene™ Patients versus Transvene™ Patients with 6 mo Follow-up - 2/1/93

a1

E.1 Implant Data

Implants of the PCD® Device may use two or three Transvene™ leads. The physician has the flexibility to use whichever lead system best meets the patient's needs.

Table E-4 illustrates the lowest energy of defibrillation (LED) and defibrillation threshold (DFT) for the implanted lead systems. The implant criteria for the PCD® Device was 3 of 4 episodes of VF successfully terminated at 18 Joules or less with a given lead configuration. Some patients did not have a LED at implant. The LED is only identified if the investigator reported the induced rhythm as VF. Conversion of VT or V Flutter (as defined by the physician) to sinus rhythm was not included in the determination of the LED. In addition, it is not a protocol requirement to obtain a DFT at implant. However, recommendations have been provided to those institutions that prefer to obtain DFT's during the implant procedure.

PCD® Transvene™ System **Mean LED and DFT Values**				
Lead System	**Implant Frequency**	**Mean LED**	**Implant Frequency**	**Mean DFT**
All Systems	702	16.0J	316	14.8J
RV-SVC-SQ	455	16.7J	187	15.8J
RV-CS-SQ	210	14.6J	110	12.8J
RV-CS-SVC	37	15.2J	19	16.0J

Table E-4: PCD® Transvene™ System - LED and DFT Values - 2/1/93

The mean implant Lowest Energy of Defibrillation (LED) for all lead systems was 16.0J and mean implant Defibrillation threshold (DFT) for all lead systems was 14.8J. As the mean DFT's and LED's indicate, VF was reliably terminated at an energy value below the maximum output (34 Joules) of the PCD® Device.

E.2 Spontaneous VT and VF Episode Experience

A total of 458 patients (60.5%) have experienced a spontaneous ventricular tachyarrhythmia episode that has been detected and treated by the PCD® Device. A total of 141 patients experrienced VT only, 142 patients (18.8%) experienced VF only and 175 patients (23.1%) experienced both an episode of VT and VF.

There have been a total of 12,009 episodes of spontaneous VT or VF as detected by the PCD®. The overall PCD® Device success rate in terminating spontaneous VT/VF episodes as detected by the PCD® is presented in Table E-5.

PCD® Transvene™ System
Success Rate in Terminating Spontaneous VT/VF Episodes

	Number of Episodes Successful	Total Number of Episodes	Efficacy Rate
VT	9864	10,027	98.4%
VF	1951	1982	98.4%
Total	11,815	12,009	98.4%

Table E-5: PCD® Transvene™ System - Success Rate for Spontaneous VT/VF Episodes - 2/1/93

E.2.1 Spontaneous VT

For the purposes of this clinical trial, spontaneous VT was defined as those episodes that satisfied the programmed VT detection criteria. Specifically, all programmed VT detection criteria must be fulfilled to detect a VT episode. Successful termination of the episode was defined as satisfying the VT episode termination criteria.

To date, 10,027 spontaneous episodes of VT have been detected by the PCD® Device in 316 patients. The mean number of episodes per patient with VT was 31.7 and ranged from 1 - 531 episodes.

Most spontaneous VT episodes (90.7%) were successfully treated with VT Therapy #1 and 98.4% were successfully treated with one of the four programmable VT therapies.

Of the 9864 successfully terminated spontaneous VT episodes, 91.4% were treated with one of the programmed antitachycardia pacing therapies incorporated in the PCD® Transvene™ System. The clinical benefit of tiered therapy is the reduction of delivery of high energy shocks for the treatment of stable recurrent ventricular tachycardia. This greatly enhances the patient acceptance of ICD therapy since antitachycardia pacing is usually not perceived by the patient.

Sixty patients experienced 163 (1.6%) episodes in which the PCD® Device was ineffective in terminating a spontaneous episode of VT despite delivery of all four programmed VT therapies. Thirty-nine patients experienced 95 ineffective episodes that were due to sinus tachycardia or atrial fibrillation/flutter (SVT) with a rapid ventricular response that had been detected as VT. These episodes were resolved with either modification of programmed parameters or of antiarrhythmic drug therapy. It should be noted that the PCD® Device responded appropriately based on the programmed detection parameters.

The remaining 68 episodes occurred in 21 patients in which the programmed VT therapies were ineffective in terminating a spontaneous VT episode. **No patient deaths occurred as a result of ineffective VT therapy**. Reprogramming and pharmacologic intervention resolved these events.

E.2.2 Spontaneous VT Episode Experience By Primary Indication

The primary indications for implant of the PCD Transvene System were sudden cardiac death (**SCD**), recurrent sustained ventricular tachycardia (**VT**) and sudden cardiac death associated with recurrent sustained ventricular tachycardia (**SCD/VT**). Spontaneous VT episode efficacy by primary indication is provided in Table E-6. The overall efficacy for spontaneous VT episodes is greater than 98% for each of the patient groups. There is no difference in therapy efficacy among the patient's indications. Table E-6 contains the spontaneous VT episode therapeutic efficacy.

PCD® Transvene™ System
Spontaneous VT Episode Therapeutic Efficacy
By Primary Indication

Indication	# Episodes Successful	# Total Episodes	% Success
SCD	1148	1157	99.2%
VT	7450	7591	98.1%
SCD/VT	1266	1279	99.0%
Total	9864	10027	98.4%

Table E-6: PCD® Transvene™ System - Spontaneous VT Episode Efficacy by Primary Indication -2/1/93

E.2.3 Spontaneous VT Episode Experience By Therapy Type

The PCD® Device incorporates three programmable VT therapy types, RAMP, BURST and CARDIOVERSION, for the treatment of recurrent ventricular tachycardia. Spontaneous VT episode efficacy by programmed therapy type is provided in Table E-7.

PCD® Transvene™ System Spontaneous VT Episode Efficacy By Programmed Therapy Type			
VT Therapy Type	**# Success**	**# Attempts**	**% Efficacy**
Ramp	4903	5374	91.2%
Burst	4266	4738	90.0%
Cardioversion	695	818	85.0%

Table E-7: Spontaneous VT Episode Efficacy by Therapy Type - 2/1/93

E.2.4 Spontaneous VF

For purposes of this clinical trial, VF is defined as those episodes that satisfy the programmed VF detection criteria. Specifically, all programmed VF detection criteria must be fulfilled to detect a VF episode. Successful termination of the episode is defined as satisfying the VF detection criterion for episode termination.

To date, 2491 spontaneous episodes of VF have been detected by the PCD® Device in 317 patients. The mean number of episodes per patient was 7.9 and ranged from 1 - 262 episodes. A review of the chart per investigator for this patient that experienced the 77 episodes of VF revealed that 75 were most likely due to atrial fibrillation. VF detection parameters were modified in this patient.

Most (91.3%) spontaneous VF episodes were successfully treated with VF Therapy #1 and 99.1% were successfully treated with one of the four programmable VF therapies.

Sixteen patients experienced 31 episodes (1.3%) in which the PCD® Device was ineffective in terminating a spontaneous episode of VF despite delivery of all four programmed VF therapies. Nine patients had 22 reported ineffective VF spontaneous episodes that were due to sinus tachycardia or atrial fibrillation with rapid ventricular response rather than VF. Reprogramming and pharmacologic intervention resolved these problems.

Four patients experienced 5 ineffective episodes that were detected as VF by the PCD® System. One of these patients (b)(6) required external defibrillation to convert the VF episode. This patient's antiarrhythmic drug regimen was modified to improve defibrillation efficacy. Another patient (b)(6) had an episode recorded as ineffective on the event counters but presented in sinus rhythm. Subsequent evaluation demonstrated appropriate PCD® function. Another of these patients (b)(6) had two spontaneous episodes of VT that were detected as VF by the PCD® while in the hospital for progressive CHF. These episodes required external cardioversion. The patient requested the PCD® be turned OFF. Patients was alive at the last known follow-up. The last of these four patients (b)(6) experienced cardiac arrest at home and was found by the paramedics to be in sinus rhythm. While on a monitor the patient developed VF. The PCD® delivered the programmed therapy which terminated the episode but the patients developed EMD, arrived at the ER comatose and died.

Four patients (one patient (b)(6) experienced 2 episodes due to AF but is described below again) experienced 4 episodes in which the PCD® detected the episodes as VF but were actually episodes due to extraordinary circumstances. One patient (b)(6) experienced an episode where all four therapies

failed secondary to RV lead fracture. The patient had Twiddlers Syndrome. Reoperation was required. It appears that the inappropriate therapy was not due to VT/VF but due to noise. Another patient ((b)(6) had a surgical procedure (CABG) where the CS lead dislodged post surgery. The episode that was detected was due to the lead dislodgment. The third patient (b)(6) had incessent episodes of fast VT (cycle length 280 ms) that were eventually resolved by drugs. The fourth patient (b)(6) was in hospital and there was an episode of VF detected. However, the device was interrogated before termination of the episode was detected. There was external intervention associated with the terminal event. The device was not interrogated again.

E.2.5 Spontaneous VF Episode Experience By Primary Indication

The primary indications for implant of the PCD® Transvene™ System were sudden cardiac death (**SCD**), recurrent sustained ventricular tachycardia (**VT**) and sudden cardiac death associated with recurrent sustained ventricular tachycardia (**SCD/VT**). Spontaneous VF episode efficacy by primary indication is provided in Table E-8. There is no difference in therapy efficacy among the patient's indications. The overall efficacy for spontaneous VF episodes is greater than 98% for each of the patient groups.

PCD® Transvene™ System
Spontaneous VF Episode Therapeutic Efficacy
By Primary Indication

Indication	# Episodes Successful	# Total Episodes	% Success
SCD	665	686	96.9%
VT	908	916	99.1%
SCD/VT	378	380	99.5%
TOTAL	1951	1982	98.4%

Table E-8: PCD® Transvene™ System - Spontaneous VF Episode Efficacy by Primary Indication -2/1/93

E.2.6 Spontaneous VF Episode Experience By Therapy Type

The PCD® Device incorporates three programmable defibrillation pathways, SEQUENTIAL, SINGLE and SIMULTANEOUS, for the treatment of ventricular fibrillation. Spontaneous VF episode efficacy by programmed defibrillation pathway is provided in Table E-9.

PCD Transvene™ System
Spontaneous VF Episode Efficacy
By Programmed Therapy Type

VF Therapy Type	# Success	# Attempts	% Efficacy
Sequential	1525	1549	98.5%
Simultaneous	426	433	98.4%

Table E-9: PCD® Transvene™ System - Spontaneous VF Episode Efficacy by Therapy Type - 2/1/93

E.3 Overall Success Rate

Of the 757 patients who received a PCD® Transvene™ System, 597 patients (78.9% - 597/757) have either experienced a spontaneous VT/VF episode or had VT/VF induced during a post implant electrophysiology study. The performance of the PCD® Transvene™ System therapies have been thoroughly evaluated and been shown to be effective in detecting and terminating episodes of ventricular tachyarrhythmia.

There have been no reports of a patient death due to the PCD® Transvene™ System not detecting a spontaneous episode of VT or VF.

The overall success rate of the PCD® Transvene™ System in terminating spontaneous episodes of either VT or VF was 98.4% with a VT success rate of 98.4% and VF success rate of 98.4%. The incidence of unsuccessful termination of an apparent "true" episode of ventricular tachycardia despite delivery of all four therapies was 0.7% (68/10027).

The incidence of unsuccessful termination of an apparent "true" episode of ventricular fibrillation despite delivery of all four therapies was 0.3% (5/1982).

The evaluation of spontaneous episode experience indicates that the PCD® Transvene™ System's VT and VF detection and therapy functions have performed safely and effectively in the indicated patient population.

F. Complications and Observations

The use of a multiprogrammable implantable cardioverter defibrillator (ICD) device allows the physician to resolve most relevant medical events by noninvasively changing programmed parameters thus, avoiding invasive procedures. However, there will continue to be certain relevant medical events which will require invasive procedures for resolution.

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following definitions:

COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

As of February 1, 1993, there have been a total of 176 complications identified in 147 patients and 214 observations identified in 180 patients in the PCD® Transvene™ System patient population. Thus, 19.4% (147/757) of the patients have experienced a clinical event which was defined as a complication and 23.8% (180/757) of the patients have experienced a clinical event which was defined as an observation. Table F-1 summarizes how these events were reported with U.S versus International.

PCD® Transvene™ System Reported Complications/Observations U.S versus International		
	# of Complications	# of Observations
U.S.	104	93
International	72	121
Total	176	214

Table IG-1: PCD® Transvene™ System Complications/Observations U.S. versus International - 2/1/93

Table IG-2 summarizes the reported PCD® Transvene™ System complications and observations by category. The reported complications and observations are recognized clinical events that may occur with **any** of the current ICD devices. These complications and observations are discussed in the PCD® device and Transvene™ manual. **None of the reported complications or observations have resulted in a patient death.**

PCD® Transvene System Reported Complications/Observations By Category		
Category	**Complications**	**Observations**
	Num (% of Pts)	Num (% of Pts)
Increased Defibrillation Requirements	9 (1.2%)	8 (1.1%)
Inappropriate VF Therapy Delivery	-	14 (1.8%)
Inappropriate VT Therapy Delivery	-	59 (7.8%)
Loss of Capture	6 (0.8%)	14 (1.8%)
Oversensing	-	54 (7.1%)
Undersensing	-	-
Skin Erosion	5 (0.7%)	1 (0.1%)
Pocket Infection	24 (3.2%)	10 (1.3%)
Seroma	6 (0.8%)	14 (1.8%)
Hematoma	6 (0.8%)	17 (2.2%)
Pneumothorax	2 (0.3%)	1 (0.1%)
Pacemaker Syndrome	-	2 (0.3%)
Right Ventricle Perforation	6 (0.8%)	-
Subclavian Vein Thrombosis	1 (0.1%)	3 (0.4%)
Lead Fracture	9 (1.2%)	-
Subcutaneous Patch Crinkling	7 (0.9%)	5 (0.7%)
Early Device Explant	4 (0.5%)	-
Total Lead Dislodgement (n = 757)	91 (12.0%)	12 (1.6%)
Total	**176**	**214**

Table IG-2: PCD® Transvene™ System: Reported Complications and Observations - 2/1/93

Table IG-3 contains a description of the lead dislodgements that have occurred in less than 30 days and in greater than 30 days.

PCD® Transvene System
Reported Complications/Observations
Lead Dislodgements <30 days and >30 days

Category	Complications		Observations	
	Num (% of Pts)		Num (% of Pts)	
	<30 days	>30 days	<30 days	>30 days
RV Lead Dislodgement n=741	14 (1.9%)	10 (1.3%)	0 (0%)	1 (0.1%)
CS Lead Dislodgement n= 261	12 (4.6%)	10 (3.8%)	2 (0.8%)	2 (0.8%)
SVC Lead Dislodgement n=535	16 (3.0%)	29 (5.4%)	1 (0.2%)	6 (1.1%)
Total Lead Dislodgement n=757	42 (5.6%)	49 (6.5%)	3 (0.4%)	9 (1.2%)

Table IG-3: PCD Transvene System: Lead Dislodgements <30 days and >30 days - 2/1/93

There have been a total of 49 lead dislodgements reported in patients at greater than 30 days. None of the lead dislodgements resulted in an ineffective therapy for a spontaneous VT of VF episode or patient death. Lead dislodgements were documented by fluoroscopic examination during electrophysiologic evaluation, chest x-ray obtained during routine follow-up, or during pacing/sensing threshold evaluation during routine follow-up. In all 48 cases, reoperation was required to reposition the lead and reestablish an effective defibrillation lead system.

Lead dislodgements are not specific to the PCD® Transvene™ System and have been reported with dual chamber pacemakers and the current market released implantable cardioverter defibrillator (ICD) system. The early history of dual chamber pacemakers witnessed a high lead dislodgement rate of at least 20% (Smyth, PND, et al. Permanent pervenous atrial sensing and pacing with a new J-shaped lead. J Thoracic Cardiovascular Surgery. 1976;72:565-570). Winkle, et al reported that the incidence of dislodgement of the superior vena cava spring leads with the current market release ICD system to be 6.3%. (Winkle, et al. Automatic Implantable Cardioverter-Defibrillator: Efficacy, Complications, and Survival in Patients with Malignant Ventricular Arrhythmias. JACC. June 1988; Vol.11, No.6:1278-86).

G. Inactive Patients

There are a total of 82 patients who had received a PCD® System and are no longer active in the study as of 2/1/93. Table G-1 shows the distribution of inactive patients by reason for no longer being active in the PCD® Transvene™ System clinical study.

PCD® Transvene™ System Inactive Patients	
Inactive Patients	**All Patients**
Patient Deaths	51
Infection (Explant)	22
Heart Transplant	9
Total	82

Table G-1: PCD® Transvene™ System - Inactive Patients - 2/1/93

H. Patient Deaths

The positive impact of implantable cardioverter defibrillator (ICD) therapy on sudden cardiac death mortality has been well documented in the medical literature. The use of device therapy for the treatment of recurrent ventricular arrhythmias has become an accepted and important clinical tool. An analysis of the sudden cardiac death survival in the PCD® Transvene™ System patient population was performed.

For purposes of the clinical study, each of the patient deaths was categorized using the following definitions:

Non-Cardiac: Deaths that occurred where the primary cause of death was determined to be non cardiac in nature, e.g. stroke, cancer, etc.

Cardiac: Deaths that occurred where the primary cause of death was determined to be cardiac in nature.

Non-Sudden: Deaths that occur greater than one hour after the onset of symptoms.

Sudden: Deaths that occur within one hour of the onset

of symptoms or where the death is unwitnessed. Sudden cardiac deaths were also categorized as being **Witnessed** or **Unwitnessed.**

Perioperative: Deaths that occur within thirty days of implant.

System Related: A death which results from a malfunction (operation not according to design specification) of a PCD® System component, or as a result of a device induced arrhythmia, or an interaction between a PCD® System component and the patient.

Procedure Related: A death which occurs as a result of a procedure required to implant, follow or test a PCD® System.

All deaths and significant complications have been and will continue to be reviewed by a committee comprised of PCD® Transvene™ System investigators and other physicians. Two committees (Clinical Event Review Committees) have been formed, one to review North American deaths and complications, and the other to review European clinical events. The primary purpose of these reviews was to determine whether the PCD® System was related to the deaths or significant complications that have occurred and, if so, what changes may be required to prevent such events in the future.

There have been a total of 51 patient deaths reported in the PCD® Transvene™ System patient population. Table H-1 summarizes how these patient deaths have been classified.

PCD® Transvene™ System
Summary of Death Classifications
(n = 757)

Classifications	Number of Deaths
Sudden Cardiac	5
Non-Sudden Cardiac	30
Noncardiac	16
Total	51

Table H-1: PCD® Transvene™ System - Summary of Death Classifications - 2/1/93

None of the patient deaths were attributed to a malfunction of the PCD® Transvene™ System.

Actuarial survival analysis on the PCD® Transvene™ System was done on all patients who were either evaluated for implantation or in whom the device was implanted. Thus, the analysis is done from the perspective of **intention to treat.** Those patients in whom the PCD® Device was OFF at the time of death or in whom no device was implanted **are** included in the survival analysis. Those patients that were screened for a PCD® Transvene™ System but failed to receive a Transvene™ system are not included in this analysis.

Projected one year survival calculations for the various death classifications are provided in Table H-2. **The actuarial projections include perioperative deaths only in the calculation of one year survival from death due to all causes (shown in the row labelled Overall).** The perioperative death rate defined as deaths which occurred within thirty days of implant was 0.7% (5/757) which is considerably less than the perioperative mortality for the PCD® System with Epicardial leads (5.3% - 39/742). Included in this table are the projected one year survival calculations for patients who ultimately received a PCD® Transvene™ System (n = 757) and all patients that were screened for a PCD® Transvene™ System (n = 854) regardless of implant outcome.

PCD® Transvene™ System One Year Actuarial Survival		
	Received PCD® Transvene™ System	**Screened for a PCD® Transvene™ System**
Sudden Cardiac Death	99.5%	99.4%
Non-Sudden Cardiac	96.2%	96.6%
All Cardiac	95.8%	96.1%
Noncardiac	98.1%	98.3%
Perioperative	0.7%	1.6%
Overall	93.3%	92.9%

Table H-2: PCD® Transvene™ System - One Year Actuarial Survival - 2/1/93

The positive impact of the PCD® Transvene™ System on patient mortality is clearly obvious from this analysis. The sudden cardiac death survival rate in this patient group is 99.5% in the patient group that received a Transvene™ System and 99.4% in those who were screened for a Transvene™ System. This is marked improvement when compared with the reported survival of similar patient groups treated with drug therapy alone of between 34% and 73% at one year.

I. Clinical Experience By Primary Indication

Medtronic is requesting approval for use of the PCD® Transvene™ System in the following patient population:

* Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or

* Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

Sudden cardiac death without recurrent VT (**SCD**) was the indication for implant in 37.1% of the patients, recurrent ventricular tachycardia without an episode of sudden cardiac death (**VT**) was the indication for implant in 49.8% of the patients, and sudden cardiac death and recurrent VT (**SCD/VT**) was the indication for implant in 13.1% of the patients.

The performance of the PCD® Transvene™ System in these three groups are summarized in Table I-1.

In all three patient groups, coronary artery disease was the predominant heart disease and the patients exhibited moderate left ventricular dysfunction as demonstrated by mean ejection fractions of less than 40%. The mean LED at the time of implant was similar among the patient groups as was the mean DFT.

The overall efficacy in terminating spontaneous VT/VF episodes in the SCD patient group was 98.4%, in the VT patient group 98.3%, and in the SCD/VT group 99.1%. Thus, independent of the indication for implant, the PCD® Transvene™ System was highly effective in terminating spontaneous episodes of VT/VF.

The one year sudden cardiac death survival rates for all groups was greater than 98.6%

This analysis indicates that the PCD® Transvene™ System has performed safely and effectively in the indicated patient groups and should be approved for use in the indicated patient population.

PCD® Transvene™ System
Data Summary by Primary Indication

	SCD	VT	SCD/VT	All Patients
# of Patients	281 (37.1%)	377 (49.8%)	99 (13.1%)	757
Number, % Male Number, % Female	212 75.4% 69 24.6%	309 82.0% 68 18.0%	89 89.9% 10 10.1%	610 80.6% 147 19.4%
Mean Age	56.8 yrs	61.2 yrs	60.0 yrs	59.4 yrs
Coronary Artery Disease	191 68.0%	292 77.5%	78 78.8%	229 72.2%
Mean Ejection Fraction	39.1% (N=259)	33.7% (N=339)	32.5% (N=90)	35.6% (N=688)
Defibrillation Pathway: Sequential Simultaneous Single	 201 71.5% 74 26.3% 6 2.2%	 295 77.6% 82 21.6% 3 0.8%	 76 76.8% 22 22.2% 1 1.0%	 574 75.3% 178 23.4% 10 1.3%
Mean LED	15.3J (N=264)	16.2J (N=351)	17.3J (N=87)	16.0J (N=702)
Mean DFT	14.0J (N=117)	15.5J (N=155)	13.9J (N=44)	14.8J (N=316)
Spontaneous VT: # of Patients # of Episodes % Success	 58 1157 99.2%	 206 7591 98.1%	 52 1279 99.0%	 316 10027 98.4%
Spontaneous VF: # of Patients # of Episodes % Success	 107 686 96.9%	 162 916 99.1%	 48 380 99.5%	 317 1982 98.4%
1 Year SCD Survival	100.0%	99.4%	98.6%	99.5%

Table I-1: PCD® Transvene™ System Data Summary by Primary Indication - 2/1/93

J. Patients Not Meeting Implant Criteria

J.1 Overview

The PCD® Transvene™ System offers a simpler and safer implantation technique for an implantable cardioverter defibrillator system. In addition, the PCD® Transvene™ System decreases the potential perioperative and long term mortality associated with current epicardial system implantation approaches.

There is a class of patients who cannot tolerate the thoracotomy required for the utilization of the epicardial patch lead defibrillation lead system and who are at high risk of sudden cardiac death. Because of the surgical risks and postsurgical complications associated with the implant of an epicardial lead system, implantation in the following patient groups may not be desirable or possible:

(1) patients in whom there is no indication for concomitant cardiovascular surgery at the time of ICD implant;

(2) patients with severe pulmonary disease who can not tolerate prolonged anesthesia or an open chest procedure;

(3) patients with severe congestive heart failure (ejection fraction < 40%) who are at increased risk for perioperative mortality following a thoracotomy procedure;

(4) patients who may eventually require open chest procedures for treatment of their coronary artery disease or cardiac transplant.

For these patients, a transvenous ICD System is the only therapy available. The PCD® Transvene™ System simplifies and greatly reduces the risk associated with lead introduction, making therapy available to these patient groups. Because there is no need to open the chest of these patients, more options for future therapy remain available; e.g. CABG is associated with increased morbidity and mortality if there has been prior open chest surgery.

However, it is expected that nonthoracotomy lead systems will have higher mean implant defibrillation thresholds as compared to traditional epicardial lead systems. In an

epicardial lead system, the lead system has a larger electrode surface area theoretically decreasing defibrillation requirements.

The smaller electrode surface areas of the PCD® Transvene™ System defibrillation leads might reduce the proportion of patients in whom the implant criteria could be met. Not meeting the implant criteria may reduce the chronic effectiveness of the lead system. Recent studies indicated that 70% of patients evaluated may be candidates for a nonthoracotomy defibrillation lead system (Wilber, D, et al. Clinical Advances in Nonepicardial Implantable Defibrillator Lead Systems. The Journal of Invasive Cardiology. Vol.3, No.6,November/December 1991).

For purposes of the PCD® Transvene™ System, the implant criteria was defined as successful VF termination at least 3 times in 4 attempts with the final lead configuration with an output energy of 18 Joules or less. The determination of a defibrillation threshold was not required.

A defibrillation threshold (**DFT**) was defined as the energy at the lowest successful defibrillation attempt, provided the patient had a failure below the lowest success or a success at $\leq$ 5J. The lowest energy of defibrillation (**LED**) was defined as the lowest programmed energy that successfully defibrillated the patient. In both cases, conversion of ventricular tachycardia or ventricular flutter to sinus rhythm was **not** included in the determination of the DFT or LED.

A total of 854 patients had an evaluation of a PCD® Transvene™ System and are divided into the following groups - (1) Patients who received a PCD® Transvene™ System; and (2) Patients screened for a PCD® Transvene™ System and received a PCD® Epicardial System. Figure 1 provides an overview of the outcome of these patients.

PCD® Transvene™ SYSTEM IMPLANT EVALUATION

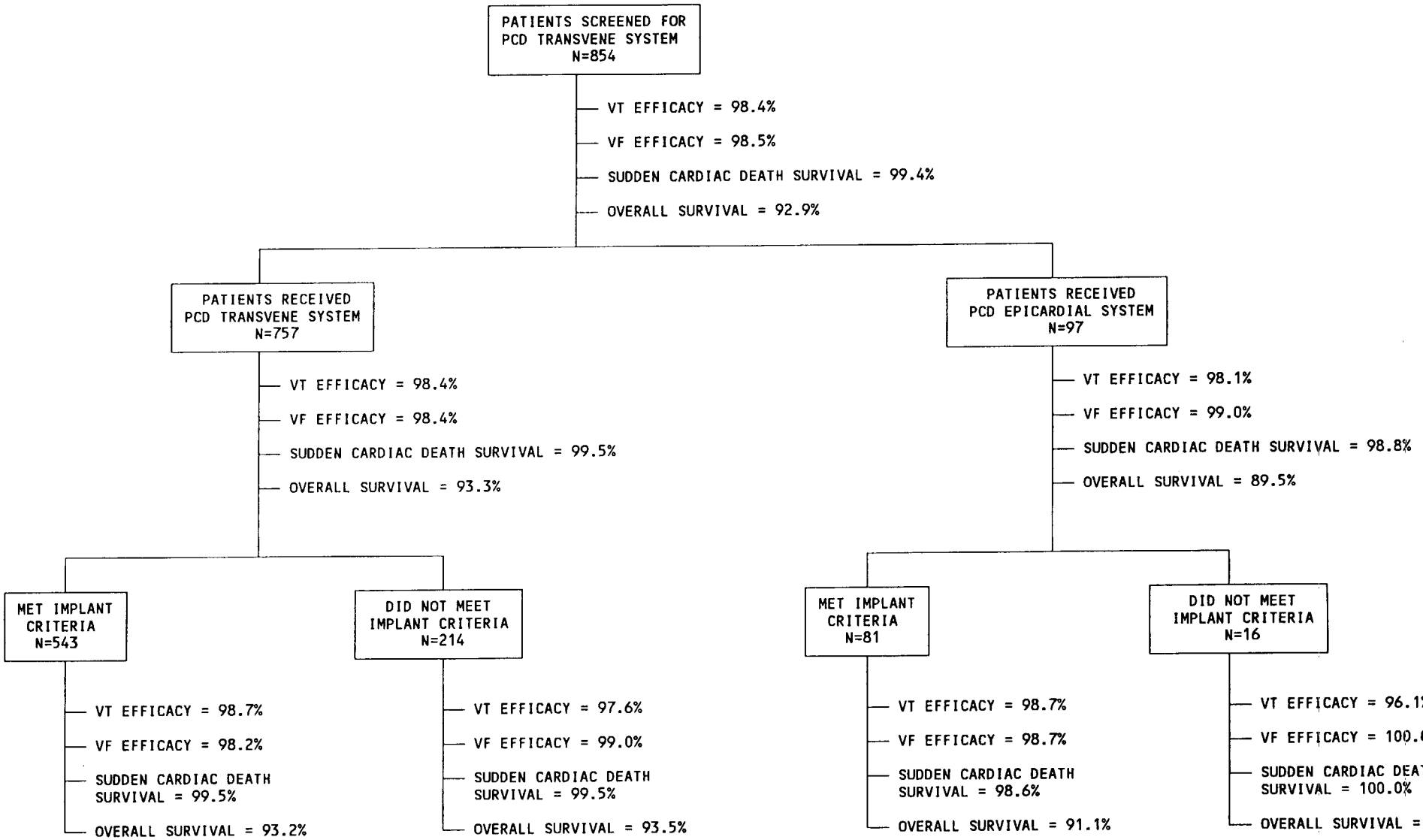

Figure 1: Patients Screened for a Transvene™ System

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As can be seen, 88.6% (757/854) of the patients who were screened for a PCD® Transvene™ System ultimately received the system. Of these 757 patients, 71.7% (543 patients) met the recommended defibrillation implant criteria which compares favorably with the predicted success rates published in the literature (Wilber et al). However, 28.3% (214/757) of the patients did not meet the recommended defibrillation efficacy implant criteria and still received the PCD® Transvene™ System. It should be noted that 97.4% of the patients (737/757) received the PCD® Transvene™ System with at least a 10 Joule defibrillation safety margin between the lowest energy of success (24J) and the maximum output (34J) of the PCD® Device.

The investigators utilized this 10 Joule safety margin as a benchmark based on the clinical experience discussed in the article, Troup P., et al. The Implanted Defibrillator: Relation of Defibrillating Lead Configuration and Clinical Variables to Defibrillation Threshold. Journal of American College of Cardiology 1985; 6:1315-1321. Finally, and perhaps most importantly, the investigators also felt that for these patients the risk associated with not meeting the recommended implant criteria was outweighed by the risk of not implanting an ICD or implanting an epicardial system.

There were twenty patients (2.6%), who received a PCD® Transvene™ System, whose cardiovascular condition precluded further completion of the PCD® Transvene™ System and adequate definition of a defibrillation safety margin. In all cases, the physician felt that the benefit of the PCD® Transvene™ System outweighed the risk of further inductions or the risk of a thoracotomy and elected not to evaluate or implant a PCD® Epicardial System.

J.2 Patients Receiving PCD® Transvene™ System & Did Not Meet Implant Criteria

For purposes of the PCD® Transvene™ System, the implant criteria was defined as successful VF termination at least 3 times in 4 attempts with the final lead configuration at an output energy of 18 Joules or less. Of the 757 patients who **received** a PCD® Transvene™ System, 214 patients (28.3%) did not meet the recommended defibrillation implant criteria and yet still received the PCD® Transvene™ System. The physicians justification for implanting the PCD® Transvene™ System despite not meeting the recommended defibrillation implant criteria are presented in Table J-1.

PCD® Transvene™ System
Reasons for Not Meeting Implant Criteria
Physician Justification

Reason	Number of Patients
Success at $\leq$ 24 Joules	170
Difficult/Unable to Induce VF	24
Patient Condition	20
Total	214

Table J-1: PCD® Transvene™ System: Physician Justification for Not Meeting Implant Criteria - 2/1/93

Further analysis of the patient who did not meet the recommended implant criteria indicates however, that 91% (194/214) had a 10 Joule safety margin between the lowest energy of successful defibrillation and the maximum output of the PCD Device (34J). Therefore, of the 757 patients who received a PCD® Transvene™ System, 97.4% (737/757) had at least a 10 Joule defibrillation safety with the implanted lead configuration.

There were 20 patients (2.6%) in whom the implant procedure was terminated due to poor patient condition. These patients received a PCD® Transvene™ System without at least a 10 Joule defibrillation safety margin. The

implant circumstances of these patients is summarized as follows:

- At least one successful defibrillation was obtained at an energy level greater than 24 Joules and or equal to 34 Joules (**N = 11**);
- Multiple inductions of VT were performed and successfully reverted with an energy level of 18 Joules or less. However, induced VF was not successfully reverted by an energy level of less than or equal to 34 Joules (**N = 6**); and
- Physician elected to terminate the procedure due to the patient's condition before inductions with the final implanted lead configuration were performed (**N = 3**).

Table J-2 provides a comparison of patient characteristics between patients who met the PCD® Transvene™ System implant criteria and those patients who did not meet the implant criteria but still received the PCD® Transvene™ System.

PCD® Transvene™ System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Patient Characteristics		
Data	**Meeting Criteria**	**Not Meeting Criteria**
Number of Patients	543	214
Mean Follow-Up	12.3 months	10.1 months
Male*	422 (77.7%)	188 (87.9%)
Female	121 (22.35)	26 (12.1%)
Mean Age	59.4 yrs	59.6 yrs
Indication*		
SCD	209 (38.5%)	72 (33.6%)
VT	278 (51.2%)	99 (46.3%)
SCD/VT	56 (10.3%)	43 (20.1%)
Cardiovascular History		
CAD	396 (72.9%)	165 (77.1%)
Cardiomyopathy	173 (31.9%)	65 (30.4%)
Mean EF*	6.3%	33.7%
NYHA Class		
I	164 (30.9%)	53 (25.8%)
II	278 (52.4%)	114 (56.6%)
III	82 (15.4%)	34 (16.6%)
IV	7 (1.3%)	92.0%)
Number ON Drugs at Implant	223 (41.1%)	97 (45.3%)
Number ON Amiodarone	78 (14.4%)	38 (17.8%)

* Statistically Significant ($p \leq 0.05$)

Table J-2: PCD® Transvene™ System: Patients Meeting Implant Criteria vs Not Meeting Implant Criteria - Comparison of Pt Characteristics - 2/1/93

Statistical analysis indicated three significant differences between these two patient groups - patient sex, indication for implant and mean ejection fraction.

Patients not meeting implant criteria had a statistically higher percentage of patients who were male ($p = 0.002$). This difference reflects that the majority of patients with

coronary disease with concomitant life threatening ventricular arrhythmias are males.

Analysis indicated the patients not meeting the implant criteria had a statistically higher percentage of patients whose primary indication for implant was sudden cardiac death associated with recurrent ventricular tachycardia ($p = 0.002$). This difference reflects the physicians use of the PCD® Transvene™ System.

Finally, patients who did meet the implant criteria had a statistically lower mean ejection fraction ($p = 0.0342$) which reflects a higher degree of underlying cardiovascular disease in these patients.

It should be noted, that none of these differences should be used as predictors for patients who should be screened for a PCD® Transvene™ System.

In order to determine if the patient's not meeting implant criteria had higher risk for morbidity and mortality, a comparison of their clinical outcome was made with those patients who did meet the implant criteria. This comparison is provided in Table J-3.

PCD® Transvene™ System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Implant Data		
Data	**Meeting Criteria**	**Not Meeting Criteria**
Number of Patients	543	214
Spontaneous VT Episode Efficacy	98.7%	97.6%
Spontaneous VF Episode Efficacy	98.7%	99.0%
Number of Patient Deaths	37	14
Perioperative Mortality	0.7%	0.5%
One Year Survival		
Sudden Cardiac	99.5%	99.5%
Non-Sudden Cardiac	95.8%	97.2%
All Cardiac	95.4%	96.7%
Noncardiac	98.5%	97.1%
Overall	93.2%	93.5%

Table J-3: PCD® Transvene™ System: Patients Not Meeting Implant Criteria versus Patients Meeting Implant Criteria - Comparison of Clinical Outcome - 2/1/93

The two patient groups had similar efficacy in the treatment of spontaneous VT/VF episodes. Importantly, in the patient population who did not meet the implant criteria there were no patients who experienced actual spontaneous VF episodes where all programmed PCD® Device therapies failed to terminate the episode.

Five patients experienced 7 episodes in which the PCD® Device was ineffective in terminating a spontaneous episode of VF despite delivery of all four programmed VF therapies. Three patients had 5 reported ineffective VF spontaneous episodes that were due to sinus tachycardia or atrial fibrillation with rapid ventricular response rather than VF. Reprogramming and pharmacologic intervention resolved these problems.

Two patients experienced 2 episodes in which the PCD® detected the episodes as VF but were actually episodes due to extraordinary circumstances. The first patient (b)(6) had incessant episodes of fast VT (cycle length 280 ms) that were eventually resolved by drugs. The second patient (b)(6) was in hospital and there was an episode of VF detected. However, the device was interrogated before termination of the episode was detected. There was external intervention associated with the terminal event. The device was not interrogated again.

Eighteen patients experienced 68 episodes in which the PCD® Device was ineffective in terminating a spontaneous episode of VT despite delivery of all four programmed VT therapies. Nine patients experienced 44 ineffective episodes that were due to sinus tachycardia or atrial fibrillation/flutter (SVT) with a rapid ventricular response that had been detected as VT. These episodes were resolved with either modification of programmed parameters or of antiarrhythmic drug therapy. It should be noted that the PCD® Device responded appropriately based on the programmed detection parameters.

The remaining 24 episodes occurred in 8 patients in which the programmed VT therapies were ineffective in terminating a spontaneous VT episode. **No patient deaths occurred as a result of ineffective VT therapy.** Reprogramming and pharmacologic intervention resolved these events.

There was no difference in the one year sudden cardiac survival or the overall survival in the two groups although follow-up was shorter for patients not meeting implant criteria (10.1 vs 12.3 months). This indicates, that despite not meeting the implant criteria these patients were not at higher risk of sudden cardiac death.

Finally, the survival of patients receiving a PCD® Transvene™ System without meeting implant criteria (N = 214) was compared to patients receiving a PCD® Epicardial System without meeting implant criteria (N = 92). This comparison is provided in Table J-4.

PCD® Transvene™ System Patients Not Meeting Implant Criteria Survival Analysis versus PCD® Epicardial System Patients Not Meeting Implant Criteria Survival Analysis		
	PCD® Transvene System Not Meeting Implant Criteria	PCD® Epicardial System Not Meeting Implant Criteria
Number of Patients	214/757 (28.5%)	92/742 (12.4%)
Number of Deaths	14	17
Sudden Cardiac	99.5%	98.6%
Non-Sudden Cardiac	97.2%	98.8%
Noncardiac	97.1%	97.3%
Overall*	93.5%	87.6%

* Statistically Significant ($p \leq 0.05$)

Table J-4: PCD® Transvene™ System: Patients Not Meeting Implant Criteria - PCD Transvene System vs PCD® Epicardial System - 2/1/93

Though the PCD® Transvene™ System had a higher incidence of patients not meeting implant criteria (28.5%) compared to the PCD® Epicardial System (12.4%), there was no statistical difference in the sudden cardiac death patient survival. However, the overall survival of patients not meeting implant criteria with the Transvene™ System was significantly better ($p = 0.037$) when compared to the PCD® Epicardial System patients not meeting implant criteria, 93.5% and 87.6%, respectively.

The investigators felt in every case that the testing performed at the time of implant, though it did not meet the recommended implant criteria, did provide an adequate demonstration of device effectiveness and justified the implant of the PCD Transvene System. Finally, there have been no patients deaths secondary to unsuccessful termination of a spontaneous VT or VF episode in this patient population.

J.3 Description of Patients Not Meeting Implant Criteria

As noted previously, the patients not meeting implant criteria (N=214) were divided into three groups (1) Successful defibrillation at an energy level of equal to or less than 24 Joules [79.4% of the patients]; (2) Difficult to induce VF [11.2% of the patients]; and (3) Implant procedure terminated due to poor patient condition [9.4% of the patients]. These patient groups are reviewed in the following discussion.

Lowest Energy of Defibrillation < 24 Joules

There were 170 patients in whom the PCD® Transvene™ System was implanted with a defibrillation safety margin of at least 10 Joules. Table J-5 provides an overview of these patients clinical experience.

These data indicate that the final implanted PCD® Transvene™ System was evaluated and significant attempts were made to meet the recommended implant criteria. In most of these patients (79.4%), a safety margin of 10 Joules was obtained between the successful defibrillation energy (24 J or less) for ventricular fibrillation and the maximum output of the PCD Device (34 J). The investigators decided in certain circumstances that this was appropriate demonstration of device effectiveness and that the PCD® Transvene™ System could be implanted.

Of these patients, 159 (93.5%) have had VT or VF induced at a chronic follow-up visit and in each case, VT or VF was successfully terminated by the PCD Transvene System (141 patients or 82.9% had only VF induced). In addition, 65 patients (38.2%) have experienced a spontaneous VF episode with an overall efficacy of 99.4%.

Thus, the clinical outcome in these patients was not adversely affected by not meeting implant criteria since their spontaneous VF episode efficacy was 99.4%% and the one year sudden cardiac death actuarial survival was also 99.4%. The duration of follow up, however, is limited to an average of 9.7 months.

PCD® Transvene™ System Patients Not Meeting Implant Criteria 10J Safety Margin Provided	
Number of Patients	170
Lowest Energy of Defibrillation:	
1 Success with 10J Safety Margin	87
2 Success with 10J Safety Margin	58
3 Success with 10J Safety Margin	18
> 3 Success with 10J Safety Margin	7
Overall Spontaneous VF Episode Efficacy	99.4%
One Year Survival:	
Sudden Cardiac	99.4%
Overall	93.8%

Table J-5: PCD® Transvene™ System: Patients Not Meeting Implant Criteria with 3/4 Successes at $\leq$ 24 Joules Clinical Experience - 2/1/93

Difficult to Induce VF

There were 24 patients who did not meet the recommended PCD® Transvene™ System implant criteria because at least three episodes of VF were not induced at the time of implant. Of these, 15 patients had ventricular tachycardia induced and successfully reverted. The remaining 9 patients had ventricular flutter induced and successfully reverted. In all 24 patients, the lowest successful energy was equal to or less than 18 Joules.

The indication for implant was sudden cardiac death (SCD) in 6 patients (25%), recurrent ventricular tachycardia (VT) in 13 patients (54.2%) and sudden cardiac death associated with recurrent ventricular tachycardia (SCD/VT) in 5 (20.8%) patients. Thus the majority of the patients, 75%, had documented recurrent ventricular tachycardia as part of their ventricular tachyarrhythmia history. Eight of the these patients (33.0%) were on Amiodarone therapy which may have contributed to the inability to induce VF.

Of the 24 patients who did not meet the recommended PCD® Transvene™ System implant criteria because at least

three episodes of VF were not induced at the time of implant, 13 patients (54.2%) have experienced a spontaneous VF episode and 21 patients (87.5%) have had VT or VF induced during a chronic follow-up. In all cases, VF was successfully reverted by the PCD® Transvene™ System.

There has been one reported patient death (b)(6) in the patient group with a resultant one year sudden cardiac death and overall actuarial survival of 100%.

Patient Condition

There were 20 patients in whom the implant procedure was terminated due to poor patient condition. These patients received a PCD® Transvene™ System without at least a 10 Joule defibrillation safety margin. The implant circumstances of these patients is summarized as follows:

- At least one successful defibrillation was obtained at an energy level greater than 24 Joules but less than 34 Joules (**N = 11 patients**);
- Multiple inductions of VT were performed and successfully reverted with an energy level of 18 Joules or less. However, induced VF was not successfully reverted by an energy level of less than or equal to 34 Joules (**N = 6 patients**); and
- Physician elected to terminate the procedure due to the patient's condition before inductions with the final implanted lead configuration were performed (**N = 3 patients**).

The mean ejection fraction of this group was 26.9%, indicating more severe underlying cardiovascular disease, and may have contributed to the physicians decision to terminate the implant procedure prior to meeting implant criteria. This group had a mean of 6.8 VF inductions, 2.2 lead configurations evaluated and a mean duration of VT/VF for the implant procedure of 220 total seconds. The circumstances of the implant procedures, mainly the duration of induced ventricular tachyarrhythmia and associated hemodynamic compromise, limited the number of inductions that could be performed and whether the recommended implant criteria could be met.

Of these 20 patients, VT or VF has been induced at a chronic follow-up visit in 16 patients (80%) and in all cases successful defibrillation with the implanted PCD® Transvene™ System was documented.

The overall spontaneous VF episode efficacy for this patient group was 96.0%. However, further reviewed indicated that one patient experienced atrial fibrillation that was detected as VF and in whom all four programmed VF therapies were ineffective. This patient's antiarrhythmic drug therapy was modified and there were no further reports of ineffective therapies.

Thus, there have been no patients who have experienced an actual spontaneous VF episode where all four programmed VF therapies failed to terminate the episode.

There have been two reported patient deaths, Patient ID (b)(6) which was classified as non-sudden cardiac secondary to end stage heart failure and Patient ID (b)(6) which was also classified as non-sudden cardiac. The one year sudden cardiac death survival in this patient population is 100% while the overall one year survival was 85.5%. This lower overall one year survival may due to the lower mean ejection fraction of this patient group.

The clinical outcome in these twenty patients was not adversely affected by not meeting implant criteria since there was no reports of failure to terminate a spontaneous VF episode and the overall one year sudden cardiac death survival was 100%.

K. Comparison to AICD System Experience

K.1 Overview

The current AICD Epicardial System is implanted only with a defibrillation lead system requiring a thoracotomy. The PCD® Transvene™ System allows the implantation of an implantable cardioverter defibrillator (ICD) system without the potential increased perioperative morbidity and mortality associated with a thoracotomy. This allows the application of ICD therapy in patients who may not otherwise be candidates for this type of therapy. Though the PCD® Transvene™ System will have complications and observations that are specific to the lead system, the overall performance should be at least equivalent to that reported with the current AICD Epicardial System.

This section provides a comparison of the PCD® Transvene™ System clinical experience to that of the reported AICD Epicardial System clinical experience. The following areas will be discussed:

- Patient characteristics
- Clinical performance
- Survival analysis

For purposes of comparison, the Ventak-P Epicardial System patient population described in the Summary of Safety and Effectiveness Data (PMA Application Number P890061) dated May 2, 1991 will be used. A copy of this summary was obtained through the Freedom of Information Act.

K.2 Comparison of Patient Characteristics

In comparing the clinical experience with the PCD® Transvene™ System to the reported Ventak-P Epicardial System clinical experience, it is important to determine that the patients who received the device are comparable.

The characteristics of the patients receiving the PCD® Transvene™ System were compared to the characteristics of patients discussed in the Ventak-P Summary of Safety and Effectiveness Data and are presented in Table K-1.

There were no differences between the two patient groups.

PCD® Transvene™ System Comparison of Patient Characteristics PCD® versus AICD		
	PCD®	Ventak-P
Number of Patients	757	292
Mean Follow-Up Time	11.7 months	6.8 months
% Males % Females	610 (81%) 147 (19%)	231 (79%) 61 (21%)
Mean Age	59.4 years	61.5 years
Primary Indication: SCD VT SCD/VT	 281 (37%) 377 (50%) 99 (13%)	 49 (16%) 169 (59%) 73 (25%)
Coronary Artery Disease	561 (74%)	228 (78%)
Mean Ejection Fraction	35.6%	34%
Drug Therapy at Implant	42%	45.0%
Concomitant Surgery	0%	18.0%

Table K-1: Comparison of Patient Characteristics, PCD® versus Ventak-P 2/1/93

The two patient groups are comparable in mean age and mean ejection fraction. Both groups had moderately depressed left ventricular function demonstrated by the mean ejection of 35.6% for the PCD® Transvene™ System patient group and 34% for the Ventak-P Epicardial System patient group.

Analysis indicated that no statistical differences between the PCD® Transvene™ System and Ventak-P Epicardial System patient populations except in the category of patient indication. There are more patients that had Sudden Cardiac Death as the primary indication in the PCD® Transvene™ population than in the AICD population ($p = 0.001$).

K.3 Comparison of Clinical Performance

Areas of clinical performance that were compared were implant defibrillation thresholds, incidence of spontaneous VT/VF events, incidence of complications and patient survival. These specific areas were selected in order to evaluate the system performance in the two patient populations.

Implant Defibrillation Thresholds

For the purposes of the PCD® Transvene™ System clinical study, determination of defibrillation threshold was not mandatory. However, the preferred method of evaluating defibrillation efficacy was to determine the defibrillation threshold using a testing sequence of 18J, 15J, 10J, 5J with a failure at any level causing a return to 18 J for the remaining attempts. For the purposes of this report a defibrillation threshold was defined as the energy at the lowest successful defibrillation attempt, provided a patient had a failure below their lowest defibrillation success or a success at $\leq$ 5J. The rhythm treated must have been VF to be included in the analysis.

It should be noted, that it was expected that the PCD® Transvene™ System would have a higher mean defibrillation threshold as compared to a traditional epicardial defibrillation lead system. In a epicardial system, the increased electrode surface area would theoretically decrease defibrillation requirements.

A total of 316 patients had a defibrillation threshold determined at the time of PCD® device implant. The mean defibrillation threshold (DFT) for all lead systems was 14.8J. The recommendation for VF Therapy #1 is to program the stored energy to twice the implant DFT or 18 Joules, whichever is greater. Thus an adequate defibrillation safety margin was provided when following the VF therapy programming recommendations.

In the Ventak-P Epicardial System, the mean defibrillation threshold at implant was 13.4J. Thus the two systems had similar defibrillation thresholds at implant despite the fact that one system utilized an epicardial defibrillation lead

system while the other utilized a transvenous defibrillation lead system.

These data indicate that the PCD® Transvene™ System had comparable implant defibrillation threshold performance when compared to the reported Ventak-P Epicardial System clinical experience.

Incidence of Spontaneous VT/VF Episodes

The incidence of spontaneous VT/VF episodes in the Ventak-P Epicardial System and PCD® Transvene™ System patient population was evaluated by utilizing the stored episode information provided by both devices.

In the Ventak-P device, the total number of shocks delivered to the patient is provided via interrogation of the device. The PCD® device provides information on the total number of VT and VF episodes detected by the PCD® device and the total number of VT and VF episodes successfully treated by the PCD® device as well as the number of VT/VF episodes where the PCD® device was ineffective. In addition, the last 20 intervals of the last episode satisfying detection criteria along with the first 10 intervals after the last therapy delivered are recorded by the device. These data assist the physician in evaluating the frequency of VT/VF episodes, the efficacy of the PCD® device programmed parameters and the need for reprogramming.

In the Ventak-P Epicardial System experience of 292 patients with a mean follow-up of 6.8 months, 137 (46.9%) received a device countershock in response to a spontaneous ventricular tachyarrhythmia episode as defined by the Ventak-P Device detection criteria.

In the PCD® Transvene™ System experience of 757 patients with a mean follow-up of 11.7 months, 458 patients (60.5%) have received device therapy in response to a spontaneous ventricular tachyarrhythmia episode as defined by the PCD® Transvene™ System detection criteria.

A total of 10,027 spontaneous VT and 1982 spontaneous VF episodes have been recorded by the PCD® device

episode counters. Of the 9864 successfully treated spontaneous VT episodes, 91.4% were treated with one of the programmed antitachycardia pacing therapies incorporated in the PCD® device. The clinical benefit of tiered therapy is the reduction of delivery of high energy shocks for the treatment of stable recurrent ventricular tachycardia that may be responsive to antitachycardia pacing.

Incidence of Complications

Table K-2 provides a comparison of reported complications and observations. The AICD clinical experience data is from the Winkle, et al Long Term Outcome with Automatic Implantable Cardioverter-Defibrillator; JACC, May 1989; 13(6); 135-161. This article was selected because it provides a detailed clinical complication experience on a large patient population, 270 patients. Note that the percentage reported in the PCD® Transvene™ System includes **both complications and observations.** In the following table, the complications are reported for the categories of Fail to Cardiovert/Defibrillate, Pocket Infection, and Erosion. Observations are reported in the Inappropriate/Problematic VT/VF Therapy Delivery category.

PCD® Transvene™ System
Comparison of Complication/Observation Rates
PCD® versus AICD

Category	PCD®%	AICD%
Fail to Cardiovert/Defibrillate	2.3%	4.1%
Inappropriate/Problematic VT/VF Therapy Delivery	9.6%*	20%
Pocket Infection	2.9%	2.2%
Erosion	0.8%	0.7%

* Includes Observations only; there were no Complications in this category.

Table K-2: Comparison of Complication/Observation Rates: PCD® Transvene™ System vs AICD Epicardial System - 2/1/93

The incidence of failure to cardiovert and/or defibrillate was lower in the PCD® Transvene™ System patient population. The instances of failure to cardiovert and/or defibrillate in the PCD® Transvene™ System patient population were associated with increased defibrillation requirements during induced episodes, none of which resulted in patient death.

The failures to cardiovert/defibrillate reported in the Winkle, et al article were associated with patch dislodgement, patch crinkling, lead conductor fracture and elevated defibrillation thresholds.

The incidence of inappropriate/problematic VT/VF therapy delivery was lower in the PCD® Transvene™ System patient population. This is to be anticipated since the device incorporates independently programmable detection algorithms for VT and VF. The reasons for inappropriate VT/VF therapy delivery included sinus tachycardia being detected as VT or VF and atrial fibrillation with rapid ventricular response being detected as VT or VF.

The overdetection circumstances reported in Winkle, et al were nonsustained VT, VT, sinus tachycardia, atrial fibrillation with rapid ventricular response, sensing lead fracture and pacemaker interaction. The patients with VT complained of receiving multiple shocks with limited or no symptoms. The incorporation of antitachycardia pacing in the PCD® device decreases the need for delivery of cardioversion shocks for the termination of stable VT and increases patient acceptance of ICD therapy.

In the Winkle, et al experience all patients with pocket infection had the devices explanted. In the PCD Transvene System experience, the incidence of device explant secondary to pocket infection was 3.2% which was comparable to Winkle's article.

Thus, the incidence of complications and observations was similar to that of the AICD Epicardial System in the categories of ineffective VT/VF therapies, infection requiring explant and erosion. The incidence of inappropriate delivery of therapy is lower in the PCD Transvene System experience than in the AICD Epicardial System experience, which is clinically significant.

This analysis indicates that the PCD® Transvene™ System offers clinical advantages in reducing the need for a thoracotomy for implantation and reducing the number of shocks due to successful antitachyarrhythmia pacing.

K.4 Comparison of One Year Actuarial Survival

The Ventak-P Epicardial System produced by Cardiac Pacemaker, Inc, has obtained market approval from the U.S. FDA to date. While there are important differences in the function of the Ventak-P Epicardial System and the PCD® Transvene™ System, there is a natural desire for comparison of the clinical outcome, particularly the impact of these devices on death rate.

A total of 51 deaths (6.7%) were reported in the PCD® Transvene™ System patient population. Of the 35 cardiac deaths, 30 were non-sudden cardiac and 5 were sudden cardiac. Sixteen deaths were classified as noncardiac. Five of the 51 total deaths occurred within the perioperative period (death less than 30 days post implant) with a resultant perioperative mortality of 0.7%.

In the Ventak-P Epicardial System patient population a total of 19 deaths (6.5%) were reported. Of the 12 cardiac deaths, 4 were classified as sudden cardiac and 8 were classified as non-sudden cardiac. Six of the deaths were classified as noncardiac and the cause of one was unknown. Eight of the deaths occurred within the perioperative period with a resultant perioperative mortality of 2.7%. The PCD® Transvene™ System population had a lower perioperative mortality, 0.7% vs 2.7% ($p = 0.006$).

For purposes of this comparison, only the **overall** actuarial survival rate includes perioperative deaths. All other calculations in both the PCD® Transvene™ System and Ventak-P Epicardial System group exclude perioperative deaths.

For the Ventak-P Epicardial System, patient deaths were **censored** if the Ventak-P device had been either electively deactivated for various reasons prior to the patient's death, thus preventing the device from attempting to convert the arrhythmia or if the pulse generators were known to be

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nonfunctional and awaiting replacement. For purposes of this comparison, 7 patient deaths were **censored** in the PCD® Transvene™ System patient population because the devices were deactivated at the time of patient death.

This PCD® Transvene™ System sudden cardiac death survival of 99.7% at one year is comparable to that of the Ventak-P Epicardial System sudden cardiac death survival rate of 98.6%. More importantly, the overall one year actuarial survival for the PCD® Transvene™ System was 94.2% as compared to 90.8% for the Ventak-P Epicardial System. This difference was primarily due to the improvement in the reported perioperative mortality in the PCD® Transvene™ System patient population. [Note: Confidence interval analysis was performed indicating that there was a statistical difference in the reported **Overall** mortality.]

This comparison of actuarial survival rates indicates that the projected sudden cardiac death survival of patients receiving a PCD® System patient population is comparable to that reported for the Ventak-P Epicardial System. Thus, the incorporation of programmable VT/VF detection and therapy algorithms has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

In addition, the elimination of a surgical thoracotomy for implant in the PCD® Transvene™ System has improved the perioperative mortality and overall one year survival when compared to the Ventak-P Epicardial System.

L. Comparison to PCD® Epicardial System Clinical Results

The PCD® Epicardial System uses the same tiered therapy device that combines features of bradycardia support pacing, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. This system has incorporated programmability and multiple detection and therapeutic options that allows the titration of device therapy to a patient's specific clinical arrhythmia history.

The PCD® Epicardial System requires a thoracotomy for implantation because of the need to insert epicardial patch leads. This exposes the patient to surgical risk and potentially limits the type of patient who may be considered for implant of the system. The need for a simpler and safer implantation technique is widely recognized. The incorporation of a nonthoracotomy lead system, such as the PCD® Transvene™ System, should decrease the potential perioperative and long term mortality and morbidity associated with current epicardial system implantation approaches.

The PCD® Epicardial System and PCD® Transvene System are identical except for the implanted defibrillation lead system. Thus, the performance of the PCD® device, associated support equipment, is similar in the two systems and therefore a comparison of clinical experience should focus on those areas where the implanted lead system may impact clinical outcome.

This section provides a comparison of the PCD® Transvene™ System clinical experience to the reported PCD® Epicardial System clinical experience. The following areas will be discussed:

- Patient characteristics
- Implant Data
- Spontaneous VT/VF Episode Efficacy
- Complications and Observations
- Survival analysis

This analysis will show that the incorporation of a nonthoracotomy defibrillation lead system has maintained the type of therapy available for the treatment of recurrent VT/VF and decreased the potential mortality and morbidity associated with epicardial implant approaches while maintaining the positive impact of ICD therapy on VT/VF episode efficacy and patient survival.

L.1 Comparison of Patient Characteristics

In comparing the clinical experience with the PCD® Transvene™ System to the PCD® Epicardial System clinical experience, it is important to determine that the patients who received the device are comparable.

Table L-1 contains the characteristics of the 757 patients receiving the PCD® Transvene™ System versus the

characteristics of the 742 patients who received the PCD® Epicardial System as of 1/5/93.

PCD® Transvene™ System
Comparison of Patient Characteristics

	PCD® Transvene™ System	PCD® Epicardial System
Number of Patients	757	742
Mean Follow-Up Time	11.7 months	16.3 months
% Males* % Females	610 80.6% 147 19.4%	637 85.8% 105 14.2%
Mean Age	59.4 years	59.6 years
Primary Indication*: SCD VT SCD/VT	 281 37.1% 377 49.8% 99 13.2%	 214 28.8% 405 54.6% 123 16.6%
Cardiovascular History: Coronary Artery Disease Cardiomyopathy	 561 74.1% 238 13.1%	 569 76.7% 222 29.9%
Mean Ejection Fraction	35.6%	34.0%
Number of Drugs Failed*	2.3	3.0

* (b)(4) (b)(4)

Table L-1: Comparison of Patient Characteristics, PCD® Transvene™ System versus PCD® Epicardial System - 2/1/93

Both groups had moderately depressed left ventricular function demonstrated by the mean ejection of 35.6% for the PCD® Transvene™ System patient group and 34.0% for the PCD® Epicardial patient group.

Analysis indicated that the PCD® Transvene™ System patient population had a higher percentage of patients whose indication for implant was sudden cardiac death ($p = 0.002$) and higher percentage of females (b)(4) (b)(4) It is not expected that these differences will result in a different clinical outcome in the PCD® Transvene™ System patient population as compared to the PCD® Epicardial System. This difference in patient indication is a reflection of the physicians use of the PCD® Transvene™ System.

It is interesting to note, that there was a statistical difference in the number of antiarrhythmic drugs tested between the two patient groups (b)(4) (b)(4) The PCD® Transvene™ System patient group failed a mean of 2.3 antiarrhythmic drugs prior to implant while the PCD® Epicardial System patient group failed a mean of 3.0 antiarrhythmic drugs. This difference is a reflection of the differences in the indications for implant between the two patient groups. The PCD® Transvene™ System patient group had a higher incidence of patients whose primary indication for implant was sudden cardiac death. These patients have a higher probability of having experienced a sudden cardiac death episode but were non-inducible during electrophysiologic testing so that drug testing was not feasible.

L.2 Spontaneous VT/VF Episodes Efficacy Comparison

The primary benefits from the use of the PCD® System center on the detection and termination of life-threatening ventricular tachyarrhythmias. An additional benefit of the PCD® Transvene™ System is the elimination of the need for a thoracotomy for implantation of the defibrillation lead system and the resultant decrease in potential patient morbidity and mortality associated with a thoracotomy. This clinical benefit should not be gained at the expense of providing effective termination of spontaneous VT and VF episodes. Table L-2 provides a comparison of the efficacy of the PCD® Transvene™ and PCD® Epicardial System in treating spontaneous episodes of VT and VF.

PCD® Transvene™ System Performance Comparison of Spontaneous VT/VF Efficacy PCD® Transvene™ vs Epicardial		
Spontaneous VT Episodes		
	PCD® Transvene™ System	**PCD® Epicardial System**
Mean Follow-Up	11.7 months	16.3 months
Number of Episodes	10,027	20,061
% Overall Efficacy	98.4%	98.3%
% Unsuccessful Termination	0.7%	1.0%
Spontaneous VF Episodes		
	PCD® Transvene System	**PCD® Epicardial System**
Mean Follow-Up	11.7 months	16.3 months
Number of Episodes	1092	2636
% Overall Efficacy	98.4%	98.7%
% Unsuccessful Termination	0.3%	0.5%

Table L-2: PCD® Transvene™ System: Comparison of Spontaneous VT/VF Episode Efficacy - 2/1/93

The overall success rate of the PCD® Transvene™ System in terminating spontaneous episodes of VT or VF is 98.5%. In addition, there have been no reported patient deaths due to ineffective termination of a spontaneous VT/VF episode. This success rate compares very favorably with the overall success rate of the PCD® Epicardial System which was 98.4%. Therefore, the PCD® Transvene™ System offers the potential of decreased patient morbidity and mortality without decreasing the treatment efficacy of spontaneous VT/VF episodes.

L.3 Incidence of Complications/Observations

A comparison of the reported complications and observations was made between the PCD® Transvene™ System and the PCD® Epicardial System. The PCD® Epicardial System patient population used for comparison included clinical experience as of January 5, 1992 with

742 patients and a mean implant duration of 16.3 months. These two patient groups are similar in the patient demographics and indication for implant of the PCD® System. In the PCD® Transvene™ System patient population, 19.4% of the patients experienced a clinical complication and 23.8% of the patients experienced a clinical observation. In the PCD® Epicardial System, 12.8% of the patients experienced a clinical complication and 25.7% of the patients experienced a clinical observation.

Table L-3 provides a comparison of the reported complications and the incidence in the two patient populations.

PCD® Transvene System
PCD® Transvene System versus PCD® Epicardial System
Reported Complications

Reported Complications	PCD® Transvene™ System (N=757)	PCD® Epicardial System (N=742)
Increased Defibrillation Requirements	1.2%	0.5%
Inappropriate Therapy	-	2.2%
Pace/Sense Related	0.8%	3.5%
Infection Related - Explant	2.9%	2.3%
Lead Related	15.1%	2.8%
Device Related	0.5%	0.9%

Table L-3: Reported Complications: PCD® Transvene™ System versus PCD® Epicardial System - 2/1/93

L.4 Survival Analysis Comparison

Despite their excellent clinical performance, epicardial defibrillation lead system have important limitations. The requirement for direct thoracic access contributes significantly to patient morbidity and mortality, patient discomfort and prolonged hospitalization. The availability of reliable nonthoracotomy lead systems should provide positive clinical impact on these issues while not negatively impacting patient survival. Therefore, a comparison of the one year actuarial survival rates for the PCD® Transvene™ and Epicardial System was performed.

Table L-4 provides a summary of the patient deaths reported in the two patient populations by classification. As a reference, the mean follow-up time for the PCD® Transvene™ System patient population was 11.7 months while for the PCD® Epicardial System it was 16.3 months.

PCD® Transvene™ System
Death Classifications
PCD® Transvene™ System versus PCD® Epicardial System

Death Classification	PCD® Transvene™ System (N = 757)	PCD® Epicardial System (N = 742)
Sudden Cardiac	5	24
Non-Sudden Cardiac	30	54
All Cardiac	35	78
Noncardiac	16	34
Total	51	112

Table L-4: Death Classifications: PCD® Transvene™ System versus PCD® Epicardial System - 2/1/93

Table L-5 provides a comparison of actuarial survival rates between the PCD® Transvene™ and PCD® Epicardial patient populations. The actuarial survival projections include perioperative deaths only in the calculation of survival from death due to all causes (shown in table row labelled **Overall**). Perioperative mortality includes those deaths

which occur in the first thirty days post implant of the PCD® System.

PCD® Transvene™ System
Comparison of Actuarial Survival
PCD® Transvene™ System versus PCD® Epicardial System

One Year Survival	PCD® Transvene™ System	PCD® Epicardial® System
Number of Patients	757	742
Sudden Cardiac	99.5%	98.9%
Non-Sudden Cardiac	96.2%	96.7%
All Cardiac	95.8%	95.7%
Noncardiac	98.1%	98.0%
Overall*	93.3%	88.6%

(b)(4)

(b)(4)

(b)(4)

*

Table L-5: Comparison of Actuarial Survival: PCD® Transvene™ System versus PCD Epicardial System - 2/1/93

There was a significant increase in overall survival in the patients receiving a PCD® Transvene System®. As previously noted, the Overall one year actuarial survival includes death from all causes. The overall one year survival for patients receiving the PCD® Transvene™ System was 93.3%. This is significantly improved as compared to the overall one year actuarial survival for the PCD® Epicardial System (88.6%) (b)(4) This improvement in overall survival is primarily due to the marked improvement in perioperative mortality, the PCD® Transvene™ System having a 0.7% (5/757) perioperative mortality versus the a perioperative mortality of 5.3% (39/742) in the PCD® Epicardial System. This improvement in perioperative mortality is primarily due to the elimination of the need for a thoracotomy and its associated morbidity and mortality.

M. PCD® System Performance

M.1 PCD® Device

Devices implanted for the treatment of recurrent ventricular tachyarrhythmias should perform safely and reliably in the indicated patient population. Device longevity, ventricular tachyarrhythmia detection, therapy performance, and analysis of explanted devices were evaluated to assess the performance of the PCD® Device.

Extended longevity of implantable cardioverter defibrillators should decrease the number of device replacements a given patient would experience over their lifetime and decrease unnecessary patient morbidity. Thus, the PCD® Device longevity, which is monitored utilizing battery voltage and charge time obtained via telemetry, was analyzed. The PCD® Device longevity data collected is consistent with the longevity projections.

The combined experience of induced and spontaneous VT/VF episode experience has shown that the PCD® Device VT/VF detection and therapies have performed safely and according to design specifications when required to treat induced and spontaneous VT/VF episodes.

There have been a total of 58 devices explanted. Reasons for explant were patient death (23), infection (22), cardiac transplant (9), low battery voltage (1) and PCD Device performance issues (3). The analysis of the device that was explanted due to lower than expected battery voltage indicated that the decreased battery voltage measurement was due to hermetic leakage at the input to one of the integrated circuits and this affected the battery indicator circuit only and did not affect the critical functions of the device. This leads to a voltage drop across a resistor where the voltage measurement is taken. Analysis indicated that the battery was performing to specifications and the hermetic leakage was a random event. Analysis of the other three devices indicated that two were due to random component failure and one due to shorting on Pulse 2 output. Thus, arcing occurred between the conductors inside the hermetically enclosed brazed ring of the high power hybrid. As a result, high voltage was momentarily

applied to the low power circuitry, including the low power hybrid. This low power hybrid lost function including the capability to pace and transmit telemetry due to excessive voltage applied. Since this is the only device that exhibited this type of failure in the field and the hybrid manufacturing process has demonstrated that it will screen out infant mortality, this failure was assumed to be a random component failure.

Based on the clinical data collected, the PCD® Device has performed safely and reliably in the indicated patient population.

M.2 Transvene™ Lead Performance

The Transvene™ Lead System consists of a Right Ventricular Lead, a Coronary Sinus/Superior Vena Cava lead, and a Subcutaneous Patch lead. There have been a total of 757 Right Ventricular leads (15 with the SP2100 and 742 with the Model 6884/6966), 796 Coronary Sinus/Superior Vena Cava leads (Model 6881/6963), and 718 Subcutaneous Patch leads (Models 6895/10317/6999) implanted with a cumulative implant duration of 8894.8 months. The reported incidence of conductor coil fracture is 0.5% (4/757).

Based on the clinical data collected, the Transvene™ leads have performed safely and reliably.

N. Summary

The overall clinical experience with the PCD® Transvene™ System indicates that the system performed according to design and specification. The reported clinical complications and patient deaths are appropriately addressed in the required labelling for the system and the patient selection criteria for implant of the device is appropriate.

The following can be drawn from this analysis of the data collected in this clinical study:

Patient Deaths

- The projected one year survival probabilities for Sudden Cardiac Death, Non-Sudden Cardiac Death, all Cardiac Deaths and Noncardiac Death were found to be 99.5%, 96.2%, 95.8%, and 98.1%, respectively.

  The incorporation of programmable VT/VF detection and therapies has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

- The sudden cardiac death survival of 99.5% at one year is comparable to that of the AICD patient population 98.0%.

- There have been no deaths due to a PCD® Device malfunction.

Complications/Observations

- Complications were reported in 19.4% of the patient population and observations were reported in 23.8% of the patient population.

- The incidence of complications was comparable to that of the market released AICD system in the categories of ineffective VT/VF therapy, pocket infection, and pocket erosion and was lower than the AICD in the category of inappropriate delivery of VT/VF therapy.

Patient Indications

- All of the patients entered into this clinical evaluation met at least one of the primary indications. Sudden cardiac death (SCD) was the primary indication in 37.1% of the patients, recurrent ventricular tachycardia (VT) was the primary indication in 49.8 % of the patients and SCD/VT was the primary indication in 13.1% of the patients.

- The number of patients (60.5%) receiving VT/VF therapy for spontaneous episodes of ventricular arrhythmias supports the conclusion that the patient selection criteria are appropriate and that the PCD® Transvene™ System was implanted in patients who benefit from this therapy.

- The one year sudden cardiac death survival rates for the SCD patient group was 100.0%, for the VT patient group 99.4% and the SCD/VT patient group 98.6%.

VT/VF Detection and Therapy Performance

- The PCD® Transvene™ System properly detects and treats VT as demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VT was 98.4%.

- The PCD® Transvene™ System properly detects and treats VF as demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VF was 98.4%.

- There were no reported patient deaths due to the nondetection of a spontaneous VT or VF episode by the PCD® Transvene™ System.

PCD® Transvene™ System Performance

- The PCD® Transvene™ System components (Model 7216A/7217B and Model 6884/6966, 6881/6963, 6895/6999 Transvene™ leads) have performed according to design and specification and are, therefore, considered safe and effective in the indicated patient population.

O. Clinical Experience Summary Conclusions

The PCD® Transvene™ System is a tiered therapy device which combines features of bradycardia pacing support, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. The incorporation of these features has allowed the physician to titrate the ICD therapy to meet specific patient clinical needs, allowed fewer shocks to be delivered for recurrent ventricular tachycardia because of antitachycardia pacing features, allowed fewer cases of inappropriate therapy delivery due to programmable detection and allowed a sudden cardiac death survival rate identical to the Ventak-P Epicardial System.

The PCD® Transvene™ System, due to the elimination of the need for a thoracotomy, has provided a marked improvement in both the perioperative and overall patient mortality as compared to the PCD® Epicardial System. In addition, due to the decreased perioperative morbidity and mortality, the post implant hospital stay has been decreased to a mean of 7.6 days as opposed to a mean of 10.6 days (b)(4) (b)(4) for the PCD® Epicardial System.

Medtronic asserts and the PCD® Transvene™ investigators unanimously agree that the findings of the clinical study support the conclusion that the Medtronic Tachyarrhythmia Control System and the Transvene™ Cardioversion and Defibrillation Electrodes are safe and effective in the indicated patient population.

H

Summary of Clinical Experience

A. Introduction

The efficacy and safety of implantable cardioverter defibrillator (ICD) therapy for recurrent ventricular tachycardia (VT) and ventricular fibrillation (VF) has been well established. The current market released device (Medtronic Model 7217B with Epicardial Cardioversion/Defibrillation Leads) incorporates multiprogrammability, multiple detection and therapeutic options for the treatment of ventricular tachycardia and fibrillation. The current system, while providing lifesaving treatment of ventricular arrhythmias, requires a significant surgical procedure (thoracotomy, median sternotomy, etc.) for the placement of the epicardial lead system. The need to reduce the surgical mortality and morbidity associated with epicardial cardioversion/defibrillation lead systems has lead to the development of the PCD® Transvene™ System.

This report represents a full report of Medtronic's clinical experience with the Medtronic PCD® Model 7217B Multiprogrammable Tachyarrhythmia Control System with Transvene™ Cardioversion and Defibrillation Electrodes (Reference IDE G870102). The data included in this analysis is all data that was received by Medtronic and entered onto the clinical database as of **February 1, 1993.**

The PCD® Model 7217B Multiprogrammable Tachyarrhythmia Control System described in this submission is identical to the system which was recommended for approval by the FDA advisory panel on February 3, 1992, with the addition of Transvene™ leads.

The data analysis is organized in functional rather than chronological categories in order to present a complete picture of each of the PCD® Device's various functions. The sections included in this summary are:

- Name, Intended Use of System
- Tachyarrhythmia Control System Features
- Indicated Patient Population
- Study Objectives and Protocol Summary
- Overview of Clinical Experience
  - Implant Data
  - Spontaneous VT/VF Episode Experience

Overall Success Rate
- Complications and Observations
- Inactive Patients
- Patient Deaths
- Clinical Experience by Primary Indication
- Patients not Meeting Implant Criteria
- Comparison to AICD Clinical Experience
- Comparison to PCD® Epicardial Clinical Experience
- PCD® Transvene™ System Performance

This summary provides an overview of the clinical experience which verifies that the PCD® Transvene™ System is safe and effective in the indicated patient population.

B. Name and Intended Use of the System

The Pacer-Cardioverter-Defibrillator (PCD®) device is an implantable, multiprogrammable, automatic tachyarrhythmia control device. The PCD® Device is used in conjunction with appropriate lead systems for the treatment of patients with ventricular tachycardia (VT) and/or ventricular fibrillation (VF). The PCD® Device also provides backup pacing in the VVI mode and noninvasive electrophysiologic (EP) study capabilities.

The PCD® Device is programmed with the market released Medtronic programmer and a unique MemoryMod™ Cartridge. The PCD® Device incorporates a two-way telemetry system which receives operational instructions from the programmer and transmits status, electrogram and event information back to the programmer for display and/or printout.

The External Tachyarrhythmia Control Device (ETCD) is an external, multiprogrammable, tachyarrhythmia control device. Its operation is similar to the PCD® Device except that cardioversion and defibrillation therapies are delivered manually. In addition, it displays measurements of cardioversion and defibrillation therapy parameters. The ETCD is used for making defibrillation threshold measurements during the PCD® Device implantation procedure.

Components

The Medtronic PCD® Transvene™ System, which is represented in Figures 1A and 1B, for which market release approval is being requested, consists of the following components:

Implanted Device and Related Programming System
Pacer-Cardioverter-Defibrillator (PCD®) Device
Model 7217B

Programmer
Model 9710 programmer and related accessories (currently market released), plus
Model 9788 MemoryMod™ Software Cartridge
Lead System
Electrode Leads:
Model 6966
Model 6963
Model 6999

Implant Measurements System
Model 5355 ETCD™ External Tachyarrhythmia Control Device
Model 5418 Patient Cable
Model 5414 Test Load
Model 5417 EGM Cable
Model 5419 Jumper Cable

The physical characteristics of the Model 7217B are summarized in Table IB-1:

PCD® Model 7217B **Physical Characteristics**	
Feature	**Model 7217B**
Volume	113 cc
Weight	198 grams
Connector Module	Four connector ports
Power Source	Wilson Greatbatch Model 8830 Lithium Silver Vanadium Oxide
Sensing Configuration	Standard Bipolar
Pacing Configuration	Integrated Bipolar

Table IB-1: Features: Model 7217B - 2/1/93

The Model 7217B PCD® Device uses the pace/sense leads for sensing, thus providing **standard bipolar** sensing. Pacing is delivered in the integrated bipolar configuration.

RV-SVC

PACE/SENSE &
SENSE 2

COMMON

PACE/SENSE,
SENSE 2, COMMON

PULSE 2

Connector Plug

(Two Cardioversion/Defibrillation Leads)

7217B PCD

Programmer Head

Printer

Programmer

RV-SVC/S

PACE/SENSE &
SENSE 2

COMMON

PACE/SENSE,
SENSE 2, COMMON

PULSE 2

PULSE 1

(Three Cardioversion/Defibrillation Leads)

7217B PCD

FIGURE 1A

7217B PCD Device and Nonthoracotomy Lead System

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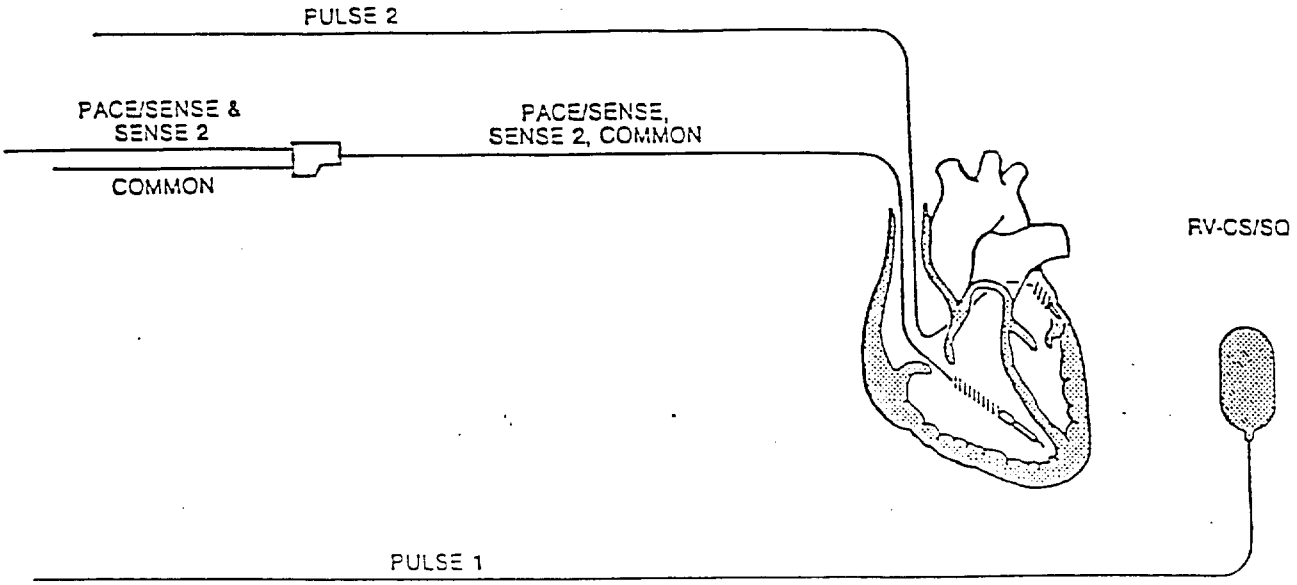
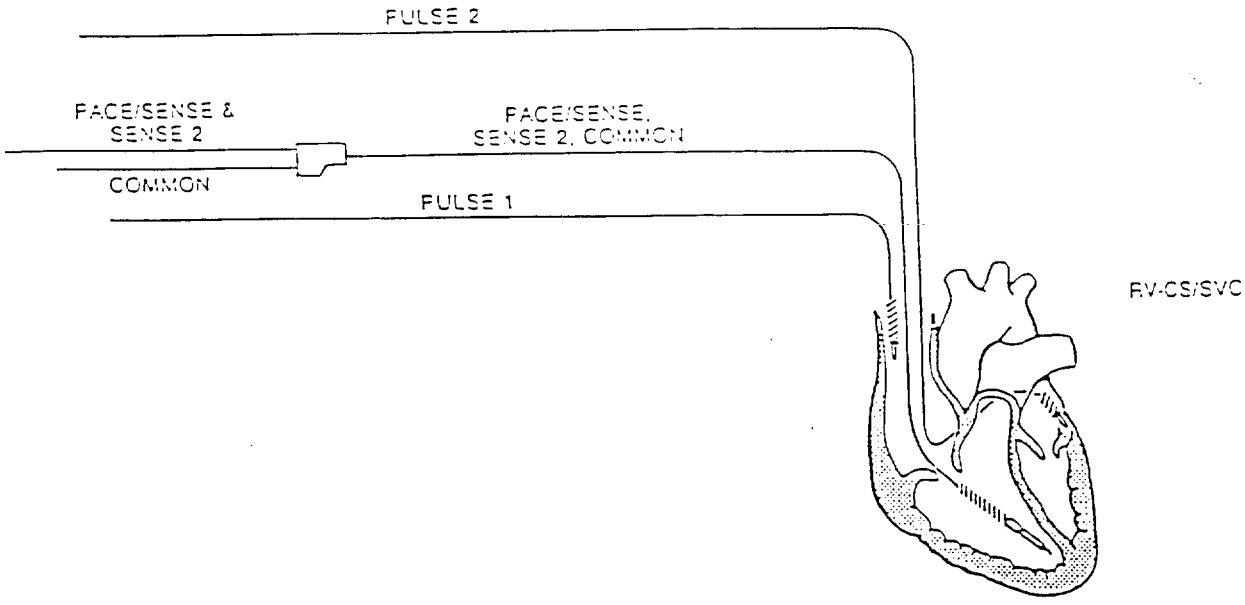
FIGURE 1B



Example of Lead Placement for Simultaneous or Sequential Path (RV-CS/SQ).



Example of Lead Placement for Simultaneous or Sequential Path (RV-CS/SVC).

C. Tachyarrhythmia Control System Features

C.1 PCD® Device

The PCD® Device is an implantable device designed to detect episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF), and upon detection, automatically deliver the appropriate therapy or progression of therapies programmed by the physician for each patient. The available therapy types that can be programmed are overdrive pacing, cardioversion, and defibrillation.

The main features of the PCD® Device include the detection and treatment of recurrent ventricular tachycardia (VT) and/or ventricular fibrillation (VF). The device has two independently programmable detection and therapy algorithms, one for VT and a second for VF. A series of up to four tiered therapies can be delivered after detection of VT and a separately programmed series of up to four therapies after the detection of VF. If a therapy does not convert the arrhythmia, the next programmed therapy is delivered.

Other features of the device include VVI back-up pacing, flexible programming, noninvasive electrophysiology study capabilities, and information reports.

VT Detection and Therapy

The VT detection algorithm includes up to three separately programmable criteria to identify the presence of a tachycardia.

The PCD® Device employs a feature that automatically adjusts signal detection sensitivity to assure proper detection while minimizing sensing of T-waves following intrinsic cardiac events. This function, **Auto-Adjusting Sensitivity**, is active during any sensing period, including VT and VF detection. It allows use of sensitive settings required for VF detection without oversensing during normal sinus rhythm.

The device utilizes interval length as the primary VT detection criterion; it also provides two additional detection

criteria to add specificity in detecting pathological VT. The two programmable parameters of the Interval Criterion are:

- **Tachycardia Detection Interval (TDI):** Intervals shorter than this value (and longer than FDI are classified as VT intervals.

- **Number of Intervals to Detect (VT NID):** This parameter determines how many consecutive VT intervals must be sensed for therapy to be delivered.

The two additional criteria are:

- **Onset Criterion:** Used to determine when the rate of change in cycle length is sufficiently abrupt to qualify as the onset of paroxysmal VT and not sinus tachycardia.

- **Stability Criterion:** Used to determine when the intervals vary sufficiently on a beat to beat basis to differentiate VT from a rapid ventricular response due to atrial fibrillation.

After a VT episode has fulfilled the programmed detection criteria, the system treats the arrhythmia by delivering one of the three types of VT therapies: Burst, Ramp, or Cardioversion Therapy. Therapy delivery is highly programmable and is "tiered" to allow progression through different therapies selected by the physician to match a patient's particular clinical needs. Up to four separate therapies may be programmed in any combination of the three types to treat each arrhythmia episode. The three therapies are detailed below:

Burst Therapy treats the VT episode by pacing the heart with a "burst" of pulses at a rate greater than that of the VT episode but adapted to the VT rate. The rate adaptive pulse intervals are a programmed percentage of actual tachycardia cycle length. If a pacing sequence is ineffective and the episode is redetected, the pulse interval of the next sequence can be decremented further resulting in a higher pacing rate.

Ramp Therapy decrements each pulse interval within a single sequence of multiple pulses with the first pulse to pulse interval adapted to the VT cycle length. Each subsequent pulse interval in the Ramp sequence is shortened from the preceding interval by a programmed value. If the pacing sequence is ineffective and the VT is redected, Ramp Therapy adds an additional stimulus in each subsequent sequence.

Cardioversion Therapy: delivers synchronized, high-energy pulses in one of the following configurations:

- A **single** pulse delivered over one pathway.
- A **simultaneous** pulse delivered over two pathways.
- Two **sequential** pulses separated by a very short interval delivered over two different pathways.

VF Detection and Therapy

In order to ensure appropriate sensing and detection of VF, the device uses a probabilistic detection algorithm that allows for missed detections due to variations in ventricular depolarization amplitudes and intervals during VF.

Similar to the VT detection algorithm, the PCD® Device detects VF by monitoring the cardiac cycle length and comparing it to the programmed VF detection criteria, which is called the VF Interval Criterion.

The two programmable parameters of this criterion are:

- **Fibrillation Detection Interval (FDI):** Intervals equal to or shorter than this value are classified as VF intervals.
- **Number of Intervals to Detect (VF NID):** This parameter determines how many VF intervals must be sensed for therapy to be delivered.

After a VF episode has fulfilled the programmed detection

criteria, the system treats the arrhythmia by delivering up to four defibrillation therapies.

Defibrillation Therapy delivers high-energy pulses in one of the following configurations:

- A **single** pulse delivered over one pathway.
- A **simultaneous** pulse delivered over two pathways.
- Two **sequential** pulses separated by a very short interval delivered over two different pathways.

Bradycardia Therapy

The PCD® Device delivers bradycardia pacing in the VVI mode.

Other Capabilities

The PCD® Device can be used to conduct noninvasive electrophysiologic studies (EPS) via the programmer with the Model 9788 MemoryMod™ software cartridge. The physician can also manually deliver various therapies via the programmer to manage an induced or spontaneous tachyarrhythmia episode.

The PCD® Device will provide the physician with information, via the Programmer about its present programmed status and data on its operation. This information may be printed and retained in the patient's file.

A programmer-generated set of symbols, termed Marker Channel, allows real-time visualization of sensing, pacing, detection, and therapy events occurring within the device.

Figure 2 provides an ECG example of an induced episode of VT detected and terminated by antitachycardia pacing and Figure 3 shows an induced episode of VF detected and terminated by a defibrillation therapy delivered by the PCD® Device.

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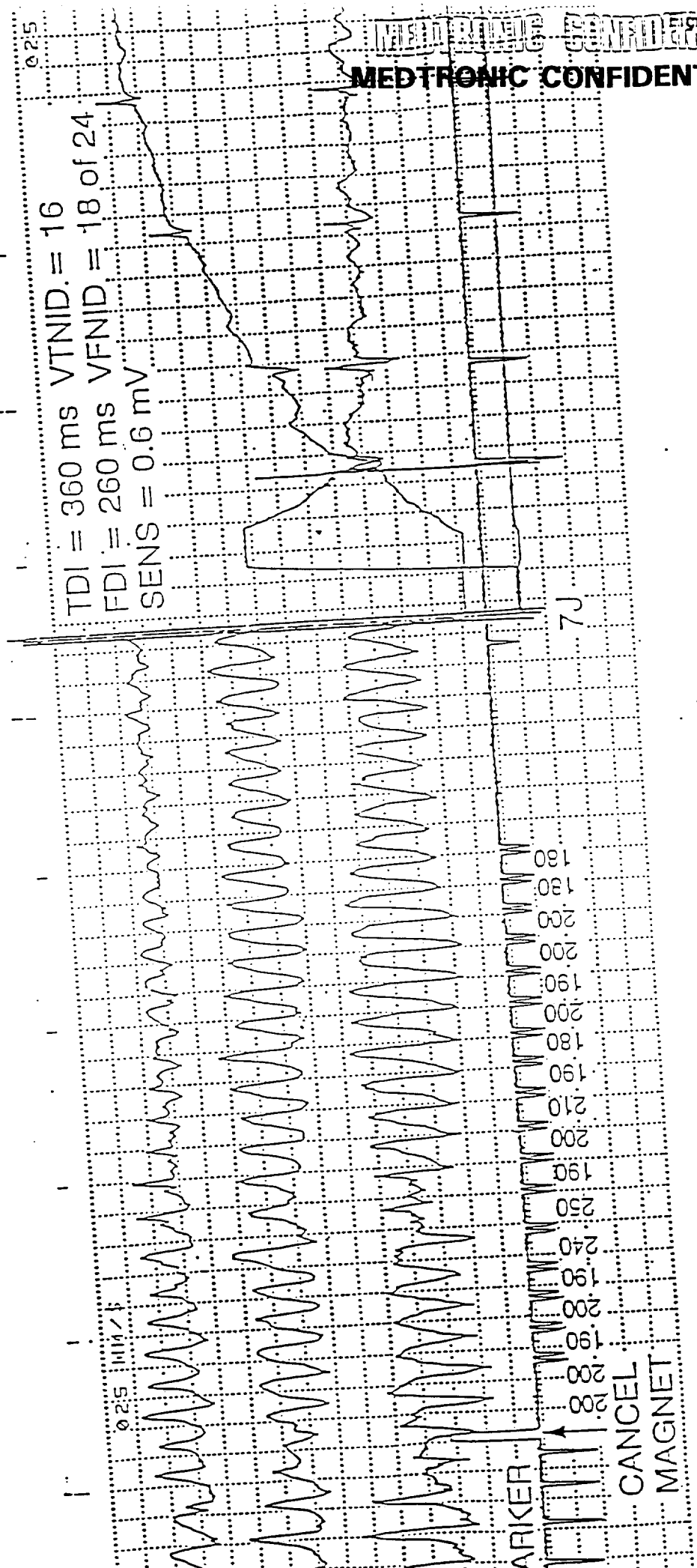
503450-001
503450-00
BURST PACING
MARKER
VT NID 16
TDI 400 ms
THERAPY Burst
PULSES 6
% RR 87%
510


TDI = 360 ms VTNID = 16
FDI = 260 ms VFNID = 18 of 24
SENS = 0.6 mV
7J
180
180
200
200
190
200
180
190
210
200
190
250
240
190
200
190
200
200
MARKER
CANCEL
MAGNET

C.2 Transvene™ Lead Systems

The PCD® Transvene™ System uses leads which do not require open-chest surgery to implant. Multiple configurations involving either two or three leads may be used to deliver cardioversion and defibrillation pulses. These configurations are based on a tri-polar, Right Ventricular (RV) lead (Model 6966), and either a Coronary Sinus (CS)/Superior Vena Cava (SVC) lead (Model 6963) or a Subcutaneous (SQ) lead (Model 6999) or all three of these leads (e.g. RV/CS/SQ, RV/SVC/SQ or RV/SQ, RV/SVC). The Model 6963 lead can be placed in either the Coronary Sinus/Great Cardiac vein or the Superior Vena Cava (SVC).

A system using two leads delivers cardioversion and defibrillation pulses between two electrodes. A system using three leads delivers cardioversion and defibrillation pulses either simultaneously or sequentially from the anode electrodes (PULSE1 and PULSE2) to the COMMON defibrillation electrode.

In these systems, the retractable, helical tip and ring of the RV lead are used for sensing, thus providing standard, bipolar sensing. The tip electrode is termed PACE/SENSE and the ring electrode is termed SENSE2. Bradycardia pacing takes place between the tip (PACE/SENSE) and the COMMON defibrillation electrode.

To detect VT/VF, the PCD® device monitors the cardiac cycle length for fulfillment of the programmed VT/VF detection criteria. When the programmed criteria are fulfilled, the PCD® device detects the VT or VF episode and delivers the first programmed therapy. If this therapy is ineffective and the VT/VF is again detected, the next programmed therapy is delivered. This progression continues until the PCD® confirms termination or delivers all programmed therapies.

The performance of the Models 6966, 6963, and 6999 are evaluated at the following times:

1) At implant by evaluating the pacing and sensing thresholds and the defibrillation efficacy in treating

induced VF;

2) Chronically by evaluating (1) the defibrillation efficacy in terminating induced episodes of VT or VF; (2) the efficacy of VT and VF therapies in treating spontaneous episodes; (3) the evaluation of pace/sense characteristics of the implanted lead system and (4) the incidence of lead complications or observations such as dislodgement or fracture.

C.3 Model 9788 MemoryMod™ Software Cartridge and 9710 Programmer

Programming and interrogation of the PCD® Device is performed using the Model 9788 MemoryMod™ software cartridge in conjunction with the Model 9710 programmer. The use of the programmer allows the modification of VT and VF detection, therapy, and bradycardia support therapy parameters. It allows the physician the ability to review and record programmed device settings, perform noninvasive EP procedures and deliver emergency therapy and review other non-programmable information including charge time, battery voltage and event recording. In addition, it allows the user to evaluate the battery status of the PCD® Device as well as determine if the device has delivered therapy for spontaneous episodes of VT and VF.

C.4 Model 5355 External Tachyarrhythmia Control Device (ETCD)

The Model 5355 ETCD is intended for use in conjunction with an antitachycardia/defibrillation lead system to evaluate VT and VF sensing and therapy efficacy for terminating ventricular tachycardia and ventricular fibrillation prior to the implantation of the PCD® system.

Testing the lead system for permanent implantation, including VF sensing and defibrillation efficacy, is done using the Model 5355 ETCD™ or Model 2394 ECVD. The 5355 is an external, multiprogrammable, tachyarrhythmia control device, which can automatically deliver bradycardia and tachycardia pacing therapies and can deliver manually initiated cardioversion or defibrillation therapies. Its operation is similar to the PCD® Device except that

cardioversion and defibrillation therapies are delivered manually. In addition, it measures and displays parameters, e.g., pathway impedance of cardioversion and defibrillation therapies. The Model 2394 ECVD is also an external cardioverter defibrillator. However, its functions are limited to only manual cardioversion and defibrillation. The output pulses are equivalent to the Model 5355 and Model 7217B PCD®. Additionally, the Model 2394 ECVD does not have the capability to deliver either bradycardia or tachycardia pacing therapies.

The Model 5355 ETCD™ is controlled via the Model 9710 programmer and the MemoryMod™ software cartridge, Model 9788. The Model 2394 ECVD is controlled manually.

D. Indicated Patient Population

The PCD® System is intended to treat patients at risk of sudden cardiac death due to ventricular tachyarrhythmias which have been shown to be reliably terminated, and in the case of VF, terminated at an energy level below the maximum output of the PCD® Device.

Results provided in this application will support Medtronic's request for market release of the PCD® System for use in the following patient population:

> Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or
>
> Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

For this patient population the primary benefits from the use of the PCD® System center on the detection and termination of life-threatening ventricular arrhythmias. The use of pacing therapies for the treatment of ventricular tachycardia reduces patient trauma associated with higher energy cardioversion pulses and extends the longevity of the PCD® pulse generator.

The PCD® System allows the titration of therapies for patients

with ventricular tachycardia while providing the critical defibrillation backup. Defibrillation backup is important in the event that an episode of VT accelerates to VF whether spontaneously or as a result of a delivered therapy. The capacity to provide programmable extrastimuli pacing allows noninvasive electrophysiologic studies to be performed. The potential benefits from permanent cardiac pacing provide support for chronic and transient episodes of bradycardia. Finally, the benefits of programmability of tachyarrhythmia detection and therapy parameters, VVI parameters and stored telemetry data on the delivery of therapy may avert the need for reoperation in the event of changing patient conditions or complications.

E. Study Objectives and Protocol Summary

The clinical study was designed to evaluate the operation, safety and effectiveness of the PCD® System components in detecting and treating episodes of ventricular tachycardia and ventricular fibrillation.

The analysis focuses on data supporting the safety and effectiveness of the PCD® system, including the implantable pulse generator and associated transvenous lead system and its therapy in this patient population. The analysis includes the clinical experience with the PCD® system, pace/sense, detection and therapy functions in both the acute and chronic implant settings. In addition, data is provided on clinical observations, clinical complications and deaths in this patient population. The analysis will also provide data demonstrating the safety and effectiveness of the Model 5355 ETCD.

The objectives of the clinical study were:

* to evaluate the sensitivity and specificity of the PCD® Device with Transvene™ lead systems to detect episodes of VT and VF, and to evaluate the ability of the system to appropriately discriminate between VT/VF and other potentially nonmalignant rhythms;

* to monitor the efficacy of the PCD® Device with Transvene™ lead systems in treating VT and VF episodes. VT/VF therapy efficacy is determined as the ratio of successful termination of episodes detected to the total number of episodes detected in which one or more therapies were delivered (Successful Termination/Number of Detected Episodes with Therapy Delivered). Investigators were free to choose from any of the available leads and VT/VF therapies that the efficacy was first evaluated acutely;

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* to evaluate the performance of the Model 6966, 6963 and 6999 Transvene™ leads;

* to monitor the patient selection criteria and patient management methods required by the PCD® Device and Transvene™ leads.

* to evaluate the safety and effectiveness of the Model 5355 ETCD™ when used during the implant procedure. Specifically, tachyarrhythmia episode induction, detection, termination and ease of use were analyzed.

* to evaluate the safety and performance of the Model 9710 Programmer and the 9788 MemoryMod™ Software Cartridges in programming sensing and therapy parameters and the appropriate delivery of noninvasive electrophysiologic stimulation.

Clinical data was collected at the following study points to support the safety and efficacy of the PCD® System:

Pre-implant Patient Assessment
Lead System Testing at Implant
Implantable Pulse Generator Testing at Implant
Pre-hospital Discharge Testing
Follow-up Evaluation 1 and 3 months post implant then at 3 month intervals

Specific data was collected at each of these points to meet the objectives of the clinical study. This included:

Pre-implant Patient Assessment - extensive pre-implant testing was performed to ensure that the general patient selection criteria were met. This testing included at least an electrophysiologic evaluation, measurement of ejection fraction, and assessment of the patient's New York Heart Association (NYHA) classification of their cardiovascular status. Depending on the patient history, cardiac catheterization and exercise testing were also conducted.

Lead System Testing - implant evaluation was performed to verify that one of the specified lead systems was capable of properly detecting and treating episodes of ventricular fibrillation and, when appropriate, ventricular tachycardia. The Model 5355 ETCD™ or the 2394 External Cardioverter Defibrillator (ECVD) was used for testing.

This testing included pacing and sensing thresholds during sinus rhythm, evaluation of VF electrogram amplitudes and defibrillation efficacy evaluation. The PCD® Device implant criteria were:

1) successful VF termination at least 3 times in 4 attempts with an output energy of 18 Joules or less and

2) a 2:1 VF sensing safety margin.

Implanted Pulse Generator Testing - this implant evaluation was performed to demonstrate proper detection and termination of ventricular fibrillation by the implanted PCD® System with VF Therapy #1 programmed to 34 Joules in addition to pacing and sensing thresholds.

Pre-hospital Discharge Testing - testing performed at the pre-hospital discharge included proper detection and termination of induced ventricular tachycardia. Final sensing and therapy parameters are programmed at the PHD.

Follow-up Evaluation - regular testing was performed to evaluate the chronic stability of detection and therapy parameters of the PCD® System. This testing included an assessment of the relative stability of the energy required to defibrillate a patient and efficacy and acceleration rate assessment of the VT therapies. The number of spontaneous VT/VF episodes treated by the PCD® Device were evaluated. Complication rates and patient mortality data were also evaluated.

Patients were evaluated prior to hospital discharge and/or one (1) month post implant, three months post-implant and then at intervals of every three months. In some cases additional testing was performed at physician discretion to evaluate spontaneous events and/or potential clinical complications.

Medtronic collected all clinical data on the PCD® System and its components under the clinical protocol outlined in the Investigational Plan. A common protocol was used on all study patients on a worldwide basis.

Clinical data presented in this summary includes experience with the Model 7216A and 7217B PCD® Devices with the Model 6966, 6963 and 6999 Transvene™ Leads. This report presents the clinical evaluation of the safety and efficacy of the PCD® Device with Transvene™ Leads implanted in 757 patients of which 657 have implant durations equal to or greater than six months.

International centers were subject to the appropriate requirements (e.g., the Declaration of Helsinki) in order that the data met the statutory requirements of the FDA. All clinical data, U.S. and International, obtained with the PCD® System with Transvene™ Leads is included in this report.

F. Overview of Clinical Experience

This report covers a total of 762 implants in 757 patients of the PCD® Device with the Transvene™ Defibrillation Lead System. A total of 78 investigative centers participated in the clinical trial with 35 centers in the U.S. and 43 Internationally. The first implant occurred internationally on October 20, 1989, and the first implant in the U.S. occurred on October 16, 1990. Table IF-1 shows the distribution of Model 7216A and Model 7217B patients between U.S. and International investigators.

PCD® Transvene™ System Implant Distribution			
	Total	**U.S.**	**Int'l**
7216A	18 (2.4%)	3 (0.7%)	15 (4.8%)
7217B	744 (97.6%)	444 (99.3%)	300 (95.2%)

Table IF-1: PCD® Transvene™ System - Implant Distributions - 2/1/93

The mean documented implant duration for this patient population is 11.7 months and ranged from implant to 37.4 months. The cumulative implant duration is 8894.8 months. There are 657 patients with implant durations equal to or greater than 6 months and 393 patients with implant durations equal to or greater than 1 year.

The patient population enrolled in the clinical trial was predominately male (80.6%) with a mean age of 59.4 years. In half of the patients (49.8%), the primary indication for implant was recurrent, sustained ventricular tachycardia without an episode of sudden cardiac death. Sudden Cardiac Death was the primary indication for 37.1% of the patients and SCD in combination with recurrent, sustained VT was the primary indication in 13.1%. Coronary artery disease was the primary heart disease in 74.1% of the patient population with a mean reported ejection fraction of 35.6% Table IF-2 provides a data summary on these patients. Also included is the data summary of the patients with 6 months and 12 months of follow-up.

PCD® Transvene™ System Data Summary			
	All Patients (3 Electrode Systems)	Patients with **6** months of Follow-up	Patients with **12** months of Follow-up
Number of Patients	757	657	393
Device Months Follow-up	8894.8	8602.6	6454.6
Mean Follow-up Time	11.7 mo	13.0 mo	16.3 mo
Maximum Follow-up Time	37.4 mo	37.4 mo	37.4 mo
Number, % Male **Number, % Female**	610 80.6% 147 19.4%	527 80.2% 130 19.8%	310 78.9% 83 21.1%
Mean Age	59.4 yrs	59.1 yrs	58.8 yrs
Primary Indication: **SCD** **VT** **SCD/VT**	 281 37.1% 377 49.8% 99 13.1%	 249 37.9% 326 49.6% 82 12.5%	 150 38.2% 191 48.6% 52 13.2%
Coronary Artery Disease	561 74.1%	483 73.5%	272 69.2%
Mean Ejection Fraction	688 35.6%	595 36.6%	357 38.0%
Defibrillation Pathway: **Sequential** **Simultaneous** **Single**	 574 75.3% 178 23.4% 10 1.3%	 496 74.9% 156 23.6% 10 1.5%	 296 74.9% 93 23.6% 6 1.5%
Mean LED	16.0J (N=702)	16.0J (N=609)	15.6J (N=365)
Mean DFT	14.8J (N=316)	14.8J (N=277)	14.3J (N=184)
Spontaneous VT: **Number of Patients** **Number of Episodes** **% Success**	 316 10027 98.4%	 288 8820 98.3%	 186 6338 99.0%
Spontaneous VF: **Number of Patients** **Number of Episodes** **% Success**	 317 1982 98.4%	 292 1742 98.3%	 176 1105 98.6%
One Year SCD Survival	99.5%	99.7%	100.0%

Table IF-2: PCD® System Data Summary - All Transvene™ Patients versus Transvene™ Patients with 6 mo Follow-up - 2/1/93

F.1 Implant Data

Implants of the PCD® Device may use two or three Transvene™ leads. The physician has the flexibility to use whichever lead system best meets the patient's needs.

Two terms were developed to accurately report defibrillation efficacy, Lowest Energy of Defibrillation (LED) and Defibrillation Threshold (DFT). They are defined as follows:

> Lowest Energy of Defibrillation (LED): The lowest programmed energy that successfully defibrillated the patient with the implanted lead system.
>
> Defibrillation Threshold (DFT): The lowest programmed energy which successfully defibrillated the heart provided there is a failure at an energy below the lowest success or a success at less than or equal to 5J.

Table IF-3 illustrates the lowest energy of defibrillation (LED) and defibrillation threshold (DFT) for the implanted lead systems. The implant criteria for the PCD® Device was 3 of 4 episodes of VF successfully terminated at 18 Joules or less with a given lead configuration. Some patients did not have a LED at implant. The LED is only identified if the investigator reported the induced rhythm as VF. Conversion of VT or V Flutter (as defined by the physician) to sinus rhythm was not included in the determination of the LED. In addition, it is not a protocol requirement to obtain a DFT at implant. However, recommendations have been provided to those institutions that prefer to obtain DFT's during the implant procedure.

PCD® Transvene™ System Mean LED and DFT Values				
Lead System	Implant Frequency	Mean LED	Implant Frequency	Mean DFT
All Systems	702	16.0J	316	14.8J
RV-SVC-SQ	455	16.7J	187	15.8J
RV-CS-SQ	210	14.6J	110	12.8J
RV-CS-SVC	37	15.2J	19	16.0J

Table IF-3: PCD® Transvene™ System - LED and DFT Values - 2/1/93

The mean implant Lowest Energy of Defibrillation (LED) for all lead systems was 16.0J and mean implant Defibrillation threshold (DFT) for all lead systems was 14.8J. As the mean DFT's and LED's indicate, VF was reliably terminated at an energy value below the maximum output (34 Joules) of the PCD® Device.

F.2 Spontaneous VT and VF Episode Experience

A total of 458 patients (60.5%) have experienced a spontaneous ventricular tachyarrhythmia episode that has been detected and treated by the PCD® Device. A total of 141 (18.6%) experienced VT only, 142 patients (18.8%) experienced VF only and 175 patients (23.1%) experienced both an episode of VT and VF.

There have been a total of 12,009 episodes of spontaneous VT or VF as detected by the PCD®. The overall PCD® Device success rate in terminating spontaneous VT/VF episodes as detected by the PCD® is presented in Table IF-4.

PCD® Transvene™ System Success Rate in Terminating Spontaneous VT/VF Episodes			
	Number of Episodes Successful	Total Number of Episodes	Efficacy Rate
VT	9864	10,027	98.4%
VF	1951	1982	98.4%
Total	11,815	12,009	98.4%

Table IF-4: PCD® Transvene™ System - Success Rate for Spontaneous VT/VF Episodes - 2/1/93

F.2.1 Spontaneous VT

For the purposes of this clinical trial, spontaneous VT was defined as those episodes that satisfied the programmed VT detection criteria. Specifically, all programmed VT detection criteria must be fulfilled to detect a VT episode. Successful termination of the episode was defined as satisfying the VT episode termination criteria.

To date, 10,027 spontaneous episodes of VT have been detected by the PCD® Device in 316 patients. The mean number of episodes per patient with VT was 31.7 and ranged from 1 - 531 episodes.

Most spontaneous VT episodes (90.7%) were successfully treated with VT Therapy #1 and 98.4% were successfully treated with one of the four programmable VT therapies.

Of the 9864 successfully terminated spontaneous VT episodes, 91.4% were treated with one of the programmed antitachycardia pacing therapies incorporated in the PCD® Transvene™ System. The clinical benefit of tiered therapy is the reduction of delivery of high energy shocks for the treatment of stable recurrent ventricular tachycardia. This greatly enhances the patient acceptance of ICD therapy since antitachycardia pacing is usually not perceived by the patient.

Sixty patients experienced 163 (1.6%) episodes in which

the PCD® Device was ineffective in terminating a spontaneous episode of VT despite delivery of all four programmed VT therapies. Thirty-nine patients experienced 95 ineffective episodes that were due to sinus tachycardia or atrial fibrillation/flutter (SVT) with a rapid ventricular response that had been detected as VT. These episodes were resolved with either modification of programmed parameters or of antiarrhythmic drug therapy. It should be noted that the PCD® Device responded appropriately based on the programmed detection parameters.

The remaining 68 episodes occurred in 21 patients in which the programmed VT therapies were ineffective in terminating a spontaneous VT episode. **No patient deaths occurred as a result of ineffective VT therapy.** Reprogramming and pharmacologic intervention resolved these events.

F.2.2 Spontaneous VF

For purposes of this clinical trial, VF is defined as those episodes that satisfy the programmed VF detection criteria. Specifically, all programmed VF detection criteria must be fulfilled to detect a VF episode. Successful termination of the episode is defined as satisfying the VF detection criterion for episode termination.

To date, 1982 spontaneous episodes of VF have been detected by the PCD® Device in 317 patients. The mean number of episodes per patient was 4.3 and ranged from 1 - 77 episodes. A review of the chart per investigator for this patient that experienced the 77 episodes of VF revealed that 75 were most likely due to atrial fibrillation. VF detection parameters were modified in this patient.

Most (89.1%) spontaneous VF episodes were successfully treated with VF Therapy #1 and 98.4% were successfully treated with one of the four programmable VF therapies.

Sixteen patients experienced 31 episodes (1.3%) in which the PCD® Device was ineffective in terminating a spontaneous episode of VF despite delivery of all four programmed VF therapies. Nine patients had 22 reported ineffective VF spontaneous episodes that were due to sinus

tachycardia or atrial fibrillation with rapid ventricular response rather than VF. Reprogramming and pharmacologic intervention resolved these problems.

Four patients experienced 5 ineffective episodes that were detected as VF by the PCD® System. One of these patients (b)(6) required external defibrillation to convert the VF episode. This patient's antiarrhythmic drug regimen was modified to improve defibrillation efficacy. Another patient (b)(6) had an episode recorded as ineffective on the event counters but presented in sinus rhythm. Subsequent evaluation demonstrated appropriate PCD® function. Another of these patients (b)(6) had two spontaneous episodes of VT that were detected as VF by the PCD® while in the hospital for progressive CHF. These episodes required external cardioversion. The patient requested the PCD® be turned OFF. Patients was alive at the last known follow-up. The last of these four patients (b)(6) experienced cardiac arrest at home and was found by the paramedics to be in sinus rhythm. While on a monitor the patient developed VF. The PCD® delivered the programmed therapy which terminated the episode but the patients developed EMD, arrived at the ER comatose and died.

Four patients (one patient (b)(6) experienced 2 episodes due to AF but is described below again) experienced 4 episodes in which the PCD® detected the episodes as VF but were actually episodes due to extraordinary circumstances. One patient (b)(6) experienced an episode where all four therapies failed secondary to RV lead fracture. The patient had Twiddlers Syndrome. Reoperation was required. It appears that the inappropriate therapy was not due to VT/VF but due to noise. Another patient (b)(6) had a surgical procedure (CABG) where the CS lead dislodged post surgery. The episode that was detected was due to the lead dislodgement. The third patient (b)(6) had incessant episodes of fast VT (cycle length 280 ms) that were eventually resolved by drugs. The fourth patient (b)(6) was in hospital and there was an episode of VF detected. However, the device was interrogated before termination of the episode was detected. There was external intervention associated with the terminal event. The device was not interrogated again.

F.3 Overall Success Rate

Of the 757 patients who received a PCD® Transvene™ System, 597 patients (78.9% - 597/757) have either experienced a spontaneous VT/VF episode or had VT/VF induced during a post implant electrophysiology study. The performance of the PCD® Transvene™ System therapies have been thoroughly evaluated and been shown to be effective in detecting and terminating episodes of ventricular tachyarrhythmia.

There have been no reports of a patient death due to the PCD® Transvene™ System not detecting a spontaneous episode of VT or VF.

The overall success rate of the PCD® Transvene™ System in terminating spontaneous episodes of either VT or VF was 98.4% with a VT success rate of 98.4% and VF success rate of 98.4%. The incidence of unsuccessful termination of an apparent "true" episode of ventricular tachycardia despite delivery of all four therapies was 0.7% (68/10027). The incidence of unsuccessful termination of an apparent "true" episode of ventricular fibrillation despite delivery of all four therapies was 0.3% (5/1982).

The evaluation of spontaneous episode experience indicates that the PCD® Transvene™ System's VT and VF detection and therapy functions have performed safely and effectively in the indicated patient population.

G. Complications and Observations

The use of a multiprogrammable implantable cardioverter defibrillator (ICD) device allows the physician to resolve most relevant medical events by noninvasively changing programmed parameters thus, avoiding invasive procedures. However, there will continue to be certain relevant medical events which will require invasive procedures for resolution.

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following definitions:

COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

As of February 1, 1993, there have been a total of 176 complications reported in 147 patients and 214 observations reported in 180 patients in the PCD® Transvene™ System patient population. Thus, 19.4% (147/757) of the patients had reported a clinical event which was categorized as a complication and 23.8% (180/757) of the patients had reported a clinical event which was categorized as an observation. Table IG-1 summarizes how these events were reported with U.S versus International.

PCD® Transvene™ System
Reported Complications/Observations
U.S versus International

	# of Complications	# of Observations
U.S.	104	93
International	72	121
Total	176	214

Table IG-1: PCD® Transvene™ System Complications/Observations U.S. versus International - 2/1/93

Table IG-2 summarizes the reported PCD® Transvene™ System complications and observations by category. The reported complications and observations are recognized clinical events that may occur with any of the current ICD devices. These complications and observations are discussed in the PCD® device and Transvene™ manual. **None of the reported complications or observations have resulted in a patient death.**

PCD® Transvene System
Reported Complications/Observations
By Category

Category	Complications	Observations
Increased Defibrillation Requirements	9 (1.2%)	8 (1.1%)
Inappropriate VF Therapy Delivery	-	14 (1.8%)
Inappropriate VT Therapy Delivery	-	59 (7.8%)
Loss of Capture	6 (0.8%)	14 (1.8%)
Oversensing	-	54 (7.1%)
Undersensing	-	-
Skin Erosion	5 (0.7%)	1 (0.1%)
Pocket Infection	24 (3.2%)	10 (1.3%)
Seroma	6 (0.8%)	14 (1.8%)
Hematoma	6 (0.8%)	17 (2.2%)
Pneumothorax	2 (0.3%)	1 (0.1%)
Pacemaker Syndrome	-	2 (0.3%)
Perforation	6 (0.8%)	-
Subclavian Vein Thrombosis	1 (0.1%)	3 (0.4%)
Lead Fracture	9 (1.2%)	-
Subcutaneous Patch Crinkling	7 (0.9%)	5 (0.7%)
Early Device Explant	4 (0.5%)	-
Total Lead Dislodgement	91 (12.0%)	12 (1.6%)
Total	**176**	**214**

Table IG-2: PCD Transvene System: Reported Complications and Observations - 2/1/93

Table IG-3 contains a description of the lead dislodgements that have occurred in less than 30 days and in greater than 30 days.

PCD® Transvene System
Reported Complications/Observations
Lead Dislodgements <30 days and >30 days

Category	Complications		Observations	
	Num (% of Pts)		Num (% of Pts)	
	<30 days	>30 days	<30 days	>30 days
RV Lead Dislodgement n=741	14 (1.9%)	10 (1.3%)	0 (0)	1 (0.1%)
CS Lead Dislodgement n= 261	12 (4.6%)	10 (3.8%)	2 (0.8%)	2 (0.8%)
SVC Lead Dislodgement n=535	16 (3.0%)	29 (5.4%)	1 (0.2%)	6 (1.1%)
Total Dislodgement n=757	42 (5.6%)	49 (6.5%)	3 (0.4%)	9 (1.2%)

Table IG-3: PCD Transvene System: Lead Dislodgements <30/>30 days - 2/1/93

There have been a total of 49 lead dislodgements reported in patients at greater than 30 days. None of the lead dislodgements resulted in an ineffective therapy for a spontaneous VT of VF episode or patient death. Lead dislodgements were documented by fluoroscopic examination during electrophysiologic evaluation, chest x-ray obtained during routine follow-up, or during pacing/sensing threshold evaluation during routine follow-up. In all 49 cases, reoperation was required to reposition the lead and reestablish an effective defibrillation lead system.

Lead dislodgements are not specific to the PCD® Transvene™ System and have been reported with dual chamber pacemakers and the current market released implantable cardioverter defibrillator (ICD) system. The early history of dual chamber pacemakers witnessed a high lead dislodgement rate of at least 20% (Smyth, PND, et al. Permanent perivenous atrial sensing and pacing with a new J-shaped lead. J Thoracic Cardiovascular Surgery. 1976;72:565-570). Winkle, et al reported that the incidence of dislodgement of the superior vena cava spring leads with the current market release ICD system to be 6.3%. (Winkle, et al. Automatic Implantable Cardioverter-Defibrillator: Efficacy, Complications, and Survival in Patients with Malignant Ventricular Arrhythmias. JACC. June 1988; Vol.11, No.6:1278-86).

H. Inactive Patients

There are a total of 82 patients who had received a PCD® System and are no longer active in the study as of 2/1/93. Table IH-1 shows the distribution of inactive patients by reason for no longer being active in the PCD® Transvene™ System clinical study.

PCD® Transvene™ System Inactive Patients	
Reason for Inactivity	**# of Patients**
Patient Deaths	51
Infection (Explant)	22
Heart Transplant	9
Total	82

Table IH-1: Inactive Patients - 2/1/93

I. Patient Deaths

The positive impact of implantable cardioverter defibrillator (ICD) therapy on sudden cardiac death mortality has been well documented in the medical literature. The use of device therapy for the treatment of recurrent ventricular arrhythmias has become an accepted and important clinical tool. An analysis of the sudden cardiac death survival in the PCD® Transvene™ System patient population was performed.

For purposes of the clinical study, each of the patient deaths was categorized using the following definitions:

Non-Cardiac: Deaths that occurred where the primary cause of death was determined to be non cardiac in nature, e.g. stroke, cancer, etc.

Cardiac: Deaths that occurred where the primary cause of death was determined to be cardiac in nature.

Non-Sudden: Deaths that occur greater than one hour after the onset of symptoms.

Sudden: Deaths that occur within one hour of the onset of symptoms or where the death is

unwitnessed. Sudden cardiac deaths were also categorized as being **Witnessed** or **Unwitnessed**.

Perioperative: Deaths that occur within thirty days of implant.

System Related: A death which results from a malfunction (operation not according to design specification) of a PCD® System component, or as a result of a device induced arrhythmia, or an interaction between a PCD® System component and the patient.

Procedure Related: A death which occurs as a result of a procedure required to implant, follow or test a PCD® System.

All deaths and significant complications have been and will continue to be reviewed by a committee comprised of PCD® Transvene™ System investigators and other physicians. Two committees (Clinical Event Review Committees) have been formed, one to review North American deaths and complications, and the other to review European clinical events. The primary purpose of these reviews was to determine whether the PCD® System was related to the deaths or significant complications that have occurred and, if so, what changes may be required to prevent such events in the future.

There have been a total of 51 patient deaths reported in the PCD® Transvene™ System patient population. Table II-1 summarizes how these patient deaths have been classified.

PCD® Transvene™ System **Summary of Death Classifications** (n = 757)	
Classifications	**Number of Deaths**
Sudden Cardiac	5
Non-Sudden Cardiac	30
Noncardiac	16
Total	51

Table II-1: PCD® Transvene™ System - Summary of Death Classifications - 2/1/93

None of the patient deaths were attributed to a malfunction of the PCD® Transvene™ System.

Actuarial survival analysis on the PCD® Transvene™ System was done on all patients who were either evaluated for implantation or in whom the device was implanted. Thus, the analysis is done from the perspective of **intention to treat.** Those patients in whom the PCD® Device was OFF at the time of death or in whom no device was implanted **are** included in the survival analysis. Those patients that were screened for a PCD® Transvene™ System but failed to receive a Transvene™ system are not included in this analysis.

Projected one year survival calculations for the various death classifications are provided in Table II-2. **The actuarial projections include perioperative deaths only in the calculation of one year survival from death due to all causes (shown in the row labelled Overall).** The perioperative death rate defined as deaths which occurred within thirty days of implant was 0.7% (5/757) which is considerably less than the perioperative mortality for the PCD® System with Epicardial leads (5.3% - 39/742). Included in this table are the projected one year survival calculations for patients who ultimately received a PCD® Transvene™ System (n = 757) and all patients that were screened for a PCD® Transvene™ System (n = 854) regardless of implant outcome.

PCD® Transvene™ System One Year Actuarial Survival		
	Received PCD® Transvene™ System	**Screened for a PCD® Transvene™ System**
Sudden Cardiac Death	99.5%	99.4%
Non-Sudden Cardiac	96.2%	96.6%
All Cardiac	95.8%	96.1%
Noncardiac	98.1%	98.3%
Perioperative	0.7%	1.6%
Overall	93.3%	92.9%

Table II-2: PCD® Transvene™ System - One Year Actuarial Survival - 2/1/93

The positive impact of the PCD® Transvene™ System on patient mortality is clearly obvious from this analysis. The sudden cardiac death survival rate in this patient group is 99.5% for those in the patient group that received a Transvene™ System and 99.4% for those who were screened for a Transvene™ System. This is marked improvement when compared with the reported survival of similar patient groups treated with drug therapy alone of between 34% and 73% at one year.

J. Clinical Experience By Primary Indication

Medtronic is requesting approval for use of the PCD® Transvene™ System in the following patient population:

* Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or

* Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

Sudden cardiac death without recurrent VT (**SCD**) was the indication for implant in 37.1% of the patients, recurrent ventricular tachycardia without an episode of sudden cardiac death (**VT**) was the indication for implant in 49.8% of the patients, and sudden cardiac death and recurrent VT (**SCD/VT**) was the indication for implant in 13.1% of the patients.

The performance of the PCD® Transvene™ System in these three groups are summarized in Table IJ-1.

In all three patient groups, coronary artery disease was the predominant heart disease and the patients exhibited moderate left ventricular dysfunction as demonstrated by mean ejection fractions of less than 40%. The mean LED at the time of implant was similar among the patient groups as was the mean DFT.

The overall efficacy in terminating spontaneous VT/VF episodes in the SCD patient group was 98.4%, in the VT patient group 98.3%, and in the SCD/VT group 99.1%. Thus, independent of the indication for implant, the PCD® Transvene™ System was highly effective in terminating spontaneous episodes of VT/VF.

The one year sudden cardiac death survival rates for all groups was greater than 98.6%

This analysis indicates that the PCD® Transvene™ System has performed safely and effectively in the indicated patient groups and should be approved for use in the indicated patient population.

PCD® Transvene™ System
Data Summary by Primary Indication

	SCD	VT	SCD/VT	All Patients
# of Patients	281 (37.1%)	377 (49.8%)	99 (13.1%)	757
Number, % Male Number, % Female	212 75.4% 69 24.6%	309 82.0% 68 18.0%	89 89.9% 10 10.1%	610 80.6% 147 19.4%
Mean Age	56.8 yrs	61.2 yrs	60.0 yrs	59.4 yrs
Coronary Artery Disease	191 68.0%	292 77.5%	78 78.8%	229 72.2%
Mean Ejection Fraction	39.1% (N=259)	33.7% (N=339)	32.5% (N=90)	35.6% (N=688)
Defibrillation Pathway: Sequential Simultaneous Single	 201 71.5% 74 26.3% 6 2.2%	 295 77.6% 82 21.6% 3 0.8%	 76 76.8% 22 22.2% 1 1.0%	 574 75.3% 178 23.4% 10 1.3%
Mean LED	15.3J (N=264)	16.2J (N=351)	17.3J (N=87)	16.0J (N=702)
Mean DFT	14.0J (N=117)	15.5J (N=155)	13.9J (N=44)	14.8J (N=316)
Spontaneous VT: # of Patients # of Episodes % Success	 58 1157 99.2%	 206 7591 98.1%	 52 1279 99.0%	 316 10027 98.4%
Spontaneous VF: # of Patients # of Episodes % Success	 107 686 96.9%	 162 916 99.1%	 48 380 99.5%	 317 1982 98.4%
1 Year SCD Survival	100.0%	99.4%	98.6%	99.5%

Table IJ-1: PCD® Transvene™ System Data Summary by Primary Indication - 2/1/93

K. Patients Not Meeting Implant Criteria

K.1 Overview

The PCD® Transvene™ System offers a simpler and safer implantation technique for an implantable cardioverter defibrillator system. In addition, the PCD® Transvene™ System decreases the potential perioperative and long term mortality associated with current epicardial system implantation approaches.

There is a class of patients who cannot tolerate the thoracotomy required for the utilization of the epicardial patch lead defibrillation lead system and who are at high risk of sudden cardiac death. Because of the surgical risks and postsurgical complications associated with the implant of an epicardial lead system, implantation in the following patient groups may not be desirable or possible:

(1) patients in whom there is no indication for concomitant cardiovascular surgery at the time of ICD implant;

(2) patients with severe pulmonary disease who can not tolerate prolonged anesthesia or an open chest procedure;

(3) patients with severe congestive heart failure (ejection fraction < 40%) who are at increased risk for perioperative mortality following a thoracotomy procedure;

(4) patients who may eventually require open chest procedures for treatment of their coronary artery disease or cardiac transplant.

For these patients, a transvenous ICD System is the only therapy available. The PCD® Transvene™ System simplifies and greatly reduces the risk associated with lead introduction, making therapy available to these patient groups. Because there is no need to open the chest of these patients, more options for future therapy remain available; e.g. CABG is associated with increased morbidity and mortality if there has been prior open chest surgery.

However, it is expected that nonthoracotomy lead systems will have higher mean implant defibrillation thresholds as compared to traditional epicardial lead systems. In an epicardial lead system, the lead system has a larger

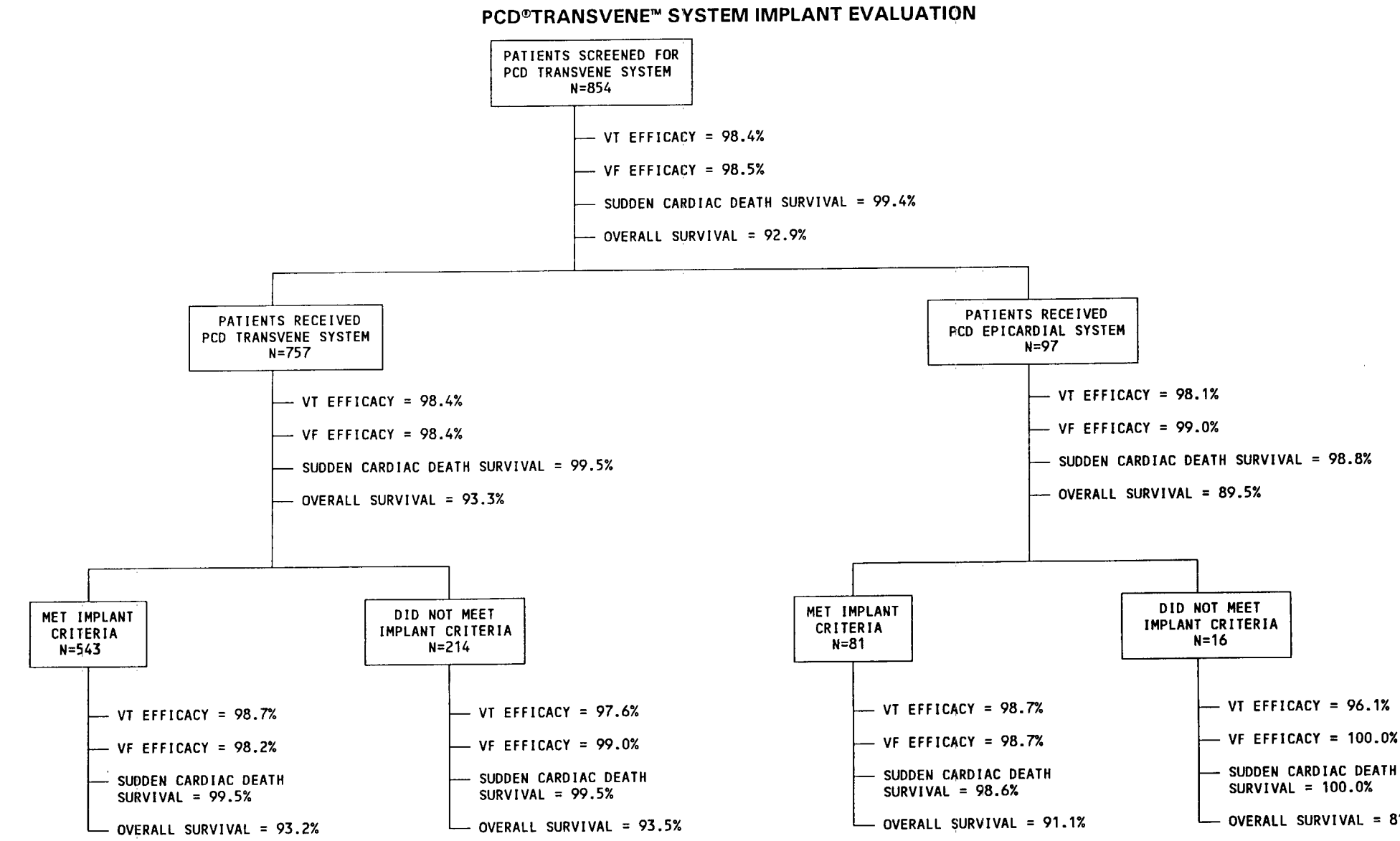
electrode surface area theoretically decreasing defibrillation requirements.

The smaller electrode surface areas of the PCD® Transvene™ System defibrillation leads might reduce the proportion of patients in whom the implant criteria could be met. Not meeting the implant criteria may reduce the chronic effectiveness of the lead system. Recent studies indicated that 70% of patients evaluated may be candidates for a nonthoracotomy defibrillation lead system (Wilber, D, et al. Clinical Advances in Nonepicardial Implantable Defibrillator Lead Systems. The Journal of Invasive Cardiology. Vol.3, No.6,November/December 1991).

For purposes of the PCD® Transvene™ System, the implant criteria was defined as successful VF termination at least 3 times in 4 attempts with the final lead configuration with an output energy of 18 Joules or less. The determination of a defibrillation threshold was not required.

A defibrillation threshold (**DFT**) was defined as the energy at the lowest successful defibrillation attempt, provided the patient had a failure below the lowest success or a success at $\leq$ 5J. The lowest energy of defibrillation (**LED**) was defined as the lowest programmed energy that successfully defibrillated the patient. In both cases, conversion of ventricular tachycardia or ventricular flutter to sinus rhythm was **not** included in the determination of the DFT or LED.

A total of 854 patients had an evaluation of a PCD® Transvene™ System and are divided into the following groups - (1) Patients who received a PCD® Transvene™ System; and (2) Patients screened for a PCD® Transvene™ System and received a PCD® Epicardial System. Figure 1 provides an overview of the outcome of these patients.



igure 1: Patients Screened for a Transvene™ System

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As can be seen, 88.6% (757/854) of the patients who were screened for a PCD® Transvene™ System ultimately received the system. Of these 757 patients, 71.7% (543 patients) met the recommended defibrillation implant criteria which compares favorably with the predicted success rates published in the literature (Wilber et al). However, 28.3% (214/757) of the patients did not meet the recommended defibrillation efficacy implant criteria and still received the PCD® Transvene™ System. It should be noted that 97.4% of the patients (737/757) received the PCD® Transvene™ System with at least a 10 Joule defibrillation safety margin between the lowest energy of success (24J) and the maximum output (34J) of the PCD® Device.

The investigators utilized this 10 Joule safety margin as a benchmark based on the clinical experience discussed in the article, Troup P., et al. The Implanted Defibrillator: Relation of Defibrillating Lead Configuration and Clinical Variables to Defibrillation Threshold. Journal of American College of Cardiology 1985; 6:1315-1321. Finally, and perhaps most importantly, the investigators also felt that for these patients the risk associated with not meeting the recommended implant criteria was outweighed by the risk of not implanting an ICD or implanting an epicardial system.

There were twenty patients (2.6%), who received a PCD® Transvene™ System, whose cardiovascular condition precluded further completion of the PCD® Transvene™ System and adequate definition of a defibrillation safety margin. In all cases, the physician felt that the benefit of the PCD® Transvene™ System outweighed the risk of further inductions or the risk of a thoracotomy and elected not to evaluate or implant a PCD® Epicardial System.

K.2 Patients Receiving PCD® Transvene™ System & Did Not Meet Implant Criteria

For purposes of the PCD® Transvene™ System, the implant criteria was defined as successful VF termination at least 3 times in 4 attempts with the final lead configuration at an output energy of 18 Joules or less. Of the 757 patients who **received** a PCD® Transvene™ System, 214 patients (28.3%) did not meet the recommended defibrillation implant criteria and yet still received the PCD® Transvene™ System. The physicians justification for implanting the PCD® Transvene™ System despite not meeting the recommended defibrillation implant criteria are presented in Table IK-1.

PCD® Transvene™ System
Reasons for Not Meeting Implant Criteria
Physician Justification

Reason	Number of Patients
Success at $\leq$ 24 Joules	170
Difficult/Unable to Induce VF	24
Patient Condition	20
Total	214

Table IK-1: PCD® Transvene™ System: Physician Justification for Not Meeting Implant Criteria - 2/1/93

Further analysis of the patient who did not meet the recommended implant criteria indicates however, that 91% (194/214) had a 10 Joule safety margin between the lowest energy of successful defibrillation and the maximum output of the PCD Device (34J). Therefore, of the 757 patients who received a PCD® Transvene™ System, 97.4% (737/757) had at least a 10 Joule defibrillation safety with the implanted lead configuration.

There were 20 patients (2.6%) in whom the implant procedure was terminated due to poor patient condition. These patients received a PCD® Transvene™ System without at least a 10 Joule defibrillation safety margin. The implant circumstances of these patients is summarized as

follows:

- At least one successful defibrillation was obtained at an energy level greater than 24 Joules and or equal to 34 Joules (**N = 11**);

- Multiple inductions of VT were performed and successfully reverted with an energy level of 18 Joules or less. However, induced VF was not successfully reverted by an energy level of less than or equal to 34 Joules (**N = 6**); and

- Physician elected to terminate the procedure due to the patient's condition before inductions with the final implanted lead configuration were performed (**N = 3**).

Table IK-2 provides a comparison of patient characteristics between patients who met the PCD® Transvene™ System implant criteria and those patients who did not meet the implant criteria but still received the PCD® Transvene™ System.

PCD® Transvene™ System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Patient Characteristics		
Data	**Meeting Criteria**	**Not Meeting Criteria**
Number of Patients	543	214
Mean Follow-Up	12.3 months	10.1 months
Male*	422 (77.7%)	188 (87.9%)
Female	121 (22.35)	26 (12.1%)
Mean Age	59.4 yrs	59.6 yrs
Indication*		
SCD	209 (38.5%)	72 (33.6%)
VT	278 (51.2%)	99 (46.3%)
SCD/VT	56 (10.3%)	43 (20.1%)
Cardiovascular History		
CAD	396 (72.9%)	165 (77.1%)
Cardiomyopathy	173 (31.9%)	65 (30.4%)
Mean EF*	36.3%	33.7%
NYHA Class		
I	164 (30.9%)	53 (25.8%)
II	278 (52.4%)	114 (56.6%)
III	82 (15.4%)	34 (16.6%)
IV	7 (1.3%)	4 (2.0%)
Number ON Drugs at Implant	223 (41.1%)	97 (45.3%)
Number ON Amiodarone	78 (14.4%)	38 (17.8%)

* Statistically Significant ($p \leq 0.05$)

Table IK-2: PCD® Transvene™ System: Patients Meeting Implant Criteria vs Not Meeting Implant Criteria - Comparison of Pt Characteristics - 2/1/93

Statistical analysis indicated three significant differences between these two patient groups - patient sex, indication for implant and mean ejection fraction.

Patients not meeting implant criteria had a statistically higher percentage of patients who were male ($p = 0.002$). This difference reflects that the majority of patients with coronary disease with concomitant life threatening

ventricular arrhythmias are males.

Analysis indicated the patients not meeting the implant criteria had a statistically higher percentage of patients whose primary indication for implant was sudden cardiac death associated with recurrent ventricular tachycardia ($p = 0.002$). This difference reflects the physicians use of the PCD® Transvene™ System.

Finally, patients who did meet the implant criteria had a statistically lower mean ejection fraction ($p = 0.0342$) which reflects a higher degree of underlying cardiovascular disease in these patients.

It should be noted, that none of these differences should be used as predictors for patients who should be screened for a PCD® Transvene™ System.

Implant data obtained in these two patient groups is presented in Table IK-3. As would be expected the patients not meeting the implant criteria had higher mean DFT and LED values when compared to the patients who did meet the implant criteria. However, the mean DFT (18.8J) and LED (19.5J) values obtained in patients not meeting implant criteria provided at least a 10 Joule defibrillation safety margin between the successful energy and the maximum output of the PCD® Device (34J) in nearly all (97.4%) of the patients.

PCD® Transvene™ System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Implant Data		
Data	**Meeting Criteria**	**Not Meeting Criteria**
Number of Patients	543	214
Mean Number of Inductions	7.0	8.2
Number of Configurations	2.0	2.7
Mean DFT	13.4J	18.8J
Mean LED	14.8J	19.5J
Implanted Lead System		
RV-SVC-SQ	351 (64.6%)	145 (67.8%)
RV-CS-SQ	159 (29.3%)	63 (29.4%)
RV-CS-SVC	33 (6.1%)	6 (2.8%)
Efficacy of 1st Lead System	396 (72.9%)	137 (64.0%)
Defibrillation Pathway		
Sequential	414 (75.7%)	160 (74.4%)
Simultaneous	127 (23.2%)	51 (23.7%)
Single	6 (1.1%)	4 (1.9%)

Table IK-3: PCD® Transvene™ System: Patients Not Meeting Implant Criteria versus Patients Meeting Implant Criteria - Comparison of Implant Data - 2/1/93

In order to determine if the patient's not meeting implant criteria had higher risk for morbidity and mortality, a comparison of their clinical outcome was made with those patients who did meet the implant criteria. This comparison is provided in Table IK-4.

PCD® Transvene™ System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Implant Data		
Data	**Meeting Criteria**	**Not Meeting Criteria**
Number of Patients	543	214
Spontaneous VT Episode Efficacy	98.7%	97.6%
Spontaneous VF Episode Efficacy	98.2%	99.0%
Number of Patient Deaths	37	14
Perioperative Mortality	0.7%	0.5%
One Year Survival		
Sudden Cardiac	99.5%	99.5%
Non-Sudden Cardiac	95.8%	97.2%
All Cardiac	95.4%	96.7%
Noncardiac	98.5%	97.1%
Overall	93.2%	93.5%

Table IK-4: PCD® Transvene™ System: Patients Not Meeting Implant Criteria versus Patients Meeting Implant Criteria - Comparison of Clinical Outcome - 2/1/93

The two patient groups had similar efficacy in the treatment of spontaneous VT/VF episodes. Importantly, in the patient population who did not meet the implant criteria there were no patients who experienced actual spontaneous VF episodes where all programmed PCD® Device therapies failed to terminate the episode.

Five patients experienced 7 episodes in which the PCD® Device was ineffective in terminating a spontaneous episode of VF despite delivery of all four programmed VF therapies. Three patients had 5 reported ineffective VF

spontaneous episodes that were due to sinus tachycardia or atrial fibrillation with rapid ventricular response rather than VF. Reprogramming and pharmacologic intervention resolved these problems.

Two patients experienced 2 episodes in which the PCD® detected the episodes as VF but were actually episodes due to extraordinary circumstances. The first patient (b)(6) had incessant episodes of fast VT (cycle length 280 ms) that were eventually resolved by drugs. The second patient (b)(6) was in hospital and there was an episode of VF detected. However, the device was interrogated before termination of the episode was detected. There was external intervention associated with the terminal event. The device was not interrogated again.

Eighteen patients experienced 68 episodes in which the PCD® Device was ineffective in terminating a spontaneous episode of VT despite delivery of all four programmed VT therapies. Nine patients experienced 44 ineffective episodes that were due to sinus tachycardia or atrial fibrillation/flutter (SVT) with a rapid ventricular response that had been detected as VT. These episodes were resolved with either modification of programmed parameters or of antiarrhythmic drug therapy. It should be noted that the PCD® Device responded appropriately based on the programmed detection parameters.

The remaining 24 episodes occurred in 8 patients in which the programmed VT therapies were ineffective in terminating a spontaneous VT episode. **No patient deaths occurred as a result of ineffective VT therapy.** Reprogramming and pharmacologic intervention resolved these events.

There was no difference in the one year sudden cardiac survival or the overall survival in the two groups although follow-up was shorter for patients not meeting implant criteria (10.1 vs 12.3 months). This indicates, that despite not meeting the implant criteria these patients were not at higher risk of sudden cardiac death.

Finally, the survival of patients receiving a PCD® Transvene™ System without meeting implant criteria

(N = 214) was compared to patients receiving a PCD® Epicardial System without meeting implant criteria (N = 92). This comparison is provided in Table IK-5.

PCD® Transvene™ System Patients Not Meeting Implant Criteria Survival Analysis versus PCD Epicardial System Patients Not Meeting Implant Criteria Survival Analysis		
	PCD Transvene System Not Meeting Implant Criteria	PCD Epicardial System Not Meeting Implant Criteria
Number of Patients	214/757 (28.5%)	92/742 (12.4%)
Number of Deaths	14	17
Sudden Cardiac	99.5%	98.6%
Non-Sudden Cardiac	97.2%	98.8%
Noncardiac	97.1%	97.3%
Overall*	93.5%	87.6%

* Statistically Significant ($p \leq 0.05$)

Table IK-5: PCD® Transvene™ System: Patients Not Meeting Implant Criteria - PCD Transvene System vs PCD® Epicardial System - 2/1/93

Though the PCD® Transvene™ System had a higher incidence of patients not meeting implant criteria (28.5%) compared to the PCD® Epicardial System (12.4%), there was no statistical difference in the sudden cardiac death patient survival. However, the overall survival of patients not meeting implant criteria with the Transvene™ System was significantly better ($p = 0.037$) when compared to the PCD® Epicardial System patients not meeting implant criteria, 93.5% and 87.6%, respectively.

The investigators felt in every case that the testing performed at the time of implant, though it did not meet the recommended implant criteria, did provide an adequate demonstration of device effectiveness and justified the implant of the PCD Transvene System. Finally, there have been no patients deaths secondary to unsuccessful termination of a spontaneous VT or VF episode in this patient population.

K.3 Description of Patients Not Meeting Implant Criteria

As noted previously, the patients not meeting implant criteria (N=214) were divided into three groups (1) Successful defibrillation at an energy level of equal to or less than 24 Joules [79.4% of the patients]; (2) Difficult to induce VF [11.2% of the patients]; and (3) Implant procedure terminated due to poor patient condition [9.4% of the patients]. These patient groups are reviewed in the following discussion.

Lowest Energy of Defibrillation < 24 Joules

There were 170 patients in whom the PCD® Transvene™ System was implanted with a defibrillation safety margin of at least 10 Joules. Table IK-6 provides an overview of these patients clinical experience.

These data indicate that the final implanted PCD® Transvene™ System was evaluated and significant attempts were made to meet the recommended implant criteria. In most of these patients (79.4%), a safety margin of 10 Joules was obtained between the successful defibrillation energy (24 J or less) for ventricular fibrillation and the maximum output of the PCD Device (34 J). The investigators decided in certain circumstances that this was appropriate demonstration of device effectiveness and that the PCD® Transvene™ System could be implanted.

Of these patients, 159 (93.5%) have had VT or VF induced at a chronic follow-up visit and in each case, VT or VF was successfully terminated by the PCD Transvene System. In addition, 65 patients (38.2%) have experienced a spontaneous VF episode with an overall efficacy of 99.4%.

Thus, the clinical outcome in these patients was not adversely affected by not meeting implant criteria since their spontaneous VF episode efficacy was 99.4% and the one year sudden cardiac death actuarial survival was also 99.4%. The duration of follow up, however, is limited to an average of 9.7 months.

PCD® Transvene™ System Patients Not Meeting Implant Criteria 10J Safety Margin Provided	
Number of Patients	170
Lowest Energy of Defibrillation	
1 Success with 10J Safety Margin	87
2 Success with 10J Safety Margin	58
3 Success with 10J Safety Margin	18
> 3 Success with 10J Safety Margin	7
Overall Spontaneous VF Episode Efficacy	99.4%
One Year Survival:	
Sudden Cardiac	99.4%
Overall	93.8%

Table IK-6: PCD® Transvene™ System: Patients Not Meeting Implant Criteria with 3/4 Successes at $\leq$ 24 Joules Clinical Experience - 2/1/93

Difficult to Induce VF

There were 24 patients who did not meet the recommended PCD® Transvene™ System implant criteria because at least three episodes of VF were not induced at the time of implant. Of these, 15 patients had ventricular tachycardia induced and successfully reverted. The remaining 9 patients had ventricular flutter induced and successfully reverted. In all 24 patients, the lowest successful energy was equal to or less than 18 Joules.

The indication for implant was sudden cardiac death (SCD) in 6 patients (25%), recurrent ventricular tachycardia (VT) in 13 patients (54.2%) and sudden cardiac death associated with recurrent ventricular tachycardia (SCD/VT) in 5 (20.8%) patients. Thus the majority of the patients, 75%, had documented recurrent ventricular tachycardia as part of their ventricular tachyarrhythmia history. Eight of the these patients (33.0%) were on Amiodarone therapy which may have contributed to the inability to induce VF.

Of the 24 patients who did not meet the recommended PCD® Transvene™ System implant criteria because at least three episodes of VF were not induced at the time of

implant, 13 patients (54.2%) have experienced a spontaneous VF episode and 21 patients (87.5%) have had VT or VF induced during a chronic follow-up. In all cases, VF was successfully reverted by the PCD® Transvene™ System.

There has been one reported patient death (b)(6) in this patient group. Since this patient died after one year, the one year sudden cardiac death and overall actuarial survival remains 100%.

Patient Condition

There were 20 patients in whom the implant procedure was terminated due to poor patient condition. These patients received a PCD® Transvene™ System without at least a 10 Joule defibrillation safety margin. The implant circumstances of these patients is summarized as follows:

- At least one successful defibrillation was obtained at an energy level greater than 24 Joules but less than 34 Joules (**N = 11 patients**);
- Multiple inductions of VT were performed and successfully reverted with an energy level of 18 Joules or less. However, induced VF was not successfully reverted by an energy level of less than or equal to 34 Joules (**N = 6 patients**); and
- Physician elected to terminate the procedure due to the patient's condition before inductions with the final implanted lead configuration were performed (**N = 3 patients**).

The mean ejection fraction of this group was 26.9%, indicating more severe underlying cardiovascular disease, and may have contributed to the physicians decision to terminate the implant procedure prior to meeting implant criteria. This group had a mean of 6.8 VF inductions, 2.2 lead configurations evaluated and a mean duration of VT/VF for the implant procedure of 220 total seconds. The circumstances of the implant procedures, mainly the duration of induced ventricular tachyarrhythmia and associated hemodynamic compromise, limited the number of inductions that could be performed and whether the recommended implant criteria could be met.

Of these 20 patients, VT or VF has been induced at a

chronic follow-up visit in 16 patients (80%) and in all cases successful defibrillation with the implanted PCD® Transvene™ System was documented.

The overall spontaneous VF episode efficacy for this patient group was 96.0%. However, examination of events indicated that one patient experienced atrial fibrillation that was detected as VF and in whom all four programmed VF therapies were ineffective. This patient's antiarrhythmic drug therapy was modified and there were no further reports of ineffective therapies.

Thus there have been no patients who have experienced an actual spontaneous VF episode where all four programmed VF therapies failed to terminate the episode.

There have been two reported patient deaths, Patient ID (b)(6) which was classified as non-sudden cardiac secondary to end stage heart failure and Patient ID (b)(6) which was also classified as non-sudden cardiac. The one year sudden cardiac death survival in this patient population is 100% while the overall one year survival was 85.5%. This lower overall one year survival may due to the lower mean ejection fraction of this patient group.

The clinical outcome in these twenty patients was not adversely affected by not meeting implant criteria since there was no reports of failure to terminate a spontaneous VF episode and the overall one year sudden cardiac death survival was 100%.

Conclusion

In conclusion, 214 patients received the PCD® Transvene™ System despite not meeting the recommended implant criteria. These 214 patients are divided into the following groups:

- successful defibrillation of VF at 24 Joules or less (170/214),
- difficult to induce at least three episodes of VF at implant (24/214), and
- worsening patient condition which prevented further inductions (20/214).

It should be noted that 91 % (194/214) of the patients not meeting the recommended implant criteria had at least one successful termination of induced ventricular tachyarrhythmia (VT, VFlutter or VF) at 24 Joules or less.

L. Comparison to AICD System Experience

L.1 Overview

The current AICD Epicardial System is implanted only with a defibrillation lead system requiring a thoracotomy. The PCD® Transvene™ System allows the implantation of an implantable cardioverter defibrillator (ICD) system without the potential increased perioperative morbidity and mortality associated with a thoracotomy. This allows the application of ICD therapy in patients who may not otherwise be candidates for this type of therapy. Though the PCD® Transvene™ System will have complications and observations that are specific to the lead system, the overall performance should be at least equivalent to that reported with the current AICD Epicardial System.

This section provides a comparison of the PCD® Transvene™ System clinical experience to that of the reported AICD Epicardial System clinical experience. The following areas will be discussed:

- Patient characteristics
- Clinical performance
- Survival analysis

For purposes of comparison, the Ventak-P Epicardial System patient population described in the Summary of Safety and Effectiveness Data (PMA Application Number P890061) dated May 2, 1991 will be used. A copy of this summary was obtained through the Freedom of Information Act.

L.2 Comparison of Patient Characteristics

In comparing the clinical experience with the PCD® Transvene™ System to the reported Ventak-P Epicardial System clinical experience, it is important to determine that the patients who received the device are comparable.

The characteristics of the patients receiving the PCD® Transvene™ System were compared to the characteristics of patients discussed in the Ventak-P Summary of Safety and Effectiveness Data and are presented in Table IL-1. There were no differences between the two patient groups.

PCD® Transvene™ System
Comparison of Patient Characteristics
PCD® versus AICD

	PCD®	Ventak-P
Number of Patients	757	292
Mean Follow-Up Time	11.7 months	6.8 months
% Males **% Females**	610 (81%) 147 (19%)	231 (79%) 61 (21%)
Mean Age	59.4 years	61.5 years
Primary Indication: **SCD** **VT** **SCD/VT**	 281 (37%) 377 (50%) 99 (13%)	 49 (16%) 169 (59%) 73 (25%)
Coronary Artery Disease	561 (74%)	228 (78%)
Mean Ejection Fraction	35.6%	34%
Drug Therapy at Implant	42%	45.0%
Concomitant Surgery	0%	18.0%

Table IL-1: Comparison of Patient Characteristics, PCD® versus Ventak-P 2/1/93

The two patient groups are comparable in mean age and mean ejection fraction. Both groups had moderately depressed left ventricular function demonstrated by the mean ejection of 35.6% for the PCD® Transvene™ System patient group and 34% for the Ventak-P Epicardial System patient group.

Analysis indicated that no statistical differences between the PCD® Transvene™ System and Ventak-P Epicardial System patient populations except in the category of patient indication. There are more patients that had Sudden Cardiac Death as the primary indication in the PCD® Transvene™ population than in the AICD population ($p = 0.001$).

L.3 Comparison of Clinical Performance

Areas of clinical performance that were compared were implant defibrillation thresholds, incidence of spontaneous VT/VF events, incidence of complications and patient survival. These specific areas were selected in order to evaluate the system performance in the two patient populations.

Implant Defibrillation Thresholds

For the purposes of the PCD® Transvene™ System clinical study, determination of defibrillation threshold was not mandatory. However, the preferred method of evaluating defibrillation efficacy was to determine the defibrillation threshold using a testing sequence of 18J, 15J, 10J, 5J with a failure at any level causing a return to 18 J for the remaining attempts. For the purposes of this report a defibrillation threshold was defined as the energy at the lowest successful defibrillation attempt, provided a patient had a failure below their lowest defibrillation success or a success at $\leq$ 5J. The rhythm treated must have been VF to be included in the analysis.

It should be noted, that it was expected that the PCD® Transvene™ System would have a higher mean defibrillation threshold as compared to a traditional epicardial defibrillation lead system. In a epicardial system, the increased electrode surface area would theoretically decrease defibrillation requirements.

A total of 316 patients had a defibrillation threshold determined at the time of PCD® device implant. The mean defibrillation threshold (DFT) for all lead systems was 14.8J. The recommendation for VF Therapy #1 is to program the stored energy to twice the implant DFT or 18 Joules, whichever is greater. Thus an adequate defibrillation safety margin was provided when following the VF therapy programming recommendations.

In the Ventak-P Epicardial System, the mean defibrillation threshold at implant was 13.4J. Thus the two systems had similar defibrillation thresholds at implant despite the fact that one system utilized an epicardial defibrillation lead

system while the other utilized a transvenous defibrillation lead system.

These data indicate that the PCD® Transvene™ System had comparable implant defibrillation threshold performance when compared to the reported Ventak-P Epicardial System clinical experience.

Incidence of Spontaneous VT/VF Episodes

The incidence of spontaneous VT/VF episodes in the Ventak-P Epicardial System and PCD® Transvene™ System patient population was evaluated by utilizing the stored episode information provided by both devices.

In the Ventak-P device, the total number of shocks delivered to the patient is provided via interrogation of the device. The PCD® device provides information on the total number of VT and VF episodes detected by the PCD® device and the total number of VT and VF episodes successfully treated by the PCD® device as well as the number of VT/VF episodes where the PCD® device was ineffective. In addition, the last 20 intervals of the last episode satisfying detection criteria along with the first 10 intervals after the last therapy delivered are recorded by the device. These data assist the physician in evaluating the frequency of VT/VF episodes, the efficacy of the PCD® device programmed parameters and the need for reprogramming.

In the Ventak-P Epicardial System experience of 292 patients with a mean follow-up of 6.8 months, 137 (46.9%) received a device countershock in response to a spontaneous ventricular tachyarrhythmia episode as defined by the Ventak-P Device detection criteria.

In the PCD® Transvene™ System experience of 757 patients with a mean follow-up of 11.7 months, 458 patients (60.5%) have received device therapy in response to a spontaneous ventricular tachyarrhythmia episode as defined by the PCD® Transvene™ System detection criteria.

A total of 10027 spontaneous VT and 1982 spontaneous VF episodes have been recorded by the PCD® device

episode counters. Of the 9864 successfully treated spontaneous VT episodes, 91.4% were treated with one of the programmed antitachycardia pacing therapies incorporated in the PCD® device. The clinical benefit of tiered therapy is the reduction of delivery of high energy shocks for the treatment of stable recurrent ventricular tachycardia that may be responsive to antitachycardia pacing.

Incidence of Complications

Table IL-2 provides a comparison of reported complications and observations. The AICD clinical experience data is from the Winkle, et al Long Term Outcome with Automatic Implantable Cardioverter-Defibrillator; JACC, May 1989; 13(6); 135-161. This article was selected because it provides a detailed clinical complication experience on a large patient population, 270 patients. Note that the percentage reported in the PCD® Transvene™ System includes **both complications and observations.** In the following table, the complications are reported for the categories of Fail to Cardiovert/Defibrillate, Pocket Infection, and Erosion. Observations are reported in the Inappropriate/Problematic VT/VF Therapy Delivery category.

PCD® Transvene™ System
Comparison of Complication/Observation Rates
PCD® versus AICD

Category	PCD®%	AICD%
Fail to Cardiovert/Defibrillate	2.3%	4.1%
Inappropriate/Problematic VT/VF Therapy Delivery	9.6%*	20%
Pocket Infection (explant)	2.9%	2.2%
Erosion	0.8%	0.7%

* Includes Observations only; there were no Complications in this category.

Table IL-2: Comparison of Complication/Observation Rates: PCD® Transvene™ System vs AICD Epicardial System - 2/1/93

The incidence of failure to cardiovert and/or defibrillate was lower in the PCD® Transvene™ System patient population. The instances of failure to cardiovert and/or defibrillate in

the PCD® Transvene™ System patient population were associated with increased defibrillation requirements during induced episodes, none of which resulted in patient death.

The failures to cardiovert/defibrillate reported in the Winkle, et al article were associated with patch dislodgement, patch crinkling, lead conductor fracture and elevated defibrillation thresholds.

The incidence of inappropriate/problematic VT/VF therapy delivery was lower in the PCD® Transvene™ System patient population. This is to be anticipated since the device incorporates independently programmable detection algorithms for VT and VF. The reasons for inappropriate VT/VF therapy delivery included sinus tachycardia being detected as VT or VF and atrial fibrillation with rapid ventricular response being detected as VT or VF.

The overdetection circumstances reported in Winkle, et al were nonsustained VT, VT, sinus tachycardia, atrial fibrillation with rapid ventricular response, sensing lead fracture and pacemaker interaction. The patients with VT complained of receiving multiple shocks with limited or no symptoms. The incorporation of antitachycardia pacing in the PCD® device decreases the need for delivery of cardioversion shocks for the termination of stable VT and increases patient acceptance of ICD therapy.

In the Winkle, et al experience all patients with pocket infection had the devices explanted. In the PCD Transvene System experience, the incidence of device explant secondary to pocket infection was 3.2% which was comparable to Winkle's article.

Thus, the incidence of complications and observations was similar to that of the AICD Epicardial System in the categories of ineffective VT/VF therapies, infection requiring explant and erosion. The incidence of inappropriate delivery of therapy is lower in the PCD Transvene System experience than in the AICD Epicardial System experience, which is clinically significant.

This analysis indicates that the PCD® Transvene™ System offers clinical advantages in reducing the need for a

thoracotomy for implantation and reducing the number of shocks due to successful antitachyarrhythmia pacing.

L.4 Comparison of One Year Actuarial Survival

The Ventak-P Epicardial System produced by Cardiac Pacemaker, Inc, has obtained market approval from the U.S. FDA to date. While there are important differences in the function of the Ventak-P Epicardial System and the PCD® Transvene™ System, there is a natural desire for comparison of the clinical outcome, particularly the impact of these devices on death rate.

A total of 51 deaths (6.7%) were reported in the PCD® Transvene™ System patient population. Of the 35 cardiac deaths, 30 were non-sudden cardiac and 5 were sudden cardiac. Sixteen deaths were classified as noncardiac. Five of the 51 total deaths occurred within the perioperative period (death less than 30 days post implant) with a resultant perioperative mortality of 0.7%.

In the Ventak-P Epicardial System patient population a total of 19 deaths (6.5%) were reported. Of the 12 cardiac deaths, 4 were classified as sudden cardiac and 8 were classified as non-sudden cardiac. Six of the deaths were classified as noncardiac and the cause of one was unknown. Eight of the deaths occurred within the perioperative period with a resultant perioperative mortality of 2.7%. The PCD® Transvene™ System population had a lower perioperative mortality, 0.7% vs 2.7% ($p = 0.006$).

For purposes of this comparison, only the **overall** actuarial survival rate includes perioperative deaths. All other calculations in both the PCD® Transvene™ System and Ventak-P Epicardial System group exclude perioperative deaths.

For the Ventak-P Epicardial System, patient deaths were **censored** if the Ventak-P device had been either electively deactivated for various reasons prior to the patient's death, thus preventing the device from attempting to convert the arrhythmia or if the pulse generators were known to be nonfunctional and awaiting replacement. For purposes of this comparison, seven patient deaths were **censored** in the

PCD® Transvene™ System patient population because the devices were deactivated at the time of patient death.

This PCD® Transvene™ System sudden cardiac death survival of 99.7% at one year is comparable to that of the Ventak-P Epicardial System sudden cardiac death survival rate of 98.6%. More importantly, the overall one year actuarial survival for the PCD® Transvene™ System was 94.2% as compared to 90.8% for the Ventak-P Epicardial System. This difference was primarily due to the improvement in the reported perioperative mortality in the PCD® Transvene™ System patient population. [Note: Confidence interval analysis was performed indicating that there was a statistical difference in the reported **Overall** mortality.]

This comparison of actuarial survival rates indicates that the projected sudden cardiac death survival of patients receiving a PCD® System patient population is comparable to that reported for the Ventak-P Epicardial System. Thus, the incorporation of programmable VT/VF detection and therapy algorithms has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

In addition, the elimination of a surgical thoracotomy for implant in the PCD® Transvene™ System has improved the perioperative mortality and overall one year survival when compared to the Ventak-P Epicardial System.

M. Comparison to PCD® Epicardial System Clinical Results

The PCD® Epicardial System uses the same tiered therapy device that combines features of bradycardia support pacing, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. This system has incorporated programmability and multiple detection and therapeutic options that allows the titration of device therapy to a patient's specific clinical arrhythmia history.

The PCD® Epicardial System requires a thoracotomy for implantation because of the need to insert epicardial patch leads. This exposes the patient to surgical risk and potentially limits the

type of patient who may be considered for implant of the system. The need for a simpler and safer implantation technique is widely recognized. The incorporation of a nonthoracotomy lead system, such as the PCD® Transvene™ System, should decrease the potential perioperative and long term mortality and morbidity associated with current epicardial system implantation approaches.

The PCD® Epicardial System and PCD® Transvene System are identical except for the implanted defibrillation lead system. Thus, the performance of the PCD® device, associated support equipment, is similar in the two systems and therefore a comparison of clinical experience should focus on those areas where the implanted lead system may impact clinical outcome.

This section provides a comparison of the PCD® Transvene™ System clinical experience to the reported PCD® Epicardial System clinical experience. The following areas will be discussed:

- Patient characteristics
- Implant Data
- Spontaneous VT/VF Episode Efficacy
- Complications and Observations
- Survival analysis

This analysis will show that the incorporation of a nonthoracotomy defibrillation lead system has maintained the type of therapy available for the treatment of recurrent VT/VF and decreased the potential mortality and morbidity associated with epicardial implant approaches while maintaining the positive impact of ICD therapy on VT/VF episode efficacy and patient survival.

M.1 Comparison of Patient Characteristics

In comparing the clinical experience with the PCD® Transvene™ System to the PCD® Epicardial System clinical experience, it is important to determine that the patients who received the device are comparable.

Table IM-1 contains the characteristics of the 757 patients receiving the PCD® Transvene™ System versus the characteristics of the 742 patients who received the PCD® Epicardial System as of 1/5/93.

PCD® Transvene™ System Comparison of Patient Characteristics		
	PCD® Transvene System	**PCD® Epicardial System**
Number of Patients	757	742
Mean Follow-Up Time	11.7 months	16.3 months
% Males*	610 80.6%	637 85.8%
% Females	147 19.4%	105 14.2%
Mean Age	59.4 years	59.6 years
Primary Indication*		
SCD	281 37.1%	214 28.8%
VT	377 49.8%	405 54.6%
SCD/VT	99 13.2%	123 16.6%
Cardiovascular History		
Coronary Artery Disease	561 74.1%	569 76.7%
Cardiomyopathy	238 13.1%	222 29.9%
Mean Ejection Fraction	35.6%	34.0%
Number of Drugs Failed*	2.3	3.0

* **Statistically Significant**

Table IM-1: Comparison of Patient Characteristics, PCD® Transvene™ System versus PCD® Epicardial System - 2/1/93

Both groups had moderately depressed left ventricular function demonstrated by the mean ejection of 35.6% for the PCD® Transvene™ System patient group and 34.0% for the PCD® Epicardial patient group.

Analysis indicated that the PCD® Transvene™ System patient population had a higher percentage of patients whose indication for implant was sudden cardiac death ($p = 0.002$) and higher percentage of females ($p = 0.007$). It is not expected that these differences will result in a different clinical outcome in the PCD® Transvene™ System patient population as compared to the PCD® Epicardial System. This difference in patient indication is a reflection of the physicians use of the PCD® Transvene™ System.

It is interesting to note, that there was a statistical difference in the number of antiarrhythmic drugs tested

between the two patient groups ($p = 0.001$). The PCD® Transvene™ System patient group failed a mean of 2.3 antiarrhythmic drugs prior to implant while the PCD® Epicardial System patient group failed a mean of 3.0 antiarrhythmic drugs. This difference is a reflection of the differences in the indications for implant between the two patient groups. The PCD® Transvene™ System patient group had a higher incidence of patients whose primary indication for implant was sudden cardiac death. These patients have a higher probability of having experienced a sudden cardiac death episode but were non-inducible during electrophysiologic testing so that drug testing was not feasible.

M.2 Implant Data Comparison

In both systems, lead system testing was performed to verify that one of the specified lead systems was capable of properly detecting and treating episodes of ventricular fibrillation and, when appropriate ventricular tachycardia. This testing included pacing and sensing thresholds during sinus rhythm, evaluation of VF electrogram amplitudes and defibrillation efficacy evaluation. The implant criteria for both systems was identical and were:

1. Successful VF termination at least 3 times in 4 attempts with an output energy of 18 Joules or less and

2. At least a 2:1 VF sensing safety margin

Pace/Sense Performance

In both the PCD® Transvene™ and PCD® Epicardial Systems, sensing is performed in a standard bipolar configuration and pacing is performed in the integrated bipolar configuration. The pace/sense implant criteria for both systems was:

Pacing Threshold:	$\leq$ 1.5V @ 0.5 ms
R-Wave Amplitude:	$\geq$ 5 mV
Slew Rate:	$\geq$ 0.75 volt/sec
Resistance:	200 - 880 ohms

Table IM-2 provides a comparison of the mean pace/sense values obtained at the time of implant for the PCD® Transvene™ and Epicardial Systems. It should be noted

that the pace/sense values presented for the PCD® Epicardial System are for the Model 7217B PCD® Device.

PCD® Transvene™ System Performance Comparison Implant Pace/Sense Parameters		
Parameter	**PCD® Transvene System**	**PCD® Epicardial System**
Pacing Threshold*	0.87 V (0.1-3.6V)	0.98 V (0.2-5.3 V)
R Wave Amplitude*	14.2 mV (1.3-32 mV)	13.5 mV (2.2-37.2 mV)
Slew Rate*	1.66 v/S (0.25-9.8 v/S)	1.38 v/S (0.15-7.2 v/S)
Resistance*	575 ohms (264-1381 ohms)	438 ohms (157-1206)

* Statistically Significant

Table IM-2: PCD® Transvene™ System: Comparison of Implant Pace/Sense Parameters - 2/1/93

The implant pace/sense parameters obtained for the PCD® Transvene™ System indicates that the lead system provided adequate pacing and safety margins. There was a statistically significant difference in all of the implant pace/sense parameters ($p = 0.001$). This is anticipated because endocardial pace/sense parameters are better than epicardial values for bradycardia pacing electrode systems. This difference has no clinical impact on the pacing and sensing performance of the PCD® Transvene™ System.

Electrogram amplitudes were evaluated at follow-up evaluations of both systems to evaluate the performance of the pace/sense lead system and assure adequate safety margin for detection of both baseline rhythms and ventricular tachyarrhythmias. In addition, pacing thresholds were also evaluated at follow-up evaluations to assure an adequate safety margin for capture during both bradycardia and antitachycardia pacing therapies. A comparison of the chronic pace/sense performance for the two systems is presented in Table IM-3. It should be noted that there was no statistical difference in the chronic pace/sense performance of the two systems.

PCD® Transvene™ System Performance Comparison Chronic Pace/Sense Parameters		
Parameter	**PCD® Transvene System**	**PCD® Epicardial System**
Electrogram Amplitude	10.0 mV (0.5 - 25 mV)	9.5 mV (0.5 - 40 mV)
Pulse Width Threshold	0.24 ms (0.03-1.59 ms)	0.24 ms (0.03-1.59 ms)

Table IM-3: PCD® Transvene™ System: Comparison of Chronic Pace/Sense Parameters - 2/1/93

The incidence of loss of capture requiring lead system modification in the PCD® Transvene™ System was 0.8% while the incidence in the PCD® Epicardial System was 2.0%. There were no reports of undersensing requiring lead modification in the PCD® Transvene™ System while the incidence in the PCD® Epicardial System was 0.8%.

This comparison of implant and chronic pace/sense data performance indicates that the performance of the PCD® Transvene™ System is similar to that reported with the PCD® Epicardial System. The PCD® Transvene™ System provides appropriate acute and chronic safety margins for sensing of sinus rhythm and ventricular tachyarrhythmia as well as appropriate safety margins for pacing therapy.

Implant Defibrillation Thresholds

For the purposes of both systems, determination of defibrillation threshold was not mandatory. However, the preferred method of evaluating defibrillation efficacy was to determine the defibrillation threshold using a testing sequence of 18J, 15J, 10J, 5J with a failure at any level causing a return to 18 J for the remaining attempts.

A defibrillation threshold was defined as the energy at the lowest successful defibrillation attempt, provided a patient had a failure below their lowest defibrillation success or a success at $\leq$ 5J. The rhythm treated must have been VF to be included in the analysis.

Table IM-4 provides a comparison of defibrillation thresholds determined at implant for the PCD® Transvene™ and PCD® Epicardial Systems.

PCD® Transvene™ System Performance Comparison Implant Defibrillation Thresholds	
System	**Mean DFT**
PCD® Transvene™ System*	14.8J
PCD® Epicardial System	9.8J

* **Statistically Significant ($p \leq 0.05$)**

Table IM-4: PCD® Transvene™ System: Comparison of Implant DFT - 2/1/93

The PCD® Transvene™ System did have a significantly higher mean implant defibrillation threshold ($p = 0.0001$). It should be noted, that it was expected that the PCD® Transvene™ System would have a higher mean defibrillation threshold as compared to a traditional epicardial defibrillation lead system. In a traditional epicardial system, the increased electrode surface area would theoretically decrease defibrillation requirements.

The programmed defibrillation pathways for the two patient populations is presented in Table IM-5. The implanted PCD® Transvene™ Systems are almost exclusively three lead systems and this explains the decreased use of SINGLE pathway. The use of SIMULTANEOUS pathway is higher in the PCD® Transvene™ System and indicates that in a group of patients the incorporation of multiple defibrillation pathways allowed an increase in the ability to meet the PCD® Transvene™ System implant criteria. Most of the PCD® Epicardial System implants used a two patch system resulting in the increased use of the SINGLE pathway.

PCD® Transvene System Performance Comparison Programmed Defibrillation Pathway		
Defibrillation Pathway	**PCD® Transvene System**	**PCD® Epicardial System**
Sequential	574 (75.3%)	251 (33.0%)
Simultaneous	178 (23.4%)	14 (1.8%)
Single	10 (1.3%)	496 (65.2%)

Table IM-5: PCD® Transvene™ System: Comparison of Programmed Defibrillation Pathway - 2/1/93

The differences in the programmed status of the PCD® device in the PCD® Transvene™ System are a reflection of the type of patients who received the device and the defibrillation energy requirements for each lead system. It is important to note that the PCD® device performed safely and effectively in both patient populations.

M.3 Spontaneous VT/VF Episodes Efficacy Comparison

The primary benefits from the use of the PCD® System center on the detection and termination of life-threatening ventricular tachyarrhythmias. An additional benefit of the PCD® Transvene™ System is the elimination of the need for a thoracotomy for implantation of the defibrillation lead system and the resultant decrease in potential patient morbidity and mortality associated with a thoracotomy. This clinical benefit should not be gained at the expense of providing effective termination of spontaneous VT and VF episodes. Table IM-6 provides a comparison of the efficacy of the PCD® Transvene™ and PCD® Epicardial System in treating spontaneous episodes of VT and VF.

PCD® Transvene™ System Performance Comparison		
Spontaneous VT Episodes		
	PCD® Transvene™ System	**PCD® Epicardial System**
Mean Follow-Up	11.7 months	16.3 months
Number of Episodes	10,027	20,061
% Overall Efficacy	98.4%	98.3%
% Unsuccessful Termination	0.7%	1.0%
Spontaneous VF Episodes		
	PCD® Transvene System	**PCD® Epicardial System**
Mean Follow-Up	11.7 months	16.3 months
Number of Episodes	1982	2636
% Overall Efficacy	98.4%	98.7%
% Unsuccessful Termination	0.3%	0.5%

Table IM-6: PCD® Transvene™ System: Comparison of Spontaneous VT/VF Episode Efficacy - 2/1/93

The overall success rate of the PCD® Transvene™ System in terminating spontaneous episodes of VT or VF is 98.5%. In addition, there have been no reported patient deaths due to ineffective termination of a spontaneous VT/VF episode. This success rate compares very favorably with the overall success rate of the PCD® Epicardial System which was 98.4%. Therefore, the PCD® Transvene™ System offers the potential of decreased patient morbidity and mortality without decreasing the treatment efficacy of spontaneous VT/VF episodes.

M.4 Incidence of Complications/Observations

A comparison of the reported complications and observations was made between the PCD® Transvene™ System and the PCD® Epicardial System. The PCD® Epicardial System patient population used for comparison included clinical experience as of January 5, 1992 with 742 patients and a mean implant duration of 16.3 months. These two patient groups are similar in the patient demographics and indication for implant of the PCD® System. In the PCD® Transvene™ System patient population, 19.4% of the patients experienced a clinical complication and 23.8% of the patients experienced a clinical observation. In the PCD® Epicardial System, 14.2% of the patients experienced a clinical complication and 32.9% of the patients experienced a clinical observation.

Table IM-7 and IM-8 provide a comparison of the reported complications/observations and their incidence in the two patient populations.

PCD® Transvene System
PCD® Transvene System versus PCD® Epicardial System
Reported Complications

Reported Complications	PCD® Transvene™ System (N = 757)	PCD® Epicardial System (N = 742)
Increased Defibrillation Requirements	1.2%	0.5%
Inappropriate Therapy	-	2.2%
Pace/Sense Related	0.8%	3.5%
Infection Related - Explant	2.9%	2.3%
Lead Related	15.1%	2.8%
Device Related	0.5%	0.9%

Table IM-7: Reported Complications: PCD® Transvene™ System versus PCD® Epicardial System - 2/1/93

PCD® Transvene™ System PCD® Transvene System versus PCD® Epicardial System Reported Observations		
Reported Observations	**PCD® Transvene™ System (N=757)**	**PCD® Epicardial System (N=742)**
Ineffective Therapy	1.1%	1.1%
Inappropriate Therapy	9.6%	13.6%
Pace/Sense Related	9.0%	14.0%
Infection Related	5.3%	2.5%
Lead Related	2.3%	1.2%
Device Related	-	-

Table IM-8: Reported Observations: PCD® Transvene System versus PCD® Epicardial System - 2/1/93

M.5 Survival Analysis Comparison

Despite their excellent clinical performance, epicardial defibrillation lead system have important limitations. The requirement for direct thoracic access contributes significantly to patient morbidity and mortality, patient discomfort and prolonged hospitalization. The availability of reliable nonthoracotomy lead systems should provide positive clinical impact on these issues while not negatively impacting patient survival. Therefore, a comparison of the one year actuarial survival rates for the PCD® Transvene™ and Epicardial System was performed.

Table IM-9 provides a summary of the patient deaths reported in the two patient populations by classification. As a reference, the mean follow-up time for the PCD® Transvene™ System patient population was 11.7 months while for the PCD® Epicardial System it was 16.3 months.

PCD® Transvene™ System Death Classifications PCD® Transvene™ System versus PCD® Epicardial System		
Death Classification	**PCD® Transvene™ System (N = 757)**	**PCD® Epicardial System (N = 742)**
Sudden Cardiac	5	24
Non-Sudden Cardiac	30	54
All Cardiac	35	78
Noncardiac	16	34
TOTAL	51	112

Table IM-9: Death Classifications: PCD® Transvene™ System versus PCD® Epicardial System - 2/1/93

Table IM-10 provides a comparison of actuarial survival rates between the PCD® Transvene™ and PCD® Epicardial patient populations. The actuarial survival projections include perioperative deaths only in the calculation of survival from death due to all causes (shown in table row labelled **Overall**). Perioperative mortality includes those deaths which occur in the first thirty days post implant of the PCD® System.

PCD® Transvene™ System Comparison of Actuarial Survival PCD® Transvene™ System versus PCD® Epicardial System			(b)(4)
One Year Survival	**PCD® Transvene™ System**	**PCD® Epicardial System**	
Number of Patients	757	742	
Sudden Cardiac	99.5%	98.9%	
Non-Sudden Cardiac	96.2%	96.7%	(b)(4)
All Cardiac	95.8%	95.7%	
Noncardiac	98.1%	98.0%	
Overall*	93.3%	88.6%	

* (b)(4) (b)(4)

Table IM-10: Comparison of Actuarial Survival: PCD® Transvene™ System versus PCD Epicardial System - 2/1/93

There was a significant increase in overall survival in the patients receiving a PCD® Transvene System™. As previously noted, the Overall one year actuarial survival includes death from all causes. The overall one year survival for patients receiving the PCD® Transvene™ System was 93.3%. This is significantly improved as compared to the overall one year actuarial survival for the PCD® Epicardial System (88.6%) (b)(4) (b)(4) This improvement in overall survival is primarily due to the marked improvement in perioperative mortality, the PCD® Transvene™ System having a 0.7% (5/757) perioperative mortality versus the a perioperative mortality of 5.3% (39/742) in the PCD® Epicardial System. This improvement in perioperative mortality is primarily due to the elimination of the need for a thoracotomy and its associated morbidity and mortality.

N. PCD® System Performance

N.1 PCD® Device

Devices implanted for the treatment of recurrent ventricular tachyarrhythmias should perform safely and reliably in the indicated patient population. Device longevity, ventricular tachyarrhythmia detection, therapy performance, and analysis of explanted devices were evaluated to assess the performance of the PCD® Device.

Extended longevity of implantable cardioverter defibrillators should decrease the number of device replacements a given patient would experience over their lifetime and decrease unnecessary patient morbidity. Thus, the PCD® Device longevity, which is monitored utilizing battery voltage and charge time obtained via telemetry, was analyzed. The PCD® Device longevity data collected is consistent with the longevity projections.

The combined experience of induced and spontaneous VT/VF episode experience has shown that the PCD® Device VT/VF detection and therapies have performed safely and according to design specifications when required to treat induced and spontaneous VT/VF episodes.

There have been a total of 58 devices explanted. Reasons

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for explant were patient death (23), infection (22), cardiac transplant (9), low battery voltage (1) and PCD Device performance issues (3). The analysis of the device that was explanted due to lower than expected battery voltage indicated that the decreased battery voltage measurement was due to hermetic leakage at the input to one of the integrated circuits and this affected the battery indicator circuit only and did not affect the critical functions of the device. This leads to a voltage drop across a resistor where the voltage measurement is taken. Analysis indicated that the battery was performing to specifications and the hermetic leakage was a random event. Analysis of the other three devices indicated that two were due to random component failure and one due to shorting on Pulse 2 output. Thus, arcing occurred between the conductors inside the hermetically enclosed brazed ring of the high power hybrid. As a result, high voltage was momentarily applied to the low power circuitry, including the low power hybrid. This low power hybrid lost function including the capability to pace and transmit telemetry due to excessive voltage applied. Since this is the only device that exhibited this type of failure in the field and the hybrid manufacturing process has demonstrated that it will screen out infant mortality, this failure was assumed to be a random component failure.

Based on the clinical data collected, the PCD® Device has performed safely and reliably in the indicated patient population.

N.2 Transvene™ Lead Performance

The Transvene™ Lead System consists of a Right Ventricular Lead, a Coronary Sinus/Superior Vena Cava lead, and a Subcutaneous Patch lead. There have been a total of 757 Right Ventricular leads (15 with the SP2100 and 742 with the Model 6884/6966), 796 Coronary Sinus/Superior Vena Cava leads (Model 6881/6963), and 718 Subcutaneous Patch leads (Models 6895/10317/6999) implanted with a cumulative implant duration of 8894.8 months. The reported incidence of conductor coil fracture is 0.5% (4/757).

Based on the clinical data collected, the Transvene™ leads

have performed safely and reliably.

O. Summary

The overall clinical experience with the PCD® Transvene™ System indicates that the system performed according to design and specification. The reported clinical complications and patient deaths are appropriately addressed in the required labelling for the system and the patient selection criteria for implant of the device is appropriate.

The following can be drawn from this analysis of the data collected in this clinical study:

Patient Deaths

- The projected one year survival probabilities for Sudden Cardiac Death, Non-Sudden Cardiac Death, all Cardiac Deaths and Noncardiac Death were found to be 99.5%, 96.2%, 95.8%, and 98.1%, respectively.

  The incorporation of programmable VT/VF detection and therapies has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

- The sudden cardiac death survival of 99.5% at one year is comparable to that of the AICD patient population 98.0%.

- There have been no deaths due to a PCD® Device malfunction.

Complications/Observations

- Complications were reported in 19.4% of the patient population and observations were reported in 23.8% of the patient population.

- The incidence of complications was comparable to that of the market released AICD system in the categories of ineffective VT/VF therapy, pocket infection, and pocket erosion and was lower than the AICD in the category of inappropriate delivery of VT/VF therapy.

Patient Indications

- All of the patients entered into this clinical evaluation met at least one of the primary indications. Sudden cardiac death (SCD) was the primary indication in 37.1% of the patients, recurrent ventricular tachycardia (VT) was the primary indication in 49.8 % of the patients and SCD/VT was the primary indication in 13.1% of the patients.

- The number of patients (60.5%) receiving VT/VF therapy for spontaneous episodes of ventricular arrhythmias supports the conclusion that the patient selection criteria are appropriate and that the PCD® Transvene™ System was implanted in patients who benefit from this therapy.

- The one year sudden cardiac death survival rates for the SCD patient group was 100.0%, for the VT patient group 99.4% and the SCD/VT patient group 98.6%.

VT/VF Detection and Therapy Performance

- The PCD® Transvene™ System properly detects and treats VT as demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VT was 98.4%.

- The PCD® Transvene™ System properly detects and treats VF as demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VF was 98.4%.

- There were no reported patient deaths due to the nondetection of a spontaneous VT or VF episode by the PCD® Transvene™ System.

PCD® Transvene™ System Performance

- The PCD® Transvene™ System components (Model 7216A/7217B and Model 6884/6966, 6881/6963, 6895/6999 Transvene™ leads) have performed according to design and specification and are, therefore, considered safe and effective in the indicated patient population.

P. Clinical Experience Summary Conclusions

The PCD® Transvene™ System is a tiered therapy device which combines features of bradycardia pacing support, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. The incorporation of these features has allowed the physician to titrate the ICD therapy to meet specific patient clinical needs, allowed fewer shocks to be delivered for recurrent ventricular tachycardia because of antitachycardia pacing features, allowed fewer cases of inappropriate therapy delivery due to programmable detection and allowed a sudden cardiac death survival rate identical to the Ventak-P Epicardial System.

The PCD® Transvene™ System, due to the elimination of the need for a thoracotomy, has provided a marked improvement in both the perioperative and overall patient mortality as compared to the PCD® Epicardial System. In addition, due to the decreased perioperative morbidity and mortality, the post implant hospital stay has been decreased to a mean of 7.6 days as opposed to a mean of 10.6 days ($p = 0.001$) for the PCD® Epicardial System.

Medtronic asserts and the PCD® Transvene™ investigators unanimously agree that the findings of the clinical study support the conclusion that the Medtronic Tachyarrhythmia Control System and the Transvene™ Cardioversion and Defibrillation Electrodes are safe and effective in the indicated patient population.

Clinical Updates

Clinical Update

September 18, 1992

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I. Summary of Clinical Experience

I. Summary of Clinical Experience

A. Introduction

The efficacy and safety of implantable cardioverter defibrillator (ICD) therapy for recurrent ventricular tachycardia (VT) and ventricular fibrillation (VF) has been well established. The current market released device provides defibrillation therapy for VF or hemodynamically unstable VT, however, this type of therapy may not be optimal for patients with stable, well tolerated VT that is amenable to antitachycardia pacing. It is necessary to perform a significantly more invasive procedure, a thoracotomy, in order to implant the epicardial leads. Thus, the need to incorporate programmability, multiple detection and therapeutic options, and a less invasive lead system has lead to the development of a tiered therapy device, the PCD™ Transvene™ System.

This report represents a full report of Medtronic's clinical experience with the Medtronic PCD™ Model 7217B Multiprogrammable Tachyarrhythmia Control System with Transvene™ Cardioversion and Defibrillation Electrodes (Reference IDE G870102). The data included in this analysis is all data that was received by Medtronic and entered onto the clinical database as of June 24, 1992.

The PCD™ Model 7217B Multiprogrammable Tachyarrhythmia Control System described in this submission is identical to the system which was recommended for approval by the FDA advisory panel on February 3, 1992, with the addition of Transvene™ leads.

The data analysis is organized in functional rather than chronological categories in order to present a complete picture of each of the PCD™ Device's various functions. The sections included in this summary are:

- Name, Intended Use of System
- Tachyarrhythmia Control System Features
- Indicated Patient Population
- Study Objectives and Protocol Summary
- Overview of Clinical Experience
  - Implant Data
  - Spontaneous VT/VF Episode Experience
  - Overall Success Rate
- Complications and Observations
- Inactive Patients

- Patient Deaths
- Clinical Experience by Primary Indication
- Patients not Meeting Implant Criteria
- Comparison to AICD Clinical Experience
- Comparison to PCD™ Epicardial Clinical Experience
- PCD™ Transvene™ System Performance

This summary provides an overview of the clinical experience which verifies that the PCD™ Transvene™ System is safe and effective in the indicated patient population.

B. Name and Intended Use of the System

The Pacer-Cardioverter-Defibrillator (PCD™) device is an implantable, multiprogrammable, automatic tachyarrhythmia control device. The PCD™ Device is used in conjunction with appropriate lead systems for the treatment of patients with ventricular tachycardia (VT) and/or ventricular fibrillation (VF). The PCD™ Device also provides backup pacing in the VVI mode and noninvasive electrophysiologic (EP) study capabilities.

The PCD™ Device is programmed with the market released Medtronic programmer and a unique MemoryMod™ Cartridge. The PCD™ Device incorporates a two-way telemetry system which receives operational instructions from the programmer and transmits status, electrogram and event information back to the programmer for display and/or printout.

The External Tachyarrhythmia Control Device (ETCD) is an external, multiprogrammable, tachyarrhythmia control device. Its operation is similar to the PCD™ Device except that cardioversion and defibrillation therapies are delivered manually. In addition, it displays measurements of cardioversion and defibrillation therapy parameters. The ETCD is used for making defibrillation threshold measurements during the PCD™ Device implantation procedure.

Components

The Medtronic PCD™ Transvene™ System, which is represented in Figures 1A and 1B, for which market release approval is being requested, consists of the following components:

<u>Implanted Device and Related Programming System</u>
Pacer-Cardioverter-Defibrillator (PCD™) Device
Model 7217B

Programmer
Model 9710 programmer and related accessories (currently market released), plus
Model 9788 MemoryMod™ Software Cartridge
Lead System
Electrode Leads:
Model 6966
Model 6963
Model 6999

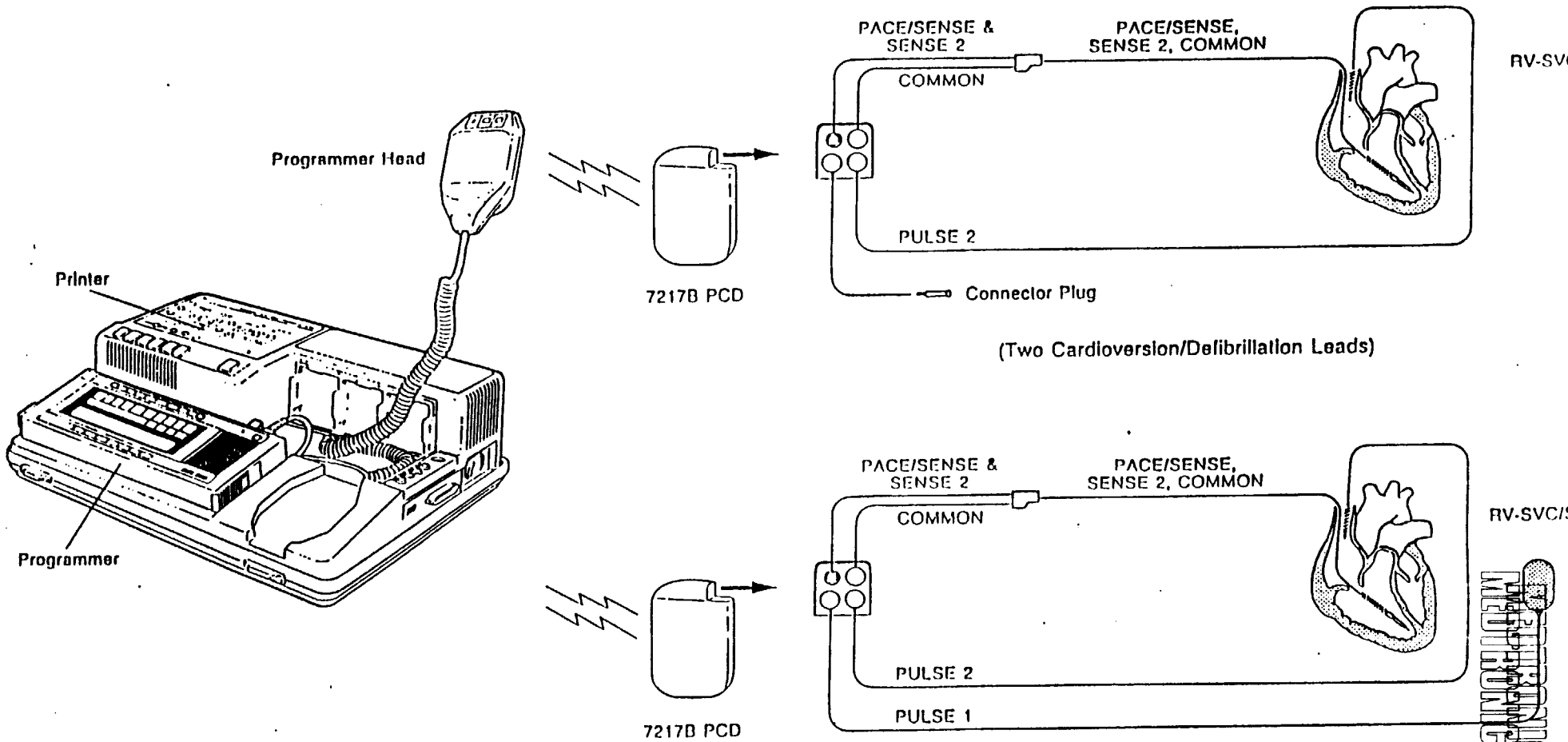
Implant Measurements System
Model 5355 ETCD™ External Tachyarrhythmia Control Device
Model 5418 Patient Cable
Model 5414 Test Load
Model 5417 EGM Cable
Model 5419 Jumper Cable

The physical characteristics of the Model 7217B are summarized in Table IB-1:

PCD™ Model 7217B Physical Characteristics	
Feature	**Model 7217B**
Volume	113 cc
Weight	198 grams
Connector Module	Four connector ports
Power Source	Wilson Greatbatch Model 8830 Lithium Silver Vanadium Oxide
Sensing Configuration	Standard Bipolar
Pacing Configuration	Integrated Bipolar

Table IB-1: Features: Model 7217B - 6/24/92

The Model 7217B PCD™ Device uses the pace/sense leads for sensing, thus providing **standard bipolar** sensing. Pacing is delivered in the integrated bipolar configuration.



7217B PCD Device and Nonthoracotomy Lead System

FIGURE 1A

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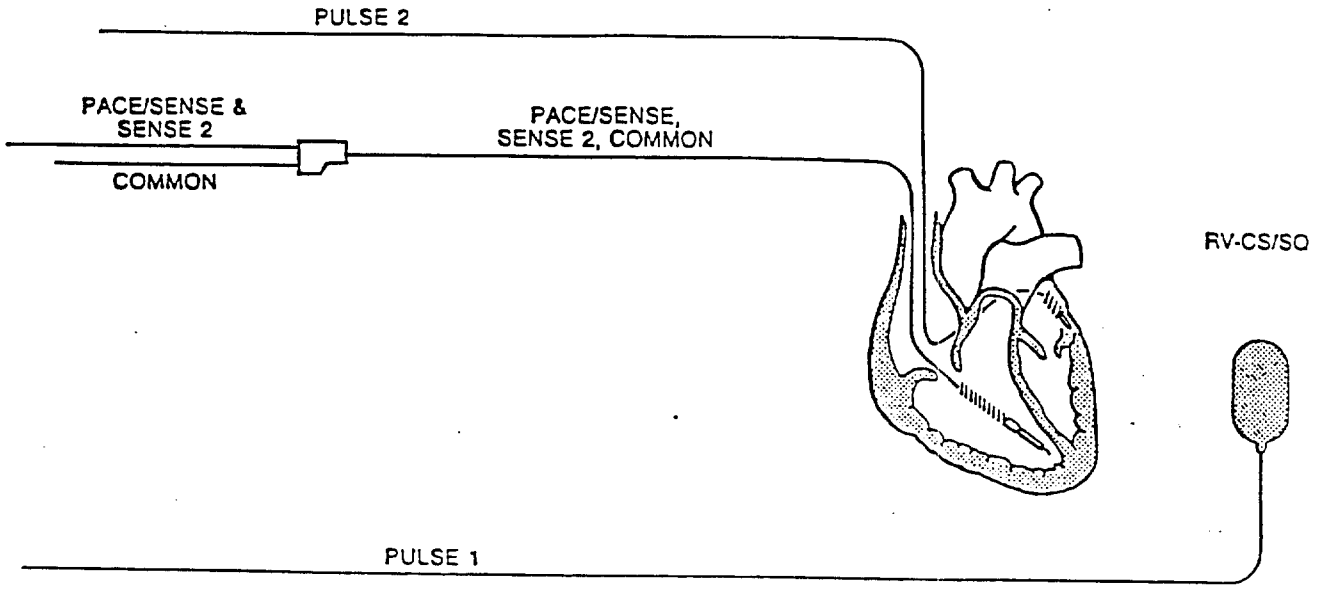
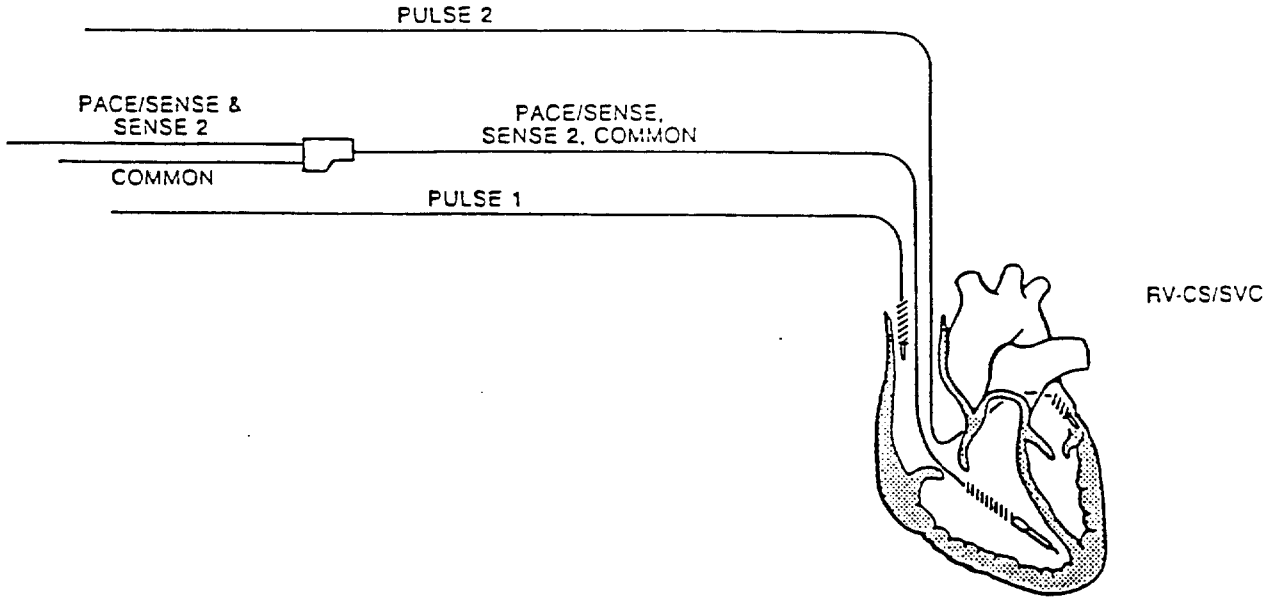
FIGURE 1B



Example of Lead Placement for Simultaneous or Sequential Path (RV-CS/SQ).



Example of Lead Placement for Simultaneous or Sequential Path (RV-CS/SVC).

C. Tachyarrhythmia Control System Features

C.1 PCD™ Device

The PCD™ Device is an implantable device designed to detect episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF), and upon detection, automatically deliver the appropriate therapy or progression of therapies programmed by the physician for each patient. The available therapy types that can be programmed are overdrive pacing, cardioversion, and defibrillation.

The main features of the PCD™ Device include the detection and treatment of recurrent ventricular tachycardia (VT) and/or ventricular fibrillation (VF). The device has two independently programmable detection and therapy algorithms, one for VT and a second for VF. A series of up to four tiered therapies can be delivered after detection of VT and a separately programmed series of up to four therapies after the detection of VF. If a therapy does not convert the arrhythmia, the next programmed therapy is delivered.

Other features of the device include VVI back-up pacing, flexible programming, noninvasive electrophysiology study capabilities, and information reports.

VT Detection and Therapy

The VT detection algorithm includes up to three separately programmable criteria to identify the presence of a tachycardia.

The PCD™ Device employs a feature that automatically adjusts signal detection sensitivity to assure proper detection while minimizing sensing of T-waves following intrinsic cardiac events. This function, **Auto-Adjusting Sensitivity**, is active during any sensing period, including VT and VF detection. It allows use of sensitive settings required for VF detection without oversensing during normal sinus rhythm.

The device utilizes interval length as the primary VT detection criterion; it also provides two additional detection

criteria to add specificity in detecting pathological VT. The two programmable parameters of the Interval Criterion are:

- **Tachycardia Detection Interval (TDI):** Intervals shorter than this value (and longer than FDI are classified as VT intervals.

- **Number of Intervals to Detect (VT NID):** This parameter determines how many consecutive VT intervals must be sensed for therapy to be delivered.

The two additional criteria are:

- **Onset Criterion:** Used to determine when the rate of change in cycle length is sufficiently abrupt to qualify as the onset of paroxysmal VT and not sinus tachycardia.

- **Stability Criterion:** Used to determine when the intervals vary sufficiently on a beat to beat basis to differentiate VT from a rapid ventricular response due to atrial fibrillation.

After a VT episode has fulfilled the programmed detection criteria, the system treats the arrhythmia by delivering one of the three types of VT therapies: Burst, Ramp, or Cardioversion Therapy. Therapy delivery is highly programmable and is "tiered" to allow progression through different therapies selected by the physician to match a patient's particular clinical needs. Up to four separate therapies may be programmed in any combination of the three types to treat each arrhythmia episode. The three therapies are detailed below:

Burst Therapy treats the VT episode by pacing the heart with a "burst" of pulses at a rate greater than that of the VT episode but adapted to the VT rate. The rate adaptive pulse intervals are a programmed percentage of actual tachycardia cycle length. If a pacing sequence is ineffective and the episode is redetected, the pulse interval of the next sequence can be decremented further resulting in a higher pacing rate.

Ramp Therapy decrements each pulse interval within a single sequence of multiple pulses with the first pulse to pulse interval adapted to the VT cycle length. Each subsequent pulse interval in the Ramp sequence is shortened from the preceding interval by a programmed value. If the pacing sequence is ineffective and the VT is redected, Ramp Therapy adds an additional stimulus in each subsequent sequence.

Cardioversion Therapy: delivers synchronized, high-energy pulses in one of the following configurations:

- A **single** pulse delivered over one pathway.
- A **simultaneous** pulse delivered over two pathways.
- Two **sequential** pulses separated by a very short interval delivered over two different pathways.

VF Detection and Therapy

In order to ensure appropriate sensing and detection of VF, the device uses a probabilistic detection algorithm that allows for missed detections due to variations in ventricular depolarization amplitudes and intervals during VF.

Similar to the VT detection algorithm, the PCD™ Device detects VF by monitoring the cardiac cycle length and comparing it to the programmed VF detection criteria, which is called the VF Interval Criterion.

The two programmable parameters of this criterion are:

- **Fibrillation Detection Interval (FDI):** Intervals equal to or shorter than this value are classified as VF intervals.
- **Number of Intervals to Detect (VF NID):** This parameter determines how many VF intervals must be sensed for therapy to be delivered.

After a VF episode has fulfilled the programmed detection

criteria, the system treats the arrhythmia by delivering up to four defibrillation therapies.

Defibrillation Therapy delivers high-energy pulses in one of the following configurations:

- A **single** pulse delivered over one pathway.
- A **simultaneous** pulse delivered over two pathways.
- Two **sequential** pulses separated by a very short interval delivered over two different pathways.

Bradycardia Therapy

The PCD™ Device delivers bradycardia pacing in the VVI mode.

Other Capabilities

The PCD™ Device can be used to conduct noninvasive electrophysiologic studies (EPS) via the programmer with the Model 9788 MemoryMod™ software cartridge. The physician can also manually deliver various therapies via the programmer to manage an induced or spontaneous tachyarrhythmia episode.

The PCD™ Device will provide the physician with information, via the Programmer about its present programmed status and data on its operation. This information may be printed and retained in the patient's file.

A programmer-generated set of symbols, termed Marker Channel, allows real-time visualization of sensing, pacing, detection, and therapy events occurring within the device.

Figure 2 provides an ECG example of an induced episode of VT detected and terminated by antitachycardia pacing and Figure 3 shows an induced episode of VF detected and terminated by a defibrillation therapy delivered by the PCD™ Device.

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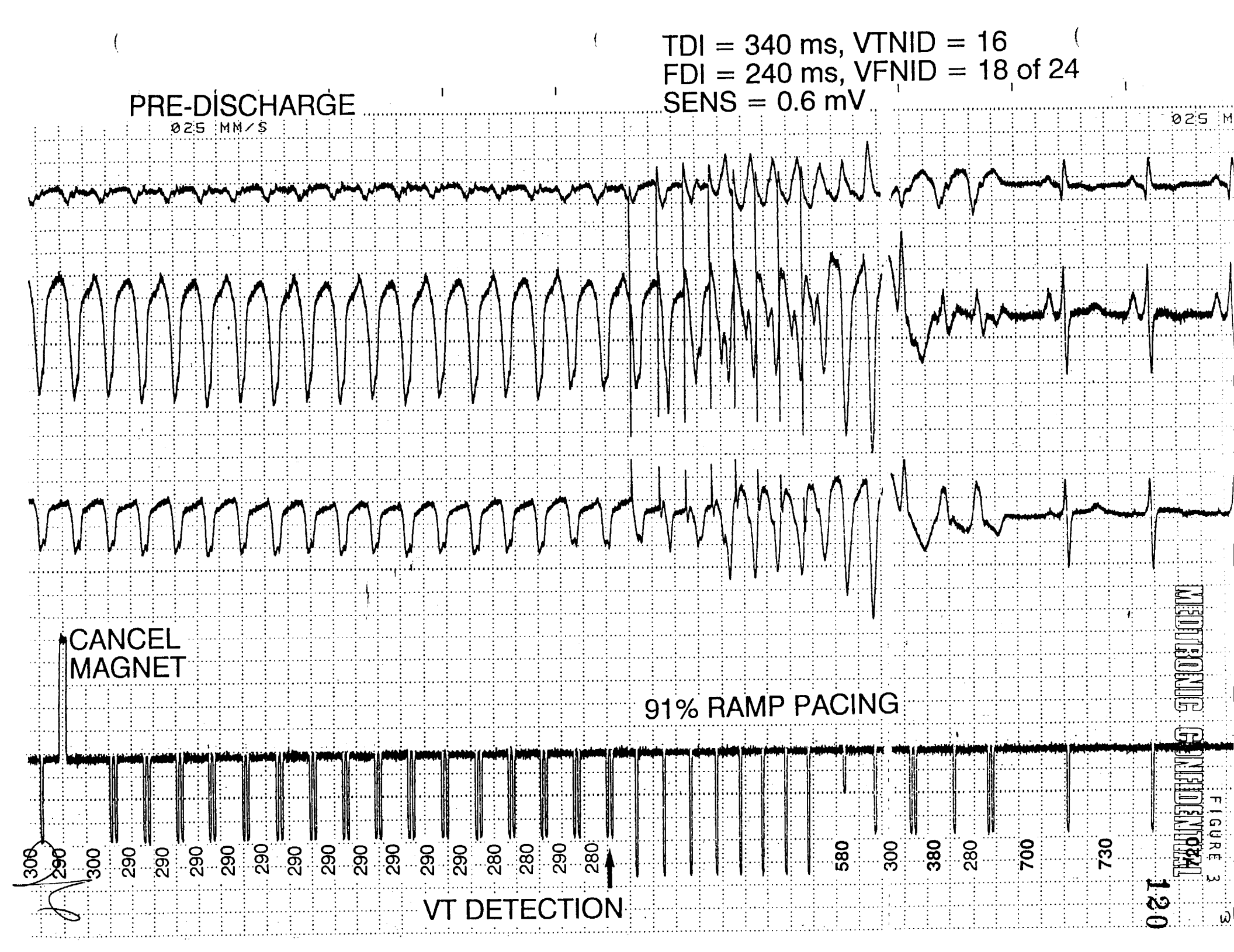
TDI = 340 ms, VTNID = 16
FDI = 240 ms, VFNID = 18 of 24
SENS = 0.6 mV
PRE-DISCHARGE
025 MM/S
025 M
CANCEL
MAGNET
91% RAMP PACING
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VT DETECTION
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FIGURE 3

C.2 Transvene™ Lead Systems

The PCD™ Transvene™ System uses leads which do not require open-chest surgery to implant. Multiple configurations involving either two or three leads may be used to deliver cardioversion and defibrillation pulses. These configurations are based on a tri-polar, Right Ventricular (RV) lead (Model 6966), and either a Coronary Sinus (CS)/Superior Vena Cava (SVC) lead (Model 6963) or a Subcutaneous (SQ) lead (Model 6999) or all three of these leads (e.g. RV/CS/SQ, RV/SVC/SQ or RV/SQ, RV/SVC). The Model 6963 lead can be placed in either the Coronary Sinus/Great Cardiac vein or the Superior Vena Cava (SVC).

A system using two leads delivers cardioversion and defibrillation pulses between two electrodes. A system using three leads delivers cardioversion and defibrillation pulses either simultaneously or sequentially from the anode electrodes (PULSE1 and PULSE2) to the COMMON defibrillation electrode.

In these systems, the retractable, helical tip and ring of the RV lead are used for sensing, thus providing standard, bipolar sensing. The tip electrode is termed PACE/SENSE and the ring electrode is termed SENSE2. Bradycardia pacing takes place between the tip (PACE/SENSE) and the COMMON defibrillation electrode.

To detect VT/VF, the PCD™ device monitors the cardiac cycle length for fulfillment of the programmed VT/VF detection criteria. When the programmed criteria are fulfilled, the PCD™ device detects the VT or VF episode and delivers the first programmed therapy. If this therapy is ineffective and the VT/VF is again detected, the next programmed therapy is delivered. This progression continues until the PCD™ confirms termination or delivers all programmed therapies.

The performance of the Models 6966, 6963, and 6999 are evaluated at the following times:

efficacy in terminating induced episodes of VT or VF; (2) the efficacy of VT and VF therapies in treating spontaneous episodes; (3) the evaluation of pace/sense characteristics of the implanted lead system and (4) the incidence of lead complications or observations such as dislodgement or fracture.

C.3 Model 9788 MemoryMod™ Software Cartridge and 9710 Programmer

Programming and interrogation of the PCD™ Device is performed using the Model 9788 MemoryMod™ software cartridge in conjunction with the Model 9710 programmer. The use of the programmer allows the modification of VT and VF detection, therapy, and bradycardia support therapy parameters. It allows the physician the ability to review and record programmed device settings, perform noninvasive EP procedures and deliver emergency therapy and review other non-programmable information including charge time, battery voltage and event recording. In addition, it allows the user to evaluate the battery status of the PCD™ Device as well as determine if the device has delivered therapy for spontaneous episodes of VT and VF.

C.4 Model 5355 External Tachyarrhythmia Control Device (ETCD)

The Model 5355 ETCD is intended for use in conjunction with an antitachycardia/defibrillation lead system to evaluate VT and VF sensing and therapy efficacy for terminating ventricular tachycardia and ventricular fibrillation prior to the implantation of the PCD™ system.

Testing the lead system for permanent implantation, including VF sensing and defibrillation efficacy, is done using the Model 5355 ETCD™ or Model 2394 ECVD. The 5355 is an external, multiprogrammable, tachyarrhythmia control device, which can automatically deliver bradycardia and tachycardia pacing therapies and can deliver manually initiated cardioversion or defibrillation therapies. Its operation is similar to the PCD™ Device except that cardioversion and defibrillation therapies are delivered manually. In addition, it measures and displays parameters, e.g., pathway impedance of cardioversion and defibrillation therapies. The Model 2394 ECVD is also an external cardioverter defibrillator. However, its functions are limited to only manual cardioversion and defibrillation. The output

pulses are equivalent to the Model 5355 and Model 7217B PCD™. Additionally, the Model 2394 ECVD does not have the capability to deliver either bradycardia or tachycardia pacing therapies.

The Model 5355 ETCD™ is controlled via the Model 9710 programmer and the MemoryMod™ software cartridge, Model 9788. The Model 2394 ECVD is controlled manually.

D. Indicated Patient Population

The PCD™ System is intended to treat patients at risk of sudden cardiac death due to ventricular tachyarrhythmias which have been shown to be reliably terminated, and in the case of VF, terminated at an energy level below the maximum output of the PCD™ Device.

Results provided in this application will support Medtronic's request for market release of the PCD™ System for use in the following patient population:

> Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or
>
> Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

For this patient population the primary benefits from the use of the PCD™ System center on the detection and termination of life-threatening ventricular arrhythmias. The use of pacing therapies for the treatment of ventricular tachycardia reduces patient trauma associated with higher energy cardioversion pulses and extends the longevity of the PCD™ pulse generator.

The PCD™ System allows the titration of therapies for patients with ventricular tachycardia while providing the critical defibrillation backup. Defibrillation backup is important in the event that an episode of VT accelerates to VF whether spontaneously or as a result of a delivered therapy. The capacity to provide programmable extrastimuli pacing allows noninvasive electrophysiologic studies to be performed. The potential benefits from permanent cardiac pacing provide support for chronic and transient episodes of bradycardia. Finally, the benefits of programmability of tachyarrhythmia detection and therapy

parameters, VVI parameters and stored telemetry data on the delivery of therapy may avert the need for reoperation in the event of changing patient conditions or complications.

E. Study Objectives and Protocol Summary

The clinical study was designed to evaluate the operation, safety and effectiveness of the PCD™ System components in detecting and treating episodes of ventricular tachycardia and ventricular fibrillation.

The analysis focuses on data supporting the safety and effectiveness of the PCD™ system, including the implantable pulse generator and associated transvenous lead system and its therapy in this patient population. The analysis includes the clinical experience with the PCD™ system, pace/sense, detection and therapy functions in both the acute and chronic implant settings. In addition, data is provided on clinical observations, clinical complications and deaths in this patient population. The analysis will also provide data demonstrating the safety and effectiveness of the Model 5355 ETCD.

The objectives of the clinical study were:

* to evaluate the sensitivity and specificity of the PCD™ Device with Transvene™ lead systems to detect episodes of VT and VF, and to evaluate the ability of the system to appropriately discriminate between VT/VF and other potentially nonmalignant rhythms;

* to monitor the efficacy of the PCD™ Device with Transvene™ lead systems in treating VT and VF episodes. VT/VF therapy efficacy is determined as the ratio of successful termination of episodes detected to the total number of episodes detected in which one or more therapies were delivered (Successful Termination/Number of Detected Episodes with Therapy Delivered). Investigators were free to choose from any of the available leads and VT/VF therapies that the efficacy was first evaluated acutely;

* to evaluate the performance of the Model 6966, 6963 and 6999 Transvene™ leads;

* to monitor the patient selection criteria and patient management methods required by the PCD™ Device and Transvene™ leads.

* to evaluate the safety and effectiveness of the Model 5355 ETCD™ when used during the implant procedure. Specifically, tachyarrhythmia episode induction, detection, termination and ease of use were analyzed.

- to evaluate the safety and performance of the Model 9710 Programmer and the 9788 MemoryMod™ Software Cartridges in programming sensing and therapy parameters and the appropriate delivery of noninvasive electrophysiologic stimulation.

Clinical data was collected at the following study points to support the safety and efficacy of the PCD™ System:

Pre-implant Patient Assessment
Lead System Testing at Implant
Implantable Pulse Generator Testing at Implant
Pre-hospital Discharge Testing
Follow-up Evaluation 1 and 3 months post implant then at 3 month intervals

Specific data was collected at each of these points to meet the objectives of the clinical study. This included:

Pre-implant Patient Assessment - extensive pre-implant testing was performed to ensure that the general patient selection criteria were met. This testing included at least an electrophysiologic evaluation, measurement of ejection fraction, and assessment of the patient's New York Heart Association (NYHA) classification of their cardiovascular status. Depending on the patient history, cardiac catheterization and exercise testing were also conducted.

Lead System Testing - implant evaluation was performed to verify that one of the specified lead systems was capable of properly detecting and treating episodes of ventricular fibrillation and, when appropriate, ventricular tachycardia. The Model 5355 ETCD™ or the 2394 External Cardioverter Defibrillator (ECVD) was used for testing.

This testing included pacing and sensing thresholds during sinus rhythm, evaluation of VF electrogram amplitudes and defibrillation efficacy evaluation. The PCD™ Device implant criteria were:

1) successful VF termination at least 3 times in 4 attempts with an output energy of 18 Joules or less and

2) a 2:1 VF sensing safety margin.

Implanted Pulse Generator Testing - this implant evaluation was performed to demonstrate proper detection and termination of ventricular fibrillation by the implanted PCD™ System with VF Therapy #1 programmed to 34 Joules in addition to pacing and sensing thresholds.

Pre-hospital Discharge Testing - testing performed at the pre-hospital discharge included proper detection and termination of induced ventricular tachycardia. Final sensing and therapy parameters are programmed at the PHD.

Follow-up Evaluation - regular testing was performed to evaluate the chronic stability of detection and therapy parameters of the PCD™ System. This testing

included an assessment of the relative stability of the energy required to defibrillate a patient and efficacy and acceleration rate assessment of the VT therapies. The number of spontaneous VT/VF episodes treated by the PCD™ Device were evaluated. Complication rates and patient mortality data were also evaluated.

Patients were evaluated prior to hospital discharge and/or one (1) month post implant, three months post-implant and then at intervals of every three months. In some cases additional testing was performed at physician discretion to evaluate spontaneous events and/or potential clinical complications.

Medtronic collected all clinical data on the PCD™ System and its components under the clinical protocol outlined in the Investigational Plan. A common protocol was used on all study patients on a worldwide basis.

Clinical data presented in this summary includes experience with the Model 7216A and 7217B PCD™ Devices with the Model 6966, 6963 and 6999 Transvene™ Leads. This report presents the clinical evaluation of the safety and efficacy of the PCD™ Device with Transvene™ Leads implanted in 757 patients of which 329 have implant durations equal to or greater than six months.

International centers were subject to the appropriate requirements (e.g., the Declaration of Helsinki) in order that the data met the statutory requirements of the FDA. All clinical data, U.S. and International, obtained with the PCD™ System with Transvene™ Leads is included in this report.

F. Overview of Clinical Experience

This report covers a total of 762 implants in 757 patients of the PCD™ Device with the Transvene™ Defibrillation Lead System. A total of 78 investigative centers participated in the clinical trial with 35 centers in the U.S. and 43 Internationally. The first implant occurred internationally on October 20, 1989, and the first implant in the U.S. occurred on October 16, 1990. Table IF-1 shows the distribution of Model 7216A and Model 7217B patients between U.S. and International investigators.

PCD™ Transvene™ System Implant Distribution			
	Total	U.S.	Int'l
7216A	18 (2.4%)	3 (0.7%)	15 (4.8%)
7217B	744 (97.6%)	444 (99.3%)	300 (95.2%)

Table IF-1: PCD™ Transvene™ System - Implant Distributions - 6/24/92

The mean documented implant duration for this patient population is 5.6 months and ranged from implant to 28.6 months. The cumulative implant duration is 4246.4 months. There are 329 patients with implant durations equal to or greater than six months.

The patient population enrolled in the clinical trial was predominately male (80.6%) with a mean age of 59.4 years. In half of the patients (49.8%), the primary indication for implant was recurrent, sustained ventricular tachycardia without an episode of sudden cardiac death. Sudden Cardiac Death was the primary indication for 37.1% of the patients and SCD in combination with recurrent, sustained VT was the primary indication in 13.1%. Coronary artery disease was the primary heart disease in 74.1% of the patient population with a mean reported ejection fraction of 35.6% Table IF-2 provides a data summary on these patients. Also included is the data summary of the patients with 6 months of follow-up.

PCD™ Transvene™ System Data Summary		
	All Patients (3 Electrode Systems)	Patients with 6 months of Follow-up
Number of Patients	757	329
Device Months Follow-up	4246.4	3367.8
Mean Follow-up Time	5.6 mo	10.2 mo
Maximum Follow-up Time	28.6 mo	28.6 mo
Number, % Male **Number, % Female**	610 80.6% 147 19.4%	264 80.2% 65 19.8%
Mean Age	59.4 yrs	58.0 yrs
Primary Indication: **SCD** **VT** **SCD/VT**	 281 37.1% 377 49.8% 99 13.1%	 130 39.5% 152 46.2% 47 14.3%
Coronary Artery Disease	561 74.1%	228 69.3%
Mean Ejection Fraction	688 35.6%	301 38.0%
Defibrillation Pathway: **Sequential** **Simultaneous** **Single**	 574 75.3% 178 23.4% 10 1.3%	 247 74.6% 77 23.3% 7 2.1%
Mean LED	16.0J (N=702)	15.4J (N=306)
Mean DFT	14.8J (N=316)	13.9J (N=155)
Spontaneous VT: **Number of Patients** **Number of Episodes** **% Success**	 226 5430 98.7%	 130 3752 99.0%
Spontaneous VF: **Number of Patients** **Number of Episodes** **% Success**	 198 973 99.1%	 120 667 98.7%
One Year SCD Survival	99.8%	100.0%

Table IF-2: PCD™ System Data Summary - All Transvene™ Patients versus Transvene™ Patients with 6 mo Follow-up - 6/24/92

F.1 Implant Data

Implants of the PCD™ Device may use two or three Transvene™ leads. The physician has the flexibility to use whichever lead system best meets the patient's needs.

Table IF-3 illustrates the lowest energy of defibrillation (LED) and defibrillation threshold (DFT) for the implanted lead systems. The implant criteria for the PCD™ Device was 3 of 4 episodes of VF successfully terminated at 18 Joules or less with a given lead configuration. Some patients did not have a LED at implant. The LED is only identified if the investigator reported the induced rhythm as VF. Conversion of VT or V Flutter (as defined by the physician) to sinus rhythm was not included in the determination of the LED. In addition, it is not a protocol requirement to obtain a DFT at implant. However, recommendations have been provided to those institutions that prefer to obtain DFT's during the implant procedure.

PCD™ Transvene™ System Mean LED and DFT Values				
Lead System	Implant Frequency	Mean LED	Implant Frequency	Mean DFT
All Systems	702	16.0J	316	14.8J
RV-SVC-SQ	455	16.7J	187	15.8J
RV-CS-SQ	210	14.6J	110	12.8J
RV-CS-SVC	37	15.2J	19	16.0J

Table IF-3: PCD™ Transvene™ System - LED and DFT Values - 6/24/92

The mean implant Lowest Energy of Defibrillation (LED) for all lead systems was 16.0J and mean implant Defibrillation threshold (DFT) for all lead systems was 14.8J. As the mean DFT's and LED's indicate, VF was reliably terminated at an energy value below the maximum output (34 Joules) of the PCD™ Device.

F.2 Spontaneous VT and VF Episode Experience

A total of 311 patients (41.1%) have experienced a spontaneous ventricular tachyarrhythmia episode that has

been detected and treated by the PCD™ Device. One hundred and thirteen patients (14.9%) experienced VT only, 85 patients (11.2%) experienced VF only and 113 patients (14.9%) experienced both an episode of VT and VF.

There have been a total of 6403 episodes of spontaneous VT or VF as detected by the PCD™. The overall PCD™ Device success rate in terminating spontaneous VT/VF episodes as detected by the PCD™ is presented in Table IF-4.

PCD™ Transvene™ System Success Rate in Terminating Spontaneous VT/VF Episodes			
	Number of Episodes Successful	Total Number of Episodes	Efficacy Rate
VT	5362	5430	98.7%
VF	964	973	99.1%
Total	6326	6403	98.8%

Table IF-4: PCD™ Transvene™ System - Success Rate for Spontaneous VT/VF Episodes - 6/24/92

F.2.1 Spontaneous VT

For the purposes of this clinical trial, spontaneous VT was defined as those episodes that satisfied the programmed VT detection criteria. Specifically, all programmed VT detection criteria must be fulfilled to detect a VT episode. Successful termination of the episode was defined as satisfying the VT episode termination criteria.

To date, 5430 spontaneous episodes of VT have been detected by the PCD™ Device in 226 patients. The mean number of episodes per patient with VT was 24 and ranged from 1 - 413 episodes.

Most spontaneous VT episodes (91.0%) were successfully treated with VT Therapy #1 and 98.7% were successfully treated with one of the four programmable VT therapies.

Of the 5362 successfully terminated spontaneous VT episodes, 92.4% were treated with one of the programmed antitachycardia pacing therapies incorporated in the PCD™ Transvene™ System. The clinical benefit of tiered therapy is the reduction of delivery of high energy shocks for the treatment of stable recurrent ventricular tachycardia. This greatly enhances the patient acceptance of ICD therapy since antitachycardia pacing is usually not perceived by the patient.

Thirty patients experienced 68 (1.3%) episodes in which the PCD™ Device was ineffective in terminating a spontaneous episode of VT despite delivery of all four programmed VT therapies. Twenty five patients experienced 45 (0.8%) episodes that were due to sinus tachycardia or atrial fibrillation/flutter (SVT) with a rapid ventricular response that had been detected as VT. These episodes were resolved with either modification of programmed parameters or of antiarrhythmic drug therapy. It should be noted that the PCD™ Device responded appropriately based on the programmed detection parameters.

The remaining 23 episodes occurred in five patients in which the programmed VT therapies were ineffective in terminating a spontaneous VT episode. **No patient deaths occurred as a result of ineffective VT therapy.** The patient's antiarrhythmic drug regimen was modified to improve efficacy.

F.2.2 Spontaneous VF

For purposes of this clinical trial, VF is defined as those episodes that satisfy the programmed VF detection criteria. Specifically, all programmed VF detection criteria must be fulfilled to detect a VF episode. Successful termination of the episode is defined as satisfying the VF detection criterion for episode termination.

To date, 973 spontaneous episodes of VF have been detected by the PCD™ Device in 198 patients. The mean number of episodes per patient was 4.9 and ranged from 1 - 77 episodes. A review of the chart per investigator for this patient that experienced the 77 episodes of VF

revealed that 75 were most likely due to atrial fibrillation. VF detection parameters were modified in this patient.

Most (87.3%) spontaneous VF episodes were successfully treated with VF Therapy #1 and 99.1% were successfully treated with one of the four programmable VF therapies.

Five patients experienced 9 episodes (0.9%) in which the PCD™ Device was ineffective in terminating a spontaneous episode of VF despite delivery of all four programmed VF therapies. Four patients had eight reported ineffective VF spontaneous episodes that were due to sinus tachycardia or atrial fibrillation with rapid ventricular response rather than VF. Reprogramming and pharmacologic intervention resolved these problems. The other patient (b)(6) required external defibrillation to convert the VF episode. This patient's antiarrhythmic drug regimen was modified to improve defibrillation efficacy. All of these patients have subsequently done well with no more reported ineffective VF therapies.

F.3 Overall Success Rate

Of the 757 patients who received a PCD™ Transvene™ System, 443 patients (58.5% - 443/757) have either experienced a spontaneous VT/VF episode or had VT/VF induced during a post implant electrophysiology study. The performance of the PCD™ Transvene™ System therapies have been thoroughly evaluated and been shown to be effective in detecting and terminating episodes of ventricular tachyarrhythmia.

There have been no reports of a patient death due to the PCD™ Transvene™ System not detecting a spontaneous episode of VT or VF.

The overall success rate of the PCD™ Transvene™ System in terminating spontaneous episodes of either VT or VF was 98.8% with a VT success rate of 98.7% and VF success rate of 99.1%. The incidence of unsuccessful termination of an apparent "true" episode of ventricular tachycardia despite delivery of all four therapies was 0.4% (23/5430). The incidence of unsuccessful termination of an apparent "true" episode of ventricular fibrillation despite delivery of

all four therapies was 0.1% (1/973).

The evaluation of spontaneous episode experience indicates that the PCD™ Transvene™ System's VT and VF detection and therapy functions have performed safely and effectively in the indicated patient population.

G. Complications and Observations

The use of a multiprogrammable implantable cardioverter defibrillator (ICD) device allows the physician to resolve most relevant medical events by noninvasively changing programmed parameters thus, avoiding invasive procedures. However, there will continue to be certain relevant medical events which will require invasive procedures for resolution.

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following definitions:

COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

As of June 24, 1992, there have been a total of 138 complications identified in 138 patients and 157 observations identified in 157 patients in the PCD™ Transvene™ System patient population. Thus, 18.2% (138/757) of the patients have experienced a clinical event which was defined as a complication and 20.7% (157/757) of the patients have experienced a clinical event which was defined as an observation. Table IG-1 summarizes how these events were reported with U.S versus International.

PCD™ Transvene™ System Reported Complications/Observations U.S versus International		
	Complications	Observations
	# of Patients	# of Patients
U.S.	77	68
International	61	89
Total	138	157

Table IG-1: PCD™ Transvene™ System Complications/Observations U.S. versus International - 6/24/92

Table IG-2 summarizes the reported PCD™ Transvene™ System complications and observations by category. The category "Ineffective Therapies" included patients in whom increased defibrillation requirements were documented; "Inappropriate Therapies" includes patients in whom VT/VF therapies were delivered for nonpathological rhythms; "Pacing or Pace/Sense Related" includes patients in whom undersensing, oversensing or loss of capture was documented; "Infection Related" includes reports of pocket infection, seroma, and hematoma was documented; and "Device Related" includes patients in whom the device was explanted for reasons other than patient death, infection, or transplant.

The reported complications and observations are recognized clinical events that may occur with **any** of the current ICD devices. These complications and observations are discussed in the PCD™ device and Transvene™ manual. **None of the reported complications or observations have resulted in a patient death.**

PCD™ Transvene™ System Reported Complications/Observations By Category		
Category	**Complications**	**Observations**
Ineffective Therapies	0.8%	0.5%
Inappropriate Therapies	-	8.2%
Pacing or Pace/Sense Related	0.8%	4.1%
Infection Related - Device Explanted	2.0%	-
Infection Related - Device not Explanted	1.5	4.9%
Device Related	0.5%	-

Table IG-2: PCD™ Transvene™System - Complications/Observations - 6/24/92

The "Lead Related" complications/observations include perforation, lead fracture, subcutaneous patch crinkling, and lead dislodgement. Table IG-3 contains a summary of the reported "Lead Related" complications/observations.

PCD™ Transvene™ System Lead Related Complications	
Category	**Complication**
Right Ventricular Perforation	5 (0.7%)
Subclavian Vein Thrombosis	1 (0.1%)
Lead Fracture	4 (0.5%)
Subcutaneous Patch Crinkling	7 (0.9%)
Lead Dislodgement	33 (4.4%)

Table IG-3: PCD™ Transvene™ System - Lead Related Complications - 6/24/92

There have been a total of 33 lead dislodgements reported in 33 patients at greater than 30 days. None of the lead dislodgements resulted in an ineffective therapy for a spontaneous VT of VF episode or patient death. Lead dislodgements were documented by fluoroscopic examination during electrophysiologic evaluation, chest x-ray obtained during routine follow-up, or during

pacing/sensing threshold evaluation during routine follow-up. In all 33 cases, reoperation was required to reposition the lead and reestablish an effective defibrillation lead system.

Lead dislodgements are not specific to the PCD™ Transvene™ System and have been reported with dual chamber pacemakers and the current market released implantable cardioverter defibrillator (ICD) system. The early history of dual chamber pacemakers witnessed a high lead dislodgement rate of at least 20% (Smyth, PND, et al. Permanent pervenous atrial sensing and pacing with a new J-shaped lead. J Thoracic Cardiovascular Surgery. 1976;72:565-570). Winkle, et al reported that the incidence of dislodgement of the superior vena cava spring leads with the current market release ICD system to be 6.3%. (Winkle, et al. Automatic Implantable Cardioverter-Defibrillator: Efficacy, Complications, and Survival in Patients with Malignant Ventricular Arrhythmias. JACC. June 1988; Vol.11, No.6:1278-86).

H. Inactive Patients

There are a total of 34 patients who had received a PCD™ System and are no longer active in the study as of 6/24/92. Table IH-1 shows the distribution of inactive patients by reason for no longer being active in the PCD™ Transvene™ System clinical study.

PCD™ Transvene™ System Inactive Patients	
Inactive Patients	**All Patients**
Patient Deaths	22
Infection (Explant)	11
Heart Transplant	5
Total	38

Table IH-1: Inactive Patients - 6/24/92

I. Patient Deaths

The positive impact of implantable cardioverter defibrillator (ICD) therapy on sudden cardiac death mortality has been well documented in the medical literature. The use of device therapy for the treatment of recurrent ventricular arrhythmias has become

an accepted and important clinical tool. An analysis of the sudden cardiac death survival in the PCD™ Transvene™ System patient population was performed.

For purposes of the clinical study, each of the patient deaths was categorized using the following definitions:

Non-Cardiac:	Deaths that occurred where the primary cause of death was determined to be non cardiac in nature, e.g. stroke, cancer, etc.
Cardiac:	Deaths that occurred where the primary cause of death was determined to be cardiac in nature.
Non-Sudden:	Deaths that occur greater than one hour after the onset of symptoms.
Sudden:	Deaths that occur within one hour of the onset of symptoms or where the death is unwitnessed. Sudden cardiac deaths were also categorized as being **Witnessed** or **Unwitnessed.**
Perioperative:	Deaths that occur within thirty days of implant.
System Related:	A death which results from a malfunction (operation not according to design specification) of a PCD™ System component, or as a result of a device induced arrhythmia, or an interaction between a PCD™ System component and the patient.
Procedure Related:	A death which occurs as a result of a procedure required to implant, follow or test a PCD™ System.

All deaths and significant complications have been and will continue to be reviewed by a committee comprised of PCD™ Transvene™ System investigators and other physicians. Two committees (Clinical Event Review Committees) have been formed, one to review North American deaths and complications, and the other to review European clinical events. The primary purpose of these reviews was to determine whether the PCD™ System was related to the deaths or significant complications that have occurred and, if so, what changes may be required to prevent such events in the future.

There have been a total of 22 patient deaths reported in the PCD™ Transvene™ System patient population. Table II-1 summarizes how these patient deaths have been classified.

PCD™ Transvene™ System Summary of Death Classifications (n = 757)	
Classifications	**Number of Deaths**
Sudden Cardiac	3
Non-Sudden Cardiac	15
Noncardiac	4
TOTAL	22

Table II-1: PCD™ Transvene™ System - Summary of Death Classifications - 6/24/92

None of the patient deaths were attributed to a malfunction of the PCD™ Transvene™ System.

Actuarial survival analysis on the PCD™ Transvene™ System was done on all patients who were either evaluated for implantation or in whom the device was implanted. Thus, the analysis is done from the perspective of **intention to treat.** Those patients in whom the PCD™ Device was OFF at the time of death or in whom no device was implanted **are** included in the survival analysis. Those patients that were screened for a PCD™ Transvene™ System but failed to receive a Transvene™ system are not included in this analysis.

Projected one year survival calculations for the various death classifications are provided in Table II-2. **The actuarial projections include perioperative deaths only in the calculation of one year survival from death due to all causes (shown in the row labelled Overall).** The perioperative death rate defined as deaths which occurred within thirty days of implant was 0.7% (5/757) which is considerably less than the perioperative mortality for the PCD™ System with Epicardial leads (4.7% - 35/742). Included in this table are the projected one year survival calculations for patients who ultimately received a PCD™ Transvene™ System (n = 757) and all patients that were screened for a PCD™ Transvene™

System (n = 854) regardless of implant outcome.

PCD™ Transvene™ System One Year Actuarial Survival		
	Received PCD™ Transvene™ System	Screened for a PCD™ Transvene™ System
Sudden Cardiac Death	99.8%	99.8%
Non-Sudden Cardiac	96.8%	97.1%
All Cardiac	96.6%	97.0%
Noncardiac	99.4%	99.4%
Perioperative	0.7%	1.5%
Overall	95.3%	94.8%

Table II-2: PCD™ Transvene™ System - One Year Actuarial Survival - 6/24/92

The positive impact of the PCD™ Transvene™ System on patient mortality is clearly obvious from this analysis. The sudden cardiac death survival rate in this patient group is 99.8%, both in the patient group that received a Transvene™ System and those who were screened for a Transvene™ System. This is marked improvement when compared with the reported survival of similar patient groups treated with drug therapy alone of between 34% and 73% at one year.

J. Clinical Experience By Primary Indication

Medtronic is requesting approval for use of the PCD™ Transvene™ System in the following patient population:

* Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or

* Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

Sudden cardiac death without recurrent VT (**SCD**) was the indication for implant in 37.1% of the patients, recurrent

ventricular tachycardia without an episode of sudden cardiac death (**VT**) was the indication for implant in 49.8% of the patients, and sudden cardiac death and recurrent VT (**SCD/VT**) was the indication for implant in 13.1% of the patients.

The performance of the PCD™ Transvene™ System in these three groups are summarized in Table IJ.1.

In all three patient groups, coronary artery disease was the predominant heart disease and the patients exhibited moderate left ventricular dysfunction as demonstrated by mean ejection fractions of less than 40%. The mean LED at the time of implant was similar among the patient groups as was the mean DFT.

The overall efficacy in terminating spontaneous VT/VF episodes in the SCD patient group was 99.1%, in the VT patient group 98.7%, and in the SCD/VT group 99.0%. Thus, independent of the indication for implant, the PCD™ Transvene™ System was highly effective in terminating spontaneous episodes of VT/VF.

The one year sudden cardiac death survival rates for all groups was greater than 99.7%

This analysis indicates that the PCD™ Transvene™ System has performed safely and effectively in the indicated patient groups and should be approved for use in the indicated patient population.

PCD™ Transvene™ System Data Summary by Primary Indication				
	SCD	VT	SCD/VT	All Patients
# of Patients	281 (37.1%)	377 (49.8%)	99 (13.1%)	757
Number, % Male Number, % Female	212 75.4% 69 24.6%	309 82.0% 68 18.0%	89 89.9% 10 10.1%	610 80.6% 147 19.4%
Mean Age	56.8 yrs	61.2 yrs	60.0 yrs	59.4 yrs
Coronary Artery Disease	191 68.0%	292 77.5%	78 78.8%	229 72.2%
Mean Ejection Fraction	39.1% (N=259)	33.7% (N=339)	32.5% (N=90)	35.6% (N=688)
Defibrillation Pathway: Sequential Simultaneous Single	 201 71.5% 74 26.3% 6 2.2%	 295 77.6% 82 21.6% 3 0.8%	 76 76.8% 22 22.2% 1 1.0%	 574 75.3% 178 23.4% 10 1.3%
Mean LED	15.3J (N=264)	16.2J (N=351)	17.3J (N=87)	16.0J (N=702)
Mean DFT	14.0J (N=117)	15.5J (N=155)	13.9J (N=44)	14.8J (N=316)
Spontaneous VT: # of Patients # of Episodes % Success	 39 765 99.6%	 144 3735 98.6%	 43 930 98.9%	 226 5430 98.7%
Spontaneous VF: # of Patients # of Episodes % Success	 58 296 97.6%	 109 421 99.8%	 31 256 99.6%	 198 973 99.1%
1 Year SCD Survival	100.0%	99.7%	100.0%	99.8%

Table IJ-1: PCD™ Transvene™ System Data Summary by Primary Indication - 6/24/92

K. Patients Not Meeting Implant Criteria

K.1 Overview

The PCD™ Transvene™ System offers a simpler and safer implantation technique for an implantable cardioverter defibrillator system. In addition, the PCD™ Transvene™ System decreases the potential perioperative and long term mortality associated with current epicardial system implantation approaches.

There is a class of patients who cannot tolerate the thoracotomy required for the utilization of the epicardial patch lead defibrillation lead system and who are at high risk of sudden cardiac death. Because of the surgical risks and postsurgical complications associated with the implant of an epicardial lead system, implantation in the following patient groups may not be desirable or possible:

(1) patients in whom there is no indication for concomitant cardiovascular surgery at the time of ICD implant;

(2) patients with severe pulmonary disease who can not tolerate prolonged anesthesia or an open chest procedure;

(3) patients with severe congestive heart failure (ejection fraction < 40%) who are at increased risk for perioperative mortality following a thoracotomy procedure;

(4) patients who may eventually require open chest procedures for treatment of their coronary artery disease or cardiac transplant.

For these patients, a transvenous ICD System is the only therapy available. The PCD™ Transvene™ System simplifies and greatly reduces the risk associated with lead introduction, making therapy available to these patient groups. Because there is no need to open the chest of these patients, more options for future therapy remain available; e.g. CABG is associated with increased morbidity and mortality if there has been prior open chest surgery.

However, it is expected that nonthoracotomy lead systems will have higher mean implant defibrillation thresholds as compared to traditional epicardial lead systems. In an epicardial lead system, the lead system has a larger

electrode surface area theoretically decreasing defibrillation requirements.

The smaller electrode surface areas of the PCD™ Transvene™ System defibrillation leads might reduce the proportion of patients in whom the implant criteria could be met. Not meeting the implant criteria may reduce the chronic effectiveness of the lead system. Recent studies indicated that 70% of patients evaluated may be candidates for a nonthoracotomy defibrillation lead system (Wilber, D, et al. Clinical Advances in Nonepicardial Implantable Defibrillator Lead Systems. The Journal of Invasive Cardiology. Vol.3, No.6,November/December 1991).

For purposes of the PCD™ Transvene™ System, the implant criteria was defined as successful VF termination at least 3 times in 4 attempts with the final lead configuration with an output energy of 18 Joules or less. The determination of a defibrillation threshold was not required.

A defibrillation threshold (**DFT**) was defined as the energy at the lowest successful defibrillation attempt, provided the patient had a failure below the lowest success or a success at $\leq$ 5J. The lowest energy of defibrillation (**LED**) was defined as the lowest programmed energy that successfully defibrillated the patient. In both cases, conversion of ventricular tachycardia or ventricular flutter to sinus rhythm was **not** included in the determination of the DFT or LED.

A total of 854 patients had an evaluation of a PCD™ Transvene™ System and are divided into the following groups - (1) Patients who received a PCD™ Transvene™ System; and (2) Patients screened for a PCD™ Transvene™ System and received a PCD™ Epicardial System. Figure 4 provides an overview of the outcome of these patients.

PCD™ TRANSVENE™ SYSTEM IMPLANT EVALUATION

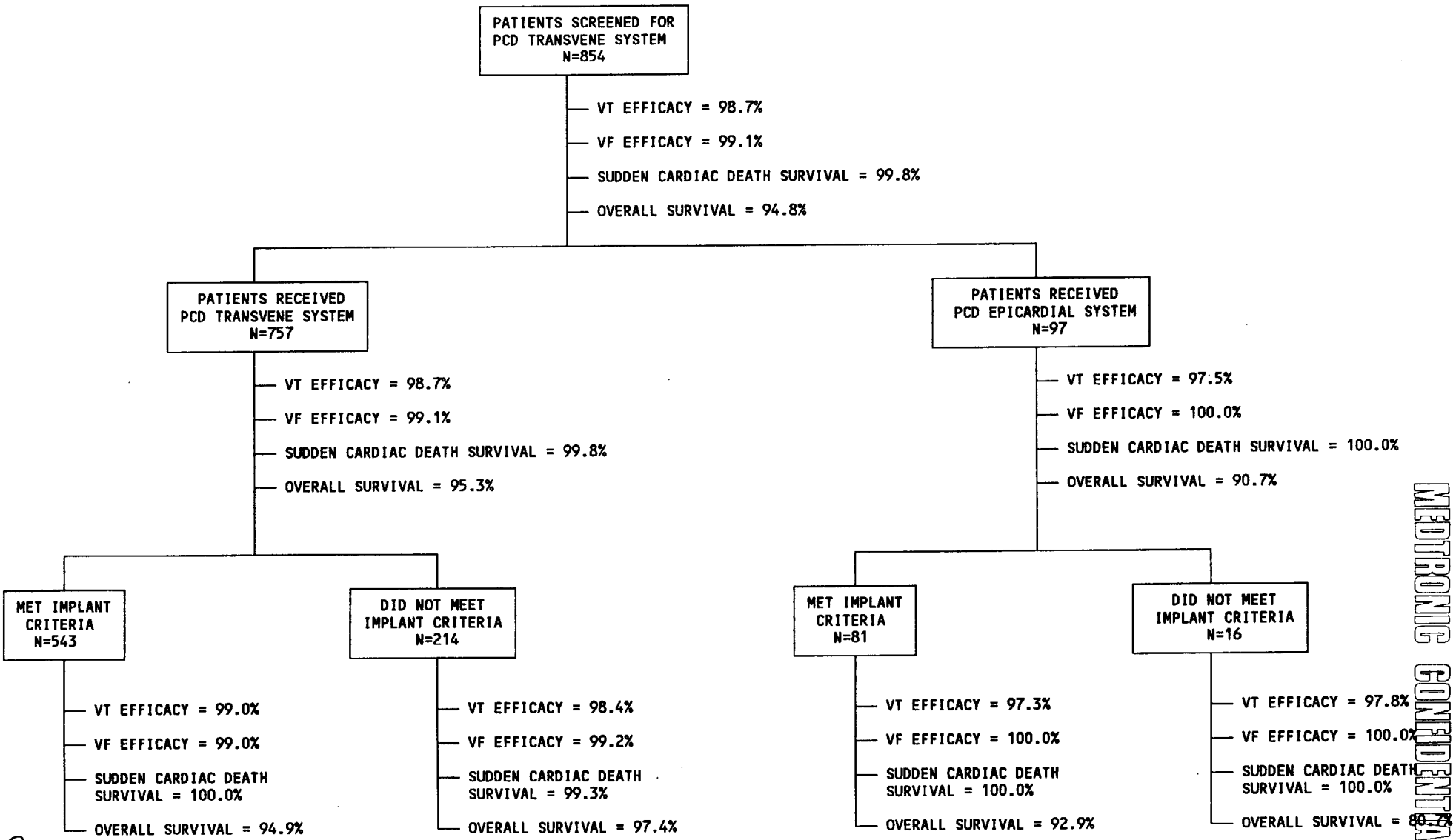

Figure IX.1: Patients Screened for a Transvene™ System

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As can be seen, 88.6% (757/854) of the patients who were screened for a PCD™ Transvene™ System ultimately received the system. Of these 757 patients, 71.7% (543 patients) met the recommended defibrillation implant criteria which compares favorably with the predicted success rates published in the literature (Wilber et al). However, 28.3% (214/757) of the patients did not meet the recommended defibrillation efficacy implant criteria and still received the PCD™ Transvene™ System. It should be noted that 97.4% of the patients (737/757) received the PCD™ Transvene™ System with at least a 10 Joule defibrillation safety margin between the lowest energy of success (24J) and the maximum output (34J) of the PCD™ Device.

The investigators utilized this 10 Joule safety margin as a benchmark based on the clinical experience discussed in the article, Troup P., et al. The Implanted Defibrillator: Relation of Defibrillating Lead Configuration and Clinical Variables to Defibrillation Threshold. Journal of American College of Cardiology 1985; 6:1315-1321. Finally, and perhaps most importantly, the investigators also felt that for these patients the risk associated with not meeting the recommended implant criteria was outweighed by the risk of not implanting an ICD or implanting an epicardial system.

There were twenty patients (2.6%), who received a PCD™ Transvene™ System, whose cardiovascular condition precluded further completion of the PCD™ Transvene™ System and adequate definition of a defibrillation safety margin. In all cases, the physician felt that the benefit of the PCD™ Transvene™ System outweighed the risk of further inductions or the risk of a thoracotomy and elected not to evaluate or implant a PCD™ Epicardial System.

K.2 Patients Receiving PCD™ Transvene™ System & Did Not Meet Implant Criteria

For purposes of the PCD™ Transvene™ System, the implant criteria was defined as successful VF termination at least 3 times in 4 attempts with the final lead configuration at an output energy of 18 Joules or less. Of the 757 patients who **received** a PCD™ Transvene™ System, 214 patients (28.3%) did not meet the recommended defibrillation implant criteria and yet still received the PCD™ Transvene™ System. The physicians justification for implanting the PCD™ Transvene™ System despite not meeting the recommended defibrillation implant criteria are presented in Table IK-1.

PCD™ Transvene™ System Reasons for Not Meeting Implant Criteria Physician Justification	
Reason	**Number of Patients**
Success at $\leq$ 24 Joules	170
Difficult/Unable to Induce VF	24
Patient Condition	20
TOTAL	214

Table IK-1: PCD™ Transvene™ System: Physician Justification for Not Meeting Implant Criteria - 6/24/92

Further analysis of the patient who did not meet the recommended implant criteria indicates however, that 91% (194/214) had a 10 Joule safety margin between the lowest energy of successful defibrillation and the maximum output of the PCD Device (34J). Therefore, of the 757 patients who received a PCD™ Transvene™ System, 97.4% (737/757) had at least a 10 Joule defibrillation safety with the implanted lead configuration.

There were 20 patients (2.6%) in whom the implant procedure was terminated due to poor patient condition. These patients received a PCD™ Transvene™ System without at least a 10 Joule defibrillation safety margin. The implant circumstances of these patients is summarized as follows:

- At least one successful defibrillation was obtained at an energy level greater than 24 Joules and or equal to 34 Joules (**N = 11**);

- Multiple inductions of VT were performed and successfully reverted with an energy level of 18 Joules or less. However, induced VF was not successfully reverted by an energy level of less than or equal to 34 Joules (**N = 6**); and

- Physician elected to terminate the procedure due to the patient's condition before inductions with the final implanted lead configuration were performed (**N = 3**).

Table IK-2 provides a comparison of patient characteristics between patients who met the PCD™ Transvene™ System implant criteria and those patients who did not meet the implant criteria but still received the PCD™ Transvene™ System.

PCD™ Transvene™ System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Patient Characteristics		
Data	**Meeting Criteria**	**Not Meeting Criteria**
Number of Patients	543	214
Mean Follow-Up	6.2 months	4.0 months
Male*	422 (77.7%)	188 (87.9%)
Female	121 (22.35)	26 (12.1%)
Mean Age	59.4 yrs	59.6 yrs
Indication*		
SCD	209 (38.5%)	72 (33.6%)
VT	278 (51.2%)	99 (46.3%)
SCD/VT	56 (10.3%)	43 (20.1%)
Cardiovascular History		
CAD	396 (72.9%)	165 (77.1%)
Cardiomyopathy	173 (31.9%)	65 (30.4%)
Mean EF*	36.3%	33.7%
NYHA Class		
I	164 (30.9%)	53 (25.8%)
II	278 (52.4%)	114 (56.6%)
III	82 (15.4%)	34 (16.6%)
IV	7 (1.3%)	4 (2.0%)
Number ON Drugs at Implant	223 (41.1%)	97 (45.3%)
Number ON Amiodarone	78 (14.4%)	38 (17.8%)

* **Statistically Significant ($p \leq 0.05$)**

Table IK-2: PCD™ Transvene™ System: Patients Meeting Implant Criteria vs Not Meeting Implant Criteria - Comparison of Pt Characteristics - 6/24/92

Statistical analysis indicated three significant differences between these two patient groups - patient sex, indication for implant and mean ejection fraction.

Patients not meeting implant criteria had a statistically higher percentage of patients who were male ($p = 0.002$). This difference reflects that the majority of patients with

coronary disease with concomitant life threatening ventricular arrhythmias are males.

Analysis indicated the patients not meeting the implant criteria had a statistically higher percentage of patients whose primary indication for implant was sudden cardiac death associated with recurrent ventricular tachycardia ($p = 0.002$). This difference reflects the physicians use of the PCD™ Transvene™ System.

Finally, patients who did meet the implant criteria had a statistically lower mean ejection fraction ($p = 0.0342$) which reflects a higher degree of underlying cardiovascular disease in these patients.

It should be noted, that none of these differences should be used as predictors for patients who should be screened for a PCD™ Transvene™ System.

Implant data obtained in these two patient groups is presented in Table IK-3. As would be expected the patients not meeting the implant criteria had higher mean DFT and LED values when compared to the patients who did meet the implant criteria. However, the mean DFT (18.8J) and LED (19.5J) values obtained in patients not meeting implant criteria provided at least a 10 Joule defibrillation safety margin between the successful energy and the maximum output of the PCD™ Device (34J) in nearly all (97.4%) of the patients.

PCD™ Transvene™ System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Implant Data		
Data	**Meeting Criteria**	**Not Meeting Criteria**
Number of Patients	543	214
Mean Number of Inductions	7.0	8.2
Number of Configurations	2.0	2.7
Mean DFT	13.4J	18.8J
Mean LED	14.8J	19.5J
Implanted Lead System **RV-SVC-SQ** **RV-CS-SQ** **RV-CS-SVC**	 351 (64.6%) 159 (29.3%) 33 (6.1%)	 145 (67.8%) 63 (29.4%) 6 (2.8%)
Efficacy of 1st Lead System	396 (72.9%)	137 (64.0%)
Defibrillation Pathway **Sequential** **Simultaneous** **Single**	 414 (75.7%) 127 (23.2%) 6 (1.1%)	 160 (74.4%) 51 (23.7%) 4 (1.9%)

Table IK-3: PCD™ Transvene™ System: Patients Not Meeting Implant Criteria versus Patients Meeting Implant Criteria - Comparison of Implant Data - 6/24/92

In order to determine if the patient's not meeting implant criteria had higher risk for morbidity and mortality, a comparison of their clinical outcome was made with those patients who did meet the implant criteria. This comparison is provided in Table IK-4.

PCD™ Transvene™ System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Implant Data		
Data	**Meeting Criteria**	**Not Meeting Criteria**
Number of Patients	543	214
Spontaneous VT Episode Efficacy	99.0%	98.4%
Spontaneous VF Episode Efficacy	99.0%	99.2%
Number of Patient Deaths	18	4
Perioperative Mortality	0.7%	0.5%
One Year Survival		
Sudden Cardiac	100%	99.3%
Non-Sudden Cardiac	96.4%	98.6%
All Cardiac	96.4%	97.9%
Noncardiac	99.2%	100%
Overall	94.9%	97.4%

Table IK-4: PCD™ Transvene™ System: Patients Not Meeting Implant Criteria versus Patients Meeting Implant Criteria - Comparison of Clinical Outcome - 6/24/92

The two patient groups had similar efficacy in the treatment of spontaneous VT/VF episodes. Importantly, in the patient population who did not meet the implant criteria there were no patients who experienced actual spontaneous VF episodes where all programmed PCD™ Device therapies failed to terminate the episode.

In one patient (Patient ID (b)(6) all four programmed VF therapies were unsuccessful in terminating a spontaneous episode of VF. However, this was an inappropriate VF therapy delivered due to atrial fibrillation with a rapid ventricular response rather than VF. Reprogramming and modification of the patient's antiarrhythmic drug therapy

corrected the problem. Thus, there were no patients who experienced an actual spontaneous VF episode where all four programmed VF therapies failed to terminate the episode.

There were eight patients (30 spontaneous VT episodes) where all four programmed VT therapies failed to terminate the episode. In four patients, the ventricular tachycardia was ineffectively terminated and the patient's drug therapy was modified in order to improve the efficacy of the programmed VT therapies. Four patients, three who experienced atrial fibrillation and the other sinus tachycardia, had episodes where all four VT therapies failed to terminate the " spontaneous VT episode". In all cases, the delivery of inappropriate VT therapy was resolved by modification of the patients' drug therapy.

There was no difference in the one year sudden cardiac survival or the overall survival in the two groups although follow-up was shorter for patients not meeting implant criteria (4.0 vs 6.2 months). This indicates, that despite not meeting the implant criteria these patients were not at higher risk of sudden cardiac death.

Finally, the survival of patients receiving a PCD™ Transvene™ System without meeting implant criteria (N=214) was compared to patients receiving a PCD™ Epicardial System without meeting implant criteria (N=92). This comparison is provided in Table IK-5.

PCD Transvene System Patients Not Meeting Implant Criteria Survival Analysis versus PCD Epicardial System Patients Not Meeting Implant Criteria Survival Analysis		
	PCD Transvene System Not Meeting Implant Criteria	PCD Epicardial System Not Meeting Implant Criteria
Number of Patients	214/757 (28.5%)	92/742 (12.4%)
Number of Deaths	4	13
Sudden Cardiac	99.3%	97.9%
Non-Sudden Cardiac	98.6%	100%
Noncardiac	100%	95.2%
Overall*	97.4%	83.8%

* (b)(4) (b)(4)

Table IK-5: PCD™ Transvene™ System: Patients Not Meeting Implant Criteria - PCD Transvene System vs PCD™ Epicardial System - 6/24/92

Though the PCD™ Transvene™ System had a higher incidence of patients not meeting implant criteria (28.5%) compared to the PCD™ Epicardial System (12.4%), there was no statistical difference in the sudden cardiac death patient survival. However, the overall survival of patients not meeting implant criteria with the Transvene™ System was significantly better (b)(4) (b)(4) when compared to the PCD™ Epicardial System patients not meeting implant criteria, 97.4% and 83.3%, respectively.

The investigators felt in every case that the testing performed at the time of implant, though it did not meet the recommended implant criteria, did provide an adequate demonstration of device effectiveness and justified the implant of the PCD Transvene System. Finally, there have been no patients deaths secondary to unsuccessful termination of a spontaneous VT or VF episode in this patient population.

K.3 Description of Patients Not Meeting Implant Criteria

As noted previously, the patients not meeting implant criteria (N=214) were divided into three groups (1) Successful defibrillation at an energy level of equal to or

less than 24 Joules [79.4% of the patients]; (2) Difficult to induce VF [11.2% of the patients]; and (3) Implant procedure terminated due to poor patient condition [9.4% of the patients]. These patient groups are reviewed in the following discussion.

Lowest Energy of Defibrillation < 24 Joules

There were 170 patients in whom the PCD™ Transvene™ System was implanted with a defibrillation safety margin of at least 10 Joules. Table IK-6 provides an overview of these patients clinical experience.

These data indicate that the final implanted PCD™ Transvene™ System was evaluated and significant attempts were made to meet the recommended implant criteria. In most of these patients (79.4%), a safety margin of 10 Joules was obtained between the successful defibrillation energy (24 J or less) for ventricular fibrillation and the maximum output of the PCD Device (34 J). The investigators decided in certain circumstances that this was appropriate demonstration of device effectiveness and that the PCD™ Transvene™ System could be implanted.

Of these patients, 148 (87.1%) have had VF induced at a chronic follow-up visit and in each case, VF was successfully terminated by the PCD Transvene System. In addition, 31 patients (18.2%) have experienced a spontaneous VF episode with an overall efficacy of 100%.

Thus, the clinical outcome in these patients was not adversely affected by not meeting implant criteria since their spontaneous VF episode efficacy was 100% and the one year sudden cardiac death actuarial survival was also 99.1%. The duration of follow up, however, is limited to an average of 4 months.

PCD™ Transvene™ System Patients Not Meeting Implant Criteria 10J Safety Margin Provided	
Number of Patients	170
Lowest Energy of Defibrillation	
1 Success with 10J Safety Margin	87
2 Success with 10J Safety Margin	58
3 Success with 10J Safety Margin	18
> 3 Success with 10J Safety Margin	7
Overall Spontaneous VF Episode Efficacy	100%
One Year Survival	
Sudden Cardiac	99.1%
Overall	97.6%

Table IK-6: PCD™ Transvene™ System: Patients Not Meeting Implant Criteria with 3/4 Successes at $\leq$ 24 Joules Clinical Experience - 6/24/92

Difficult to Induce VF

There were 24 patients who did not meet the recommended PCD™ Transvene™ System implant criteria because at least three episodes of VF were not induced at the time of implant. Of these, 15 patients had ventricular tachycardia induced and successfully reverted. The remaining 9 patients had ventricular flutter induced and successfully reverted. In all 24 patients, the lowest successful energy was equal to or less than 18 Joules.

The indication for implant was sudden cardiac death (SCD) in 6 patients (25%), recurrent ventricular tachycardia (VT) in 13 patients (54.2%) and sudden cardiac death associated with recurrent ventricular tachycardia (SCD/VT) in 5 (20.8%) patients. Thus the majority of the patients, 75%, had documented recurrent ventricular tachycardia as part of their ventricular tachyarrhythmia history. Eight of the these patients (33.0%) were on Amiodarone therapy which may have contributed to the inability to induce VF.

Of the 24 patients who did not meet the recommended PCD™ Transvene™ System implant criteria because at least three episodes of VF were not induced at the time of

implant, 8 patients (33.3%) have experienced a spontaneous VF episode and 19 patients (79.2%) have had VF induced during a chronic follow-up. In all cases, VF was successfully reverted by the PCD™ Transvene™ System.

There have been no reported patient deaths in the patient group with a resultant one year sudden cardiac death and overall actuarial survival of 100%.

Patient Condition

There were 20 patients in whom the implant procedure was terminated due to poor patient condition. These patients received a PCD™ Transvene™ System without at least a 10 Joule defibrillation safety margin. The implant circumstances of these patients is summarized as follows:

- At least one successful defibrillation was obtained at an energy level greater than 24 Joules but less than 34 Joules (**N = 11 patients**);
- Multiple inductions of VT were performed and successfully reverted with an energy level of 18 Joules or less. However, induced VF was not successfully reverted by an energy level of less than or equal to 34 Joules (**N = 6 patients**); and
- Physician elected to terminate the procedure due to the patient's condition before inductions with the final implanted lead configuration were performed (**N = 3 patients**).

The mean ejection fraction of this group was 26.9%, indicating more severe underlying cardiovascular disease, and may have contributed to the physicians decision to terminate the implant procedure prior to meeting implant criteria. This group had a mean of 6.8 VF inductions, 2.2 lead configurations evaluated and a mean duration of VT/VF for the implant procedure of 220 total seconds. The circumstances of the implant procedures, mainly the duration of induced ventricular tachyarrhythmia and associated hemodynamic compromise, limited the number of inductions that could be performed and whether the recommended implant criteria could be met.

Of these twenty patients, ventricular fibrillation has been

induced at a chronic follow-up visit in 15 patients (75%) and in all cases successful defibrillation with the implanted PCD™ Transvene™ System was documented.

The overall spontaneous VF episode efficacy for this patient group was 92.6% however further reviewed indicated that one patient experienced atrial fibrillation that was detected as VF and in whom all four programmed VF therapies were ineffective. This patient's antiarrhythmic drug therapy was modified and there were no further reports of ineffective therapies.

Thus there have been no patients who have experienced an actual spontaneous VF episode where all four programmed VF therapies failed to terminate the episode.

There has been one reported patient death, (Patient ID (b)(6) which was classified as non-sudden cardiac secondary to end stage heart failure. The one year sudden cardiac death survival in this patient population is 100% while the overall one year survival was 93.8%. This lower overall one year survival may due to the lower mean ejection fraction of this patient group.

The clinical outcome in these twenty patients was not adversely affected by not meeting implant criteria since there was no reports of failure to terminate a spontaneous VF episode and the overall one year sudden cardiac death survival was 100%.

Conclusion

In conclusion, 214 patients received the PCD™ Transvene™ System despite not meeting the recommended implant criteria. These 214 patients are divided into the following groups:

- successful defibrillation of VF at 24 Joules or less (170/214),
- difficult to induce at least three episodes of VF at implant (24/214), and
- worsening patient condition which prevented further inductions (20/214).

It should be noted that 91 % (194/214) of the patients not meeting the recommended implant criteria had at least one successful termination of induced ventricular tachyarrhythmia (VT, VFlutter or VF) at 24 Joules or less.

L. Comparison to AICD System Experience

L.1 Overview

The current AICD Epicardial System is implanted only with a defibrillation lead system requiring a thoracotomy. The PCD™ Transvene™ System allows the implantation of an implantable cardioverter defibrillator (ICD) system without the potential increased perioperative morbidity and mortality associated with a thoracotomy. This allows the application of ICD therapy in patients who may not otherwise be candidates for this type of therapy. Though the PCD™ Transvene™ System will have complications and observations that are specific to the lead system, the overall performance should be at least equivalent to that reported with the current AICD Epicardial System.

This section provides a comparison of the PCD™ Transvene™ System clinical experience to that of the reported AICD Epicardial System clinical experience. The following areas will be discussed:

- Patient characteristics
- Clinical performance
- Survival analysis

For purposes of comparison, the Ventak-P Epicardial System patient population described in the Summary of Safety and Effectiveness Data (PMA Application Number P890061) dated May 2, 1991 will be used. A copy of this summary was obtained through the Freedom of Information Act.

L.2 Comparison of Patient Characteristics

In comparing the clinical experience with the PCD™ Transvene™ System to the reported Ventak-P Epicardial System clinical experience, it is important to determine that the patients who received the device are comparable.

The characteristics of the patients receiving the PCD™ Transvene™ System were compared to the characteristics of patients discussed in the Ventak-P Summary of Safety and Effectiveness Data and are presented in Table IL-1. There were no differences between the two patient groups.

PCD™ Transvene™ System
Comparison of Patient Characteristics
PCD™ versus AICD

	PCD™	Ventak-P
Number of Patients	757	292
Mean Follow-Up Time	5.6 months	6.8 months
% Males **% Females**	610 (81%) 147 (19%)	231 (79%) 61 (21%)
Mean Age	59.4 years	61.5 years
Primary Indication: **SCD** **VT** **SCD/VT**	 281 (37%) 377 (50%) 99 (13%)	 49 (16%) 169 (59%) 73 (25%)
Coronary Artery Disease	561 (74%)	228 (78%)
Mean Ejection Fraction	35.6%	34%
Drug Therapy at Implant	42%	45.0%
Concomitant Surgery	0%	18.0%

Table IL-1: Comparison of Patient Characteristics, PCD™ versus Ventak-P 6/24/92

The two patient groups are comparable in mean age and mean ejection fraction. Both groups had moderately depressed left ventricular function demonstrated by the mean ejection of 35.6% for the PCD™ Transvene™ System patient group and 34% for the Ventak-P Epicardial System patient group.

Analysis indicated that no statistical differences between the PCD™ Transvene™ System and Ventak-P Epicardial System patient populations except in the category of patient indication. There are more patients that had Sudden Cardiac Death as the primary indication in the PCD™ Transvene™ population than in the AICD population ($p = 0.001$).

L.3 Comparison of Clinical Performance

Areas of clinical performance that were compared were implant defibrillation thresholds, incidence of spontaneous VT/VF events, incidence of complications and patient survival. These specific areas were selected in order to evaluate the system performance in the two patient populations.

Implant Defibrillation Thresholds

For the purposes of the PCD™ Transvene™ System clinical study, determination of defibrillation threshold was not mandatory. However, the preferred method of evaluating defibrillation efficacy was to determine the defibrillation threshold using a testing sequence of 18J, 15J, 10J, 5J with a failure at any level causing a return to 18 J for the remaining attempts. For the purposes of this report a defibrillation threshold was defined as the energy at the lowest successful defibrillation attempt, provided a patient had a failure below their lowest defibrillation success or a success at $\leq$ 5J. The rhythm treated must have been VF to be included in the analysis.

It should be noted, that it was expected that the PCD™ Transvene™ System would have a higher mean defibrillation threshold as compared to a traditional epicardial defibrillation lead system. In a epicardial system, the increased electrode surface area would theoretically decrease defibrillation requirements.

A total of 316 patients had a defibrillation threshold determined at the time of PCD™ device implant. The mean defibrillation threshold (DFT) for all lead systems was 14.8J. The recommendation for VF Therapy #1 is to program the stored energy to twice the implant DFT or 18 Joules, whichever is greater. Thus an adequate defibrillation safety margin was provided when following the VF therapy programming recommendations.

In the Ventak-P Epicardial System, the mean defibrillation threshold at implant was 13.4J. Thus the two systems had similar defibrillation thresholds at implant despite the fact that one system utilized an epicardial defibrillation lead

system while the other utilized a transvenous defibrillation lead system.

These data indicate that the PCD™ Transvene™ System had comparable implant defibrillation threshold performance when compared to the reported Ventak-P Epicardial System clinical experience.

Incidence of Spontaneous VT/VF Episodes

The incidence of spontaneous VT/VF episodes in the Ventak-P Epicardial System and PCD™ Transvene™ System patient population was evaluated by utilizing the stored episode information provided by both devices.

In the Ventak-P device, the total number of shocks delivered to the patient is provided via interrogation of the device. The PCD™ device provides information on the total number of VT and VF episodes detected by the PCD™ device and the total number of VT and VF episodes successfully treated by the PCD™ device as well as the number of VT/VF episodes where the PCD™ device was ineffective. In addition, the last 20 intervals of the last episode satisfying detection criteria along with the first 10 intervals after the last therapy delivered are recorded by the device. These data assist the physician in evaluating the frequency of VT/VF episodes, the efficacy of the PCD™ device programmed parameters and the need for reprogramming.

In the Ventak-P Epicardial System experience of 292 patients with a mean follow-up of 6.8 months, 137 (46.9%) received a device countershock in response to a spontaneous ventricular tachyarrhythmia episode as defined by the Ventak-P Device detection criteria.

In the PCD™ Transvene™ System experience of 757 patients with a mean follow-up of 5.6 months, 311 patients (41%) have received device therapy in response to a spontaneous ventricular tachyarrhythmia episode as defined by the PCD™ Transvene™ System detection criteria.

A total of 5430 spontaneous VT and 973 spontaneous VF episodes have been recorded by the PCD™ device episode

counters. Of the 5362 successfully treated spontaneous VT episodes, 92% were treated with one of the programmed antitachycardia pacing therapies incorporated in the PCD™ device. The clinical benefit of tiered therapy is the reduction of delivery of high energy shocks for the treatment of stable recurrent ventricular tachycardia that may be responsive to antitachycardia pacing.

Incidence of Complications

Table IL-2 provides a comparison of reported complications and observations. The AICD clinical experience data is from the Winkle, et al Long Term Outcome with Automatic Implantable Cardioverter-Defibrillator; JACC, May 1989; 13(6); 135-161. This article was selected because it provides a detailed clinical complication experience on a large patient population, 270 patients. Note that the percentage reported in the PCD™ Transvene™ System includes **both complications and observations.** In the following table, the complications are reported for the categories of Fail to Cardiovert/Defibrillate, Pocket Infection, and Erosion. Observations are reported in the Inappropriate/Problematic VT/VF Therapy Delivery category.

PCD™ Transvene™ System
Comparison of Complication/Observation Rates
PCD™ versus AICD

Category	PCD™%	AICD%
Fail to Cardiovert/Defibrillate	0.8%	4.1%
Inappropriate/Problematic VT/VF Therapy Delivery	8.2%*	20%
Pocket Infection	2.0%	2.2%
Erosion	0.3%	0.7%

* Includes Observations only; there were no Complications in this category.

Table IL-2: Comparison of Complication/Observation Rates: PCD™ Transvene™ System vs AICD Epicardial System - 6/24/92

The incidence of failure to cardiovert and/or defibrillate was lower in the PCD™ Transvene™ System patient population. The instances of failure to cardiovert and/or defibrillate in the PCD™ Transvene™ System patient population were

associated with increased defibrillation requirements during induced episodes, none of which resulted in patient death. In six cases, the implanted system was modified to provide adequate defibrillation efficacy, in four cases the patient's drug therapy was modified and in the final two cases, reprogramming provided for adequate defibrillation efficacy.

The failures to cardiovert/defibrillate reported in the Winkle, et al article were associated with patch dislodgement, patch crinkling, lead conductor fracture and elevated defibrillation thresholds.

The incidence of inappropriate/problematic VT/VF therapy delivery was lower in the PCD™ Transvene™ System patient population. This is to be anticipated since the device incorporates independently programmable detection algorithms for VT and VF. The reasons for inappropriate VT/VF therapy delivery included sinus tachycardia being detected as VT or VF and atrial fibrillation with rapid ventricular response being detected as VT or VF.

The overdetection circumstances reported in Winkle, et al were nonsustained VT, VT, sinus tachycardia, atrial fibrillation with rapid ventricular response, sensing lead fracture and pacemaker interaction. The patients with VT complained of receiving multiple shocks with limited or no symptoms. The incorporation of antitachycardia pacing in the PCD™ device decreases the need for delivery of cardioversion shocks for the termination of stable VT and increases patient acceptance of ICD therapy.

In the Winkle, et al experience all patients with pocket infection had the devices explanted. In the PCD Transvene System experience, the incidence of device explant secondary to pocket infection was 2.0% which was comparable to Winkle's article.

Thus, the incidence of complications and observations was similar to that of the AICD Epicardial System in the categories of ineffective VT/VF therapies, infection requiring explant and erosion. The incidence of inappropriate delivery of therapy is lower in the PCD Transvene System experience than in the AICD Epicardial System experience, which is clinically significant.

This analysis indicates that the PCD™ Transvene™ System offers clinical advantages in reducing the need for a thoracotomy for implantation and reducing the number of shocks due to successful antitachyarrhythmia pacing.

L.4 Comparison of One Year Actuarial Survival

The Ventak-P Epicardial System produced by Cardiac Pacemaker, Inc, has obtained market approval from the U.S. FDA to date. While there are important differences in the function of the Ventak-P Epicardial System and the PCD™ Transvene™ System, there is a natural desire for comparison of the clinical outcome, particularly the impact of these devices on death rate.

A total of 22 deaths (2.9%) were reported in the PCD™ Transvene™ System patient population. Of the 18 cardiac deaths, 15 were non-sudden cardiac and 3 were sudden cardiac. Four deaths were classified as noncardiac. Five of the 22 total deaths occurred within the perioperative period (death less than 30 days post implant) with a resultant perioperative mortality of 0.7%.

In the Ventak-P Epicardial System patient population a total of 19 deaths (6.5%) were reported. Of the 12 cardiac deaths, 4 were classified as sudden cardiac and 8 were classified as non-sudden cardiac. Six of the deaths were classified as noncardiac and the cause of one was unknown. Eight of the deaths occurred within the perioperative period with a resultant perioperative mortality of 2.7%. The PCD™ Transvene™ System population had a lower perioperative mortality, 0.7% vs 2.7% ($p = 0.006$).

For purposes of this comparison, only the **overall** actuarial survival rate includes perioperative deaths. All other calculations in both the PCD™ Transvene™ System and Ventak-P Epicardial System group exclude perioperative deaths.

For the Ventak-P Epicardial System, patient deaths were **censored** if the Ventak-P device had been either electively deactivated for various reasons prior to the patient's death, thus preventing the device from attempting to convert the arrhythmia or if the pulse generators were known to be

nonfunctional and awaiting replacement. For purposes of this comparison, two patient deaths were **censored** in the PCD™ Transvene™ System patient population because the devices were deactivated at the time of patient death.

This PCD™ Transvene™ System sudden cardiac death survival of 100% at one year is comparable to that of the Ventak-P Epicardial System sudden cardiac death survival rate of 98.6 %. More importantly, the overall one year actuarial survival for the PCD™ Transvene™ System was 95.6% as compared to 90.8% for the Ventak-P Epicardial System. This difference was primarily due to the improvement in the reported perioperative mortality in the PCD™ Transvene™ System patient population. [Note: Confidence interval analysis was performed indicating that there was a statistical difference in the reported **Overall** mortality.]

This comparison of actuarial survival rates indicates that the projected sudden cardiac death survival of patients receiving a PCD™ System patient population is comparable to that reported for the Ventak-P Epicardial System. Thus, the incorporation of programmable VT/VF detection and therapy algorithms has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

In addition, the elimination of a surgical thoracotomy for implant in the PCD™ Transvene™ System has improved the perioperative mortality and overall one year survival when compared to the Ventak-P Epicardial System.

M. Comparison to PCD™ Epicardial System Clinical Results

The PCD™ Epicardial System uses the same tiered therapy device that combines features of bradycardia support pacing, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. This system has incorporated programmability and multiple detection and therapeutic options that allows the titration of device therapy to a patient's specific clinical arrhythmia history.

The PCD™ Epicardial System requires a thoracotomy for implantation because of the need to insert epicardial patch leads. This exposes the patient to surgical risk and potentially limits the type of patient who may be considered for implant of the system. The need for a simpler and safer implantation technique is widely recognized. The incorporation of a nonthoracotomy lead system, such as the PCD™ Transvene™ System, should decrease the potential perioperative and long term mortality and morbidity associated with current epicardial system implantation approaches.

The PCD™ Epicardial System and PCD™ Transvene System are identical except for the implanted defibrillation lead system. Thus, the performance of the PCD™ device, associated support equipment, is similar in the two systems and therefore a comparison of clinical experience should focus on those areas where the implanted lead system may impact clinical outcome.

This section provides a comparison of the PCD™ Transvene™ System clinical experience to the reported PCD™ Epicardial System clinical experience. The following areas will be discussed:

- Patient characteristics
- Implant Data
- Spontaneous VT/VF Episode Efficacy
- Complications and Observations
- Survival analysis

This analysis will show that the incorporation of a nonthoracotomy defibrillation lead system has maintained the type of therapy available for the treatment of recurrent VT/VF and decreased the potential mortality and morbidity associated with epicardial implant approaches while maintaining the positive impact of ICD therapy on VT/VF episode efficacy and patient survival.

M.1 Comparison of Patient Characteristics

In comparing the clinical experience with the PCD™ Transvene™ System to the PCD™ Epicardial System clinical experience, it is important to determine that the patients who received the device are comparable.

Table IM-1 contains the characteristics of the 757 patients receiving the PCD™ Transvene™ System versus the

characteristics of the 742 patients who received the PCD™ Epicardial System as of 5/14/92.

PCD™ Transvene™ System Comparison of Patient Characteristics		
	PCD™ Transvene System	PCD™ Epicardial System
Number of Patients	757	742
Mean Follow-Up Time	5.6 months	9.7 months
% Males* % Females	610 80.6% 147 19.4%	637 85.8% 105 14.2%
Mean Age	59.4 years	59.6 years
Primary Indication* SCD VT SCD/VT	 281 37.1% 377 49.8% 99 13.2%	 214 28.8% 405 54.6% 123 16.6%
Cardiovascular History Coronary Artery Disease Cardiomyopathy	 561 74.1% 238 13.1%	 569 76.7% 222 29.9%
Mean Ejection Fraction	35.6%	34.0%
Number of Drugs Failed*	2.3	3.0

* Statistically Significant

Table IM-1: Comparison of Patient Characteristics, PCD™ Transvene™ System versus PCD™ Epicardial System - 6/24/92

Both groups had moderately depressed left ventricular function demonstrated by the mean ejection of 35.6% for the PCD™ Transvene™ System patient group and 34.0% for the PCD™ Epicardial patient group.

Analysis indicated that the PCD™ Transvene™ System patient population had a higher percentage of patients whose indication for implant was sudden cardiac death ($p = 0.002$) and higher percentage of females ($p = 0.007$). It is not expected that these differences will result in a different clinical outcome in the PCD™ Transvene™ System patient population as compared to the PCD™ Epicardial System. This difference in patient indication is a reflection of the physicians use of the PCD™ Transvene™ System.

It is interesting to note, that there was a statistical difference in the number of antiarrhythmic drugs tested between the two patient groups ($p = 0.001$). The PCD™ Transvene™ System patient group failed a mean of 2.3 antiarrhythmic drugs prior to implant while the PCD™ Epicardial System patient group failed a mean of 3.0 antiarrhythmic drugs. This difference is a reflection of the differences in the indications for implant between the two patient groups. The PCD™ Transvene™ System patient group had a higher incidence of patients whose primary indication for implant was sudden cardiac death. These patients have a higher probability of having experienced a sudden cardiac death episode but were non-inducible during electrophysiologic testing so that drug testing was not feasible.

M.2 Implant Data Comparison

In both systems, lead system testing was performed to verify that one of the specified lead systems was capable of properly detecting and treating episodes of ventricular fibrillation and, when appropriate ventricular tachycardia. This testing included pacing and sensing thresholds during sinus rhythm, evaluation of VF electrogram amplitudes and defibrillation efficacy evaluation. The implant criteria for both systems was identical and were:

1. Successful VF termination at least 3 times in 4 attempts with an output energy of 18 Joules or less and

2. At least a 2:1 VF sensing safety margin

Pace/Sense Performance

In both the PCD™ Transvene™ and PCD™ Epicardial Systems, sensing is performed in a standard bipolar configuration and pacing is performed in the integrated bipolar configuration. The pace/sense implant criteria for both systems was:

Pacing Threshold:	$\leq$ 1.5V @ 0.5 ms
R-Wave Amplitude:	$\geq$ 5 mV
Slew Rate:	$\geq$ 0.75 volt/sec
Resistance:	200 - 880 ohms

Table IM-2 provides a comparison of the mean pace/sense values obtained at the time of implant for the PCD™ Transvene™ and Epicardial Systems. It should be noted that the pace/sense values presented for the PCD™ Epicardial System are for the Model 7217B PCD™ Device.

PCD™ Transvene™ System Performance Comparison Implant Pace/Sense Parameters		
Parameter	**PCD™ Transvene System**	**PCD™ Epicardial System**
Pacing Threshold*	0.87 V (0.1-3.6V)	0.98 V (0.2-5.3 V)
R Wave Amplitude*	14.2 mV (1.3-32 mV)	13.5 mV (2.2-37.2 mV)
Slew Rate*	1.66 v/S (0.25-9.8 v/S)	1.38 v/S (0.15-7.2 v/S)
Resistance*	575 ohms (264-1381 ohms)	438 ohms (157-1206)

* **Statistically Significant**

Table IM-2: PCD™ Transvene™ System: Comparison of Implant Pace/Sense Parameters - 6/24/92

The implant pace/sense parameters obtained for the PCD™ Transvene™ System indicates that the lead system provided adequate pacing and safety margins. There was a statistically significant difference in all of the implant pace/sense parameters ($p = 0.001$). This is anticipated because endocardial pace/sense parameters are better than epicardial values for bradycardia pacing electrode systems. This difference has no clinical impact on the pacing and sensing performance of the PCD™ Transvene™ System.

Electrogram amplitudes were evaluated at follow-up evaluations of both systems to evaluate the performance of the pace/sense lead system and assure adequate safety margin for detection of both baseline rhythms and ventricular tachyarrhythmias. In addition, pacing thresholds were also evaluated at follow-up evaluations to assure an adequate safety margin for capture during both bradycardia and antitachycardia pacing therapies. A comparison of the chronic pace/sense performance for the two systems is

presented in Table IM-3. It should be noted that there was no statistical difference in the chronic pace/sense performance of the two systems.

PCD™ Transvene™ System **Performance Comparison** Chronic Pace/Sense Parameters		
Parameter	**PCD™ Transvene System**	**PCD™ Epicardial System**
Electrogram Amplitude	9.6 mV (0.2 - 25 mV)	9.6 mV (0.5-2.5 mV)
Pulse Width Threshold	0.24 ms (0.03-1.59 ms)	0.28 ms (0.03-1.59 ms)

Table IM-3: PCD™ Transvene™ System: Comparison of Chronic Pace/Sense Parameters - 6/24/92

The incidence of loss of capture requiring lead system modification in the PCD™ Transvene™ System was 0.8% while the incidence in the PCD™ Epicardial System was 2.0%. There were no reports of undersensing requiring lead modification in the PCD™ Transvene™ System while the incidence in the PCD™ Epicardial System was 0.8%.

This comparison of implant and chronic pace/sense data performance indicates that the performance of the PCD™ Transvene™ System is similar to that reported with the PCD™ Epicardial System. The PCD™ Transvene™ System provides appropriate acute and chronic safety margins for sensing of sinus rhythm and ventricular tachyarrhythmia as well as appropriate safety margins for pacing therapy.

Implant Defibrillation Thresholds

For the purposes of both systems, determination of defibrillation threshold was not mandatory. However, the preferred method of evaluating defibrillation efficacy was to determine the defibrillation threshold using a testing sequence of 18J, 15J, 10J, 5J with a failure at any level causing a return to 18 J for the remaining attempts.

A defibrillation threshold was defined as the energy at the lowest successful defibrillation attempt, provided a patient had a failure below their lowest defibrillation success or a

success at $\leq$ 5J. The rhythm treated must have been VF to be included in the analysis.

Table IM-4 provides a comparison of defibrillation thresholds determined at implant for the PCD™ Transvene™ and PCD™ Epicardial Systems.

PCD™ Transvene™ System **Performance Comparison** Implant Defibrillation Thresholds	
System	**Mean DFT**
PCD™ Transvene™ System*	14.8J
PCD™ Epicardial System	9.8J

* Statistically Significant ($p \leq 0.05$)

Table IM-4: PCD™ Transvene™ System: Comparison of Implant DFT - 6/24/92

The PCD™ Transvene™ System did have a significantly higher mean implant defibrillation threshold ($p = 0.0001$). It should be noted, that it was expected that the PCD™ Transvene™ System would have a higher mean defibrillation threshold as compared to a traditional epicardial defibrillation lead system. In a traditional epicardial system, the increased electrode surface area would theoretically decrease defibrillation requirements.

The programmed defibrillation pathways for the two patient populations is presented in Table IM-5. The implanted PCD™ Transvene™ Systems are almost exclusively three lead systems and this explains the decreased use of SINGLE pathway. The use of SIMULTANEOUS pathway is higher in the PCD™ Transvene™ System and indicates that in a group of patients the incorporation of multiple defibrillation pathways allowed an increase in the ability to meet the PCD™ Transvene™ System implant criteria. Most of the PCD™ Epicardial System implants used a two patch system resulting in the increased use of the SINGLE pathway.

PCD™ Transvene System Performance Comparison Programmed Defibrillation Pathway		
Defibrillation Pathway	**PCD™ Transvene System**	**PCD™ Epicardial System**
Sequential	574 (75.3%)	251 (33.0%)
Simultaneous	178 (23.4%)	14 (1.8%)
Single	10 (1.3%)	496 (65.2%)

Table IM-5: PCD™ Transvene™ System: Comparison of Programmed Defibrillation Pathway - 6/24/92

The differences in the programmed status of the PCD™ device in the PCD™ Transvene™ System are a reflection of the type of patients who received the device and the defibrillation energy requirements for each lead system. It is important to note that the PCD™ device performed safely and effectively in both patient populations.

M.3 Spontaneous VT/VF Episodes Efficacy Comparison

The primary benefits from the use of the PCD™ System center on the detection and termination of life-threatening ventricular tachyarrhythmias. An additional benefit of the PCD™ Transvene™ System is the elimination of the need for a thoracotomy for implantation of the defibrillation lead system and the resultant decrease in potential patient morbidity and mortality associated with a thoracotomy. This clinical benefit should not be gained at the expense of providing effective termination of spontaneous VT and VF episodes. Table IM-6 provides a comparison of the efficacy of the PCD™ Transvene™ and PCD™ Epicardial System in treating spontaneous episodes of VT and VF.

PCD™ Transvene™ System Performance Comparison		
Spontaneous VT Episodes		
	PCD™ Transvene™ System	**PCD™ Epicardial System**
Mean Follow-Up	5.6 months	9.7 months
Number of Episodes	5430	13,706
% Overall Efficacy	98.7%	98.1%
% Unsuccessful Termination	0.4%	1.0%
Spontaneous VF Episodes		
	PCD™ Transvene System	**PCD™ Epicardial System**
Mean Follow-Up	5.6 months	9.7 months
Number of Episodes	973	1694
% Overall Efficacy	99.1%	98.6%
% Unsuccessful Termination	0.1%	0.5%

Table IM-6: PCD™ Transvene™ System: Comparison of Spontaneous VT/VF Episode Efficacy - 6/24/92

The overall success rate of the PCD™ Transvene™ System in terminating spontaneous episodes of VT or VF is 98.7%. In addition, there have been no reported patient deaths due to ineffective termination of a spontaneous VT/VF episode. This success rate compares very favorably with the overall success rate of the PCD™ Epicardial System which was 98.2%. Therefore, the PCD™ Transvene™ System offers the potential of decreased patient morbidity and mortality without decreasing the treatment efficacy of spontaneous VT/VF episodes.

M.4 Incidence of Complications/Observations

A comparison of the reported complications and observations was made between the PCD™ Transvene™ System and the PCD™ Epicardial System. The PCD™ Epicardial System patient population used for comparison included clinical experience as of May 14, 1992 with 742 patients and a mean implant duration of 9.7 months. These two patient groups are similar in the patient demographics and indication for implant of the PCD™ System. In the PCD™ Transvene™ System patient population, 18.2% of the patients experienced a clinical complication and 20.8% of the patients experienced a clinical observation. In the PCD™ Epicardial System, 12.8% of the patients experienced a clinical complication and 25.7% of the patients experienced a clinical observation.

Table IM-7 and IM-8 provide a comparison of the reported complications/observations and their incidence in the two patient populations.

PCD™ Transvene System
PCD™ Transvene System versus PCD™ Epicardial System
Reported Complications

Reported Complications	PCD™ Transvene™ System (N = 757)	PCD™ Epicardial System (N = 742)
Increased Defibrillation Requirements	0.8%	0.5%
Inappropriate Therapy	-	1.8%
Pace/Sense Related	0.9%	3.5%
Infection Related - Explant	2.0%	1.9%
Lead Related	6.6%	2.8%
Device Related	0.5%	0.9%

Table IM-7: Reported Complications: PCD™ Transvene™ System versus PCD™ Epicardial System - 6/24/92

PCD™ Transvene™ System PCD™ Transvene System versus PCD™ Epicardial System Reported Observations		
Reported Observations	**PCD™ Transvene™ System (N = 757)**	**PCD™ Epicardial System (N = 742)**
Ineffective Therapy	0.5%	1.1%
Inappropriate Therapy	8.2%	10.6%
Pace/Sense Related	4.1%	10.2%
Infection Related	5.3%	2.2%
Lead Related	2.2%	1.2%
Device Related	-	-

Table IM-8: Reported Observations: PCD™ Transvene System versus PCD™ Epicardial System - 6/24/92

M.5 Survival Analysis Comparison

Despite their excellent clinical performance, epicardial defibrillation lead system have important limitations. The requirement for direct thoracic access contributes significantly to patient morbidity and mortality, patient discomfort and prolonged hospitalization. The availability of reliable nonthoracotomy lead systems should provide positive clinical impact on these issues while not negatively impacting patient survival. Therefore, a comparison of the one year actuarial survival rates for the PCD™ Transvene™ and Epicardial System was performed.

Table IM-9 provides a summary of the patient deaths reported in the two patient populations by classification. As a reference, the mean follow-up time for the PCD™ Transvene™ System patient population was 5.6 months while for the PCD™ Epicardial System it was 9.7 months.

PCD™ Transvene™ System Death Classifications PCD™ Transvene™ System versus PCD™ Epicardial System		
Death Classification	**PCD™ Transvene™ System (N=757)**	**PCD™ Epicardial System (N=742)**
Sudden Cardiac	3	20
Non-Sudden Cardiac	15	41
All Cardiac	18	61
Noncardiac	4	27
TOTAL	22	88

Table IM-9: Death Classifications: PCD™ Transvene™ System versus PCD™ Epicardial System - 6/24/92

Table IM-10 provides a comparison of actuarial survival rates between the PCD™ Transvene™ and PCD™ Epicardial patient populations. The actuarial survival projections include perioperative deaths only in the calculation of survival from death due to all causes (shown in table row labelled **Overall**). Perioperative mortality includes those deaths which occur in the first thirty days post implant of the PCD™ System.

PCD™ Transvene™ System Comparison of Actuarial Survival PCD™ Transvene™ System versus PCD™ Epicardial System			(b)(4)
One Year Survival	**PCD™ Transvene™ System**	**PCD™ Epicardial™ System**	
Number of Patients	757	742	
Sudden Cardiac	99.8%	98.7%	
Non-Sudden Cardiac	96.8%	95.7%	(b)(4)
All Cardiac	96.6%	94.4%	
Noncardiac*	99.4%	97.3%	
Overall*	95.3%	87.2%	
* (b)(4) (b)(4)			

Table IM-10: Comparison of Actuarial Survival: PCD™ Transvene™ System versus PCD Epicardial System - 6/24/92

There was a significant increase in overall survival in the patients receiving a PCD™ Transvene System™. As previously noted, the Overall one year actuarial survival includes death from all causes. The overall one year survival for patients receiving the PCD™ Transvene™ System was 95.3%. This is significantly improved as compared to the overall one year actuarial survival for the PCD™ Epicardial System (87.2%) (b)(4) (b)(4) This improvement in overall survival is primarily due to the marked improvement in perioperative mortality, the PCD™ Transvene™ System having a 0.7% perioperative mortality versus the a perioperative mortality of 4.7% in the PCD™ Epicardial System. This improvement in perioperative mortality is primarily due to the elimination of the need for a thoracotomy and its associated morbidity and mortality.

N. PCD™ System Performance

N.1 PCD™ Device

Devices implanted for the treatment of recurrent ventricular tachyarrhythmias should perform safely and reliably in the indicated patient population. Device longevity, ventricular tachyarrhythmia detection, therapy performance, and

analysis of explanted devices were evaluated to assess the performance of the PCD™ Device.

Extended longevity of implantable cardioverter defibrillators should decrease the number of device replacements a given patient would experience over their lifetime and decrease unnecessary patient morbidity. Thus, the PCD™ Device longevity, which is monitored utilizing battery voltage and charge time obtained via telemetry, was analyzed. The PCD™ Device longevity data collected is consistent with the longevity projections.

The combined experience of induced and spontaneous VT/VF episode experience has shown that the PCD™ Device VT/VF detection and therapies have performed safely and according to design specifications when required to treat induced and spontaneous VT/VF episodes.

There have been a total of 41 devices explanted. Reasons for explant were patient death (15), infection (17), cardiac transplant (5), low battery voltage (1) and PCD Device performance issues (3). The analysis of the device that was explanted due to lower than expected battery voltage indicated that the decreased battery voltage measurement was due to hermetic leakage at the input to one of the integrated circuits and this affected the battery indicator circuit only and did not affect the critical functions of the device. This leads to a voltage drop across a resistor where the voltage measurement is taken. Analysis indicated that the battery was performing to specifications and the hermetic leakage was a random event. Analysis of the other three devices indicated that two were due to random component failure and one due to shorting on Pulse 2 output. Thus, arcing occurred between the conductors inside the hermetically enclosed brazed ring of the high power hybrid. As a result, high voltage was momentarily applied to the low power circuitry, including the low power hybrid. This low power hybrid lost function including the capability to pace and transmit telemetry due to excessive voltage applied. Since this is the only device that exhibited this type of failure in the field and the hybrid manufacturing process has demonstrated that it will screen out infant mortality, this failure was assumed to be a random component failure.

Based on the clinical data collected, the PCD™ Device has performed safely and reliably in the indicated patient population.

N.2 Transvene™ Lead Performance

The Transvene™ Lead System consists of a Right Ventricular Lead, a Coronary Sinus/Superior Vena Cava lead, and a Subcutaneous Patch lead. There have been a total of 757 Right Ventricular leads (15 with the SP2100 and 742 with the Model 6884/6966), 796 Coronary Sinus/Superior Vena Cava leads (Model 6881/6963), and 718 Subcutaneous Patch leads (Models 6895/10317/6999) implanted with a cumulative implant duration of 4246 months. The reported incidence of conductor coil fracture is 0.5% (4/757).

Based on the clinical data collected, the Transvene™ leads have performed safely and reliably.

O. Summary

The overall clinical experience with the PCD™ Transvene™ System indicates that the system performed according to design and specification. The reported clinical complications and patient deaths are appropriately addressed in the required labelling for the system and the patient selection criteria for implant of the device is appropriate.

The following can be drawn from this analysis of the data collected in this clinical study:

Patient Deaths

- The projected one year survival probabilities for Sudden Cardiac Death, Non-Sudden Cardiac Death, all Cardiac Deaths and Noncardiac Death were found to be 99.8%, 96.8%, 96.6%, and 99.4%, respectively.

  The incorporation of programmable VT/VF detection and therapies has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

- The sudden cardiac death survival of 99.8% at one year is comparable to that of the AICD patient population 98.0%.

- There have been no deaths due to a PCD™ Device malfunction.

Complications/Observations

- Complications were reported in 18.2% of the patient population and observations were reported in 20.7% of the patient population.

- The incidence of complications was comparable to that of the market released AICD system in the categories of ineffective VT/VF therapy, pocket infection, and pocket erosion and was lower than the AICD in the category of inappropriate delivery of VT/VF therapy.

Patient Indications

- All of the patients entered into this clinical evaluation met at least one of the primary indications. Sudden cardiac death (SCD) was the primary indication in 37.1% of the patients, recurrent ventricular tachycardia (VT) was the primary indication in 49.8 % of the patients and SCD/VT was the primary indication in 13.1% of the patients.

- The number of patients (41.1%) receiving VT/VF therapy for spontaneous episodes of ventricular arrhythmias supports the conclusion that the patient selection criteria are appropriate and that the PCD™ Transvene™ System was implanted in patients who benefit from this therapy.

- The one year sudden cardiac death survival rates for the SCD patient group was 100.0%, for the VT patient group 99.7% and the SCD/VT patient group 100.0%.

VT/VF Detection and Therapy Performance

- The PCD™ Transvene™ System properly detects and treats VT as demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VT was 98.7%.

- The PCD™ Transvene™ System properly detects and treats VF as demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VF was 99.1%.

- There were no reported patient deaths due to the nondetection of a spontaneous VT or VF episode by the PCD™ Transvene™ System.

PCD™ Transvene™ System Performance

- The PCD™ Transvene™ System components (Model 7216A/7217B and Model 6884/6966, 6881/6963, 6895/6999 Transvene™ leads) have performed according to design and specification and are, therefore, considered safe and effective in the indicated patient population.

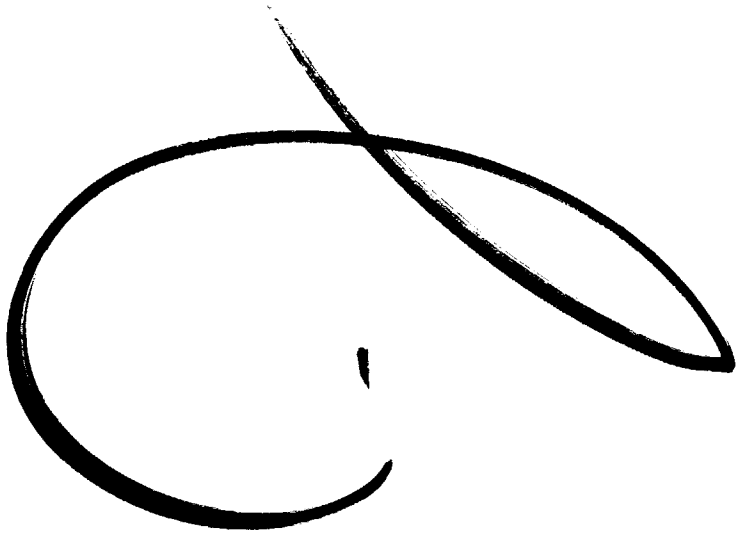
P. Clinical Experience Summary Conclusions

The PCD™ Transvene™ System is a tiered therapy device which combines features of bradycardia pacing support, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. The incorporation of these features has allowed the physician to titrate the ICD therapy to meet specific patient clinical needs, allowed fewer shocks to be delivered for recurrent ventricular tachycardia because of antitachycardia pacing features, allowed fewer cases of inappropriate therapy delivery due to programmable detection and allowed a sudden cardiac death survival rate identical to the Ventak-P Epicardial System.

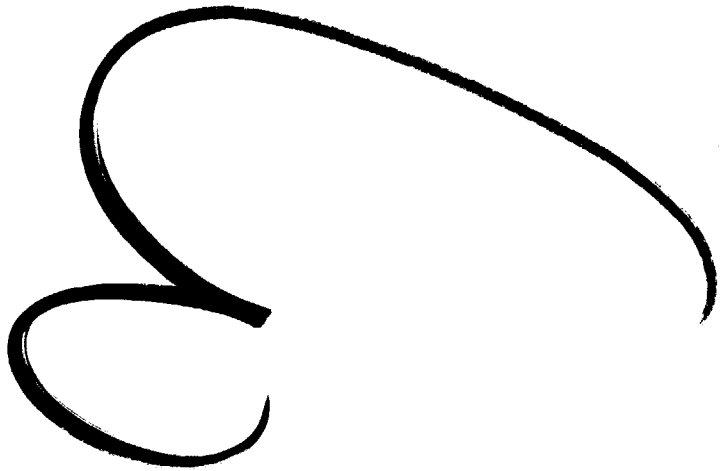
The PCD™ Transvene™ System, due to the elimination of the need for a thoracotomy, has provided a marked improvement in both the perioperative and overall patient mortality as compared to the PCD™ Epicardial System. In addition, due to the decreased perioperative morbidity and mortality, the post implant hospital stay has been decreased to a mean of seven days as opposed to a mean of fourteen days for the PCD™ Epicardial System.

Medtronic asserts and the PCD™ Transvene™ investigators unanimously agree that the findings of the clinical study support the conclusion that the Medtronic Tachyarrhythmia Control System and the Transvene™ Cardioversion and Defibrillation Electrodes are safe and effective in the indicated patient population.

II. Center/Implant Distribution



III. Compliance



II. Centers/Implant Distribution

This report involves 800 patients and 805 implant procedures. Five patients had two complete systems implanted due to infection of the first implanted systems. These five reimplants are included in the implant analysis presented in this report since the entire PCD™ system was removed and replaced. Forty-three (43) of these 800 patients received "Non-Standard" systems and are, therefore, analyzed separately (see Section VIIIG). Therefore, 762 implant procedures in 757 patients are included in the following analysis. The following table shows how these 762 implants are distributed between the Models 7216A and 7217B and between U.S. and International investigators.

PCD™ Transvene™ System Implant Distribution						
	Total		U.S.		Int'l	
7217B	744	97.6%	444	99.3%	300	95.2%
7216A	18	2.4%	3	0.7%	15	4.8%

Table II: Implant Distribution - 6/24/92

These 757 patients received their PCD™ Transvene™ Systems in 78 investigative centers in the U.S. and Internationally (35 U.S., 43 Int'l). There were a mean of 9.8 implants per center (min 1, max 60). A complete list of investigative centers, number of implants and date of first implant is provided in Appendix A.

III. Compliance

The study protocol requires that patients be followed at 1 and 3 months post implant and then every three months. Overall compliance at the six month follow-up was 93.7%. For further discussion of follow-up compliance and a definition of follow-up intervals see Appendix B.

Analysis

IV. Justification for Data Pooling

This section will describe the results of the analysis to demonstrate that the data from the U.S. and International investigative centers and the two device model numbers may be pooled. This section will also compare the three lead systems which will be presented throughout the report.

A. Comparison of U.S. and International Patients

Statistical comparisons were made between the two populations age, sex, ejection fraction, primary indication, NYHA, and previous cardiovascular history. Table F1 in Appendix F summarizes the results of statistical analysis.

All study investigators used the same:

a. patient selection criteria,
b. investigational protocol procedures, and
c. indications for implant of PCD™ Transvene™ System.

Of the variables analyzed patient age, ejection fraction, primary indication, NYHA classification, coronary artery disease and cardiomyopathy showed a statistically significant difference between the U.S. and the International patient populations at a 0.05 significance level. The difference in NYHA classification becomes insignificant when adjusting for multiple inference using the Hochberg procedure (Dunnett and Tamhane, "A Step-Up Multiple Test Procedure," Journal of the American Statistical Association, March 1992, 87:162-170). See Appendix F for multiple inference adjustments. Coronary artery disease, ejection fraction, cardiomyopathy, primary indication and age remain statistically significant after adjusting for multiple inference. The U.S. patient population has a higher percentage of patients with coronary artery disease and cardiomyopathy, lower mean ejection fraction, more patients with VT as their primary indication and a higher mean age. The difference in age may explain the differences in underlying disease and cardiac ejection fraction. These factors that are statistically significant but are not considered to be clinically significant enough to require stratification of the U.S. and International patient populations. The differences may have to do with regional attitudes toward access to health care for the aged. A breakdown of outcome variables for the U.S. and International patient populations will be provided in section VIII-I.

B. Comparison of Model 7216A and Model 7217B

Table F2 in Appendix F summarizes the results of statistical analysis comparing the Model 7216A to Model 7217B. No parameters were found to be statistically significant between the two PCD™ models at a 0.05 significance level.

C. Lead Configurations

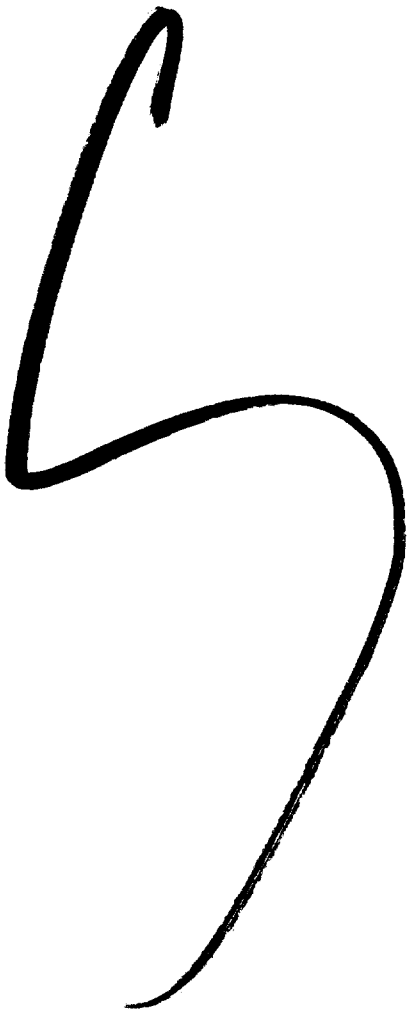
Table F3 in Appendix F shows comparisons of patient variables for the three lead systems. This was done to document that there were no significant differences in patient characteristics between the implanted lead configurations.

Of the variables analyzed in Table F3 sex and cardiomyopathy showed a statistically significant difference between the three lead configurations at a 0.05 significance level. The difference in sex and percentage of patients with cardiomyopathy becomes insignificant when adjusting for multiple inference using the Hochberg procedure (Dunnett and Tamhane, "A Step-Up Multiple Test Procedure," Journal of the American Statistical Association, March 1992, 87:162-170). See Appendix F for multiple inference adjustments.

D. Statistical Analysis Conclusions

The statistical comparisons between the U.S. and International populations indicated no clinically significant differences therefore the data may be pooled. Analysis of the patients receiving the two PCD™ models indicates no statistically significant differences therefore the data from the two devices may be pooled.

The results from the comparison of lead systems indicated no statistically significant differences in patient demographics, primary indication, or heart disease.



V. Patient Data

A. Primary Indications

The PCD™ Transvene™ System is intended for use in patients who are at risk of sudden death due to ventricular tachyarrhythmias. Patients currently identified as appropriate candidates for a PCD™ system include those who have:

1. survived at least one episode of cardiac arrest (manifested by a loss of consciousness) due to a ventricular tachyarrhythmia that was not caused by an acute myocardial infarction (abbreviated below as SCD for Sudden Cardiac Death); or

2. recurrent, sustained ventricular tachycardia that remains inducible via programmed electrical stimuli or exercise, or occurs spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated chronically by the patient (abbreviated below as VT for Ventricular Tachycardia); or

3. Congenital Long QT Syndrome with recurrent syncope despite full medical therapy (e.g. beta blockers, phenytoin, and/or phenobarbital) (abbreviated below as Long QT). (Request for approval of this indication is being withdrawn since no patient was enrolled in the study with this indication).

Although no patients in the described patient population have been implanted for Long QT Syndrome (b)(4) patients have Long Q-T Syndrome as their underlying heart disease. They have all either had an episode of SCD and/or VT, so their primary indication is reported as SCD or VT rather than Long Q-T. The sponsor continues to believe that Long Q-T Syndrome is an appropriate indication for the PCD™ System and will, therefore, continue to allow investigators to implant for this indication if they are presented with the appropriate patient. However, this indication is not included in the current labeling because it has not yet been thoroughly evaluated.

Patients with ventricular tachyarrhythmias associated with reversible causes such as ischemia (patients without diseased myocardium, positive thallium scan, and severe coronary artery

disease), drug intoxication, arrhythmogenic drug response, electrolyte imbalances, hypoxia, or other causes of transient arrhythmias, e.g., electrocution, WERE NOT considered as potential candidates for the PCD™ System.

The table below summarizes the primary indications for receiving the PCD™ Transvene™ System.

PCD™ Transvene™ System Primary Indication		
SCD	281	37.1%
VT	377	49.8%
SCD & VT	99	13.1%
Total	757	100.0%

Table V-1: Primary Indication - 6/24/92

Key: SCD - Sudden Cardiac Death survivor, without recurrent sustained VT

VT - Ventricular Tachycardia (recurrent, sustained), without an episode of sudden cardiac death

SCD & VT- Patients having had both sudden cardiac death and recurrent, sustained, ventricular tachycardia

The distribution of primary indication differs from the patient population receiving the commercially available AICD as reported in the 1988 PACE article (Thomas, et al, Implantable Defibrillation: Eight years Clinical Experience. PACE. 1988; 11(11): 2053-8)) with respect to the percent of the population with sustained ventricular tachycardia without having experienced an episode of sudden cardiac death. The article cited reported 31.5% (N = 3610) of their patients with VT and no episodes of SCD while the patient population receiving the PCD™ had 49.8% (N = 757) (Chi square $P < 0.001$). This difference is expected because of the antitachycardia pacing feature of the PCD™. The use of pacing therapies for ventricular tachycardia enhances patient acceptance over higher energy cardioversion pulses and extends the longevity of the PCD™ pulse generator.

B. Patient Demographics

(b)(4)

PCD™ Transvene™ System Patient Demographics
Patient Sex:
(b)(4)

Table V-2: Patient Demographics - 6/24/92

(b)(4)

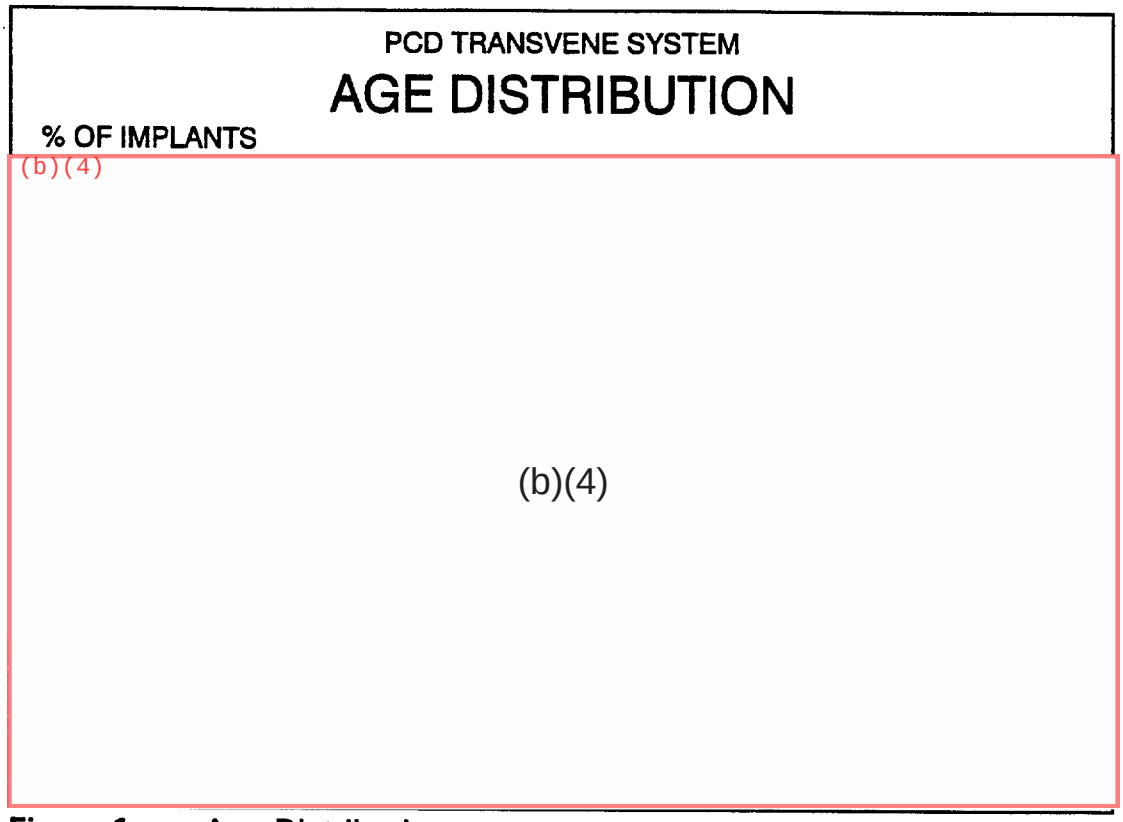


Figure 1: Age Distribution

C. Primary Cardiovascular Disease

The primary heart disease of the patients involved in the PCD™ Transvene™ clinical study is presented in Table V-3. Primary heart disease differs from primary indications for receiving the PCD™ system. The primary heart disease is generally the underlying cause of the patient's arrhythmia. The arrhythmia resulting from the underlying heart disease is the reason the patients receive the PCD™, not the underlying disease itself.

As expected, the majority (561 or 74.1) of the patient population had coronary artery disease as their primary heart disease, either alone or in combination with other conditions.

PCD™ Transvene™ System
Primary Cardiovascular Disease

(b)(4)

(b)(4)

(b)(4)

(b)(4)

100

D. Ejection Fraction

(b)(4)

(b)(4)

PCD™ Transvene™ System
Ejection Fraction

(b)(4)

(b)(4)

(b)(4)

(b)(4)

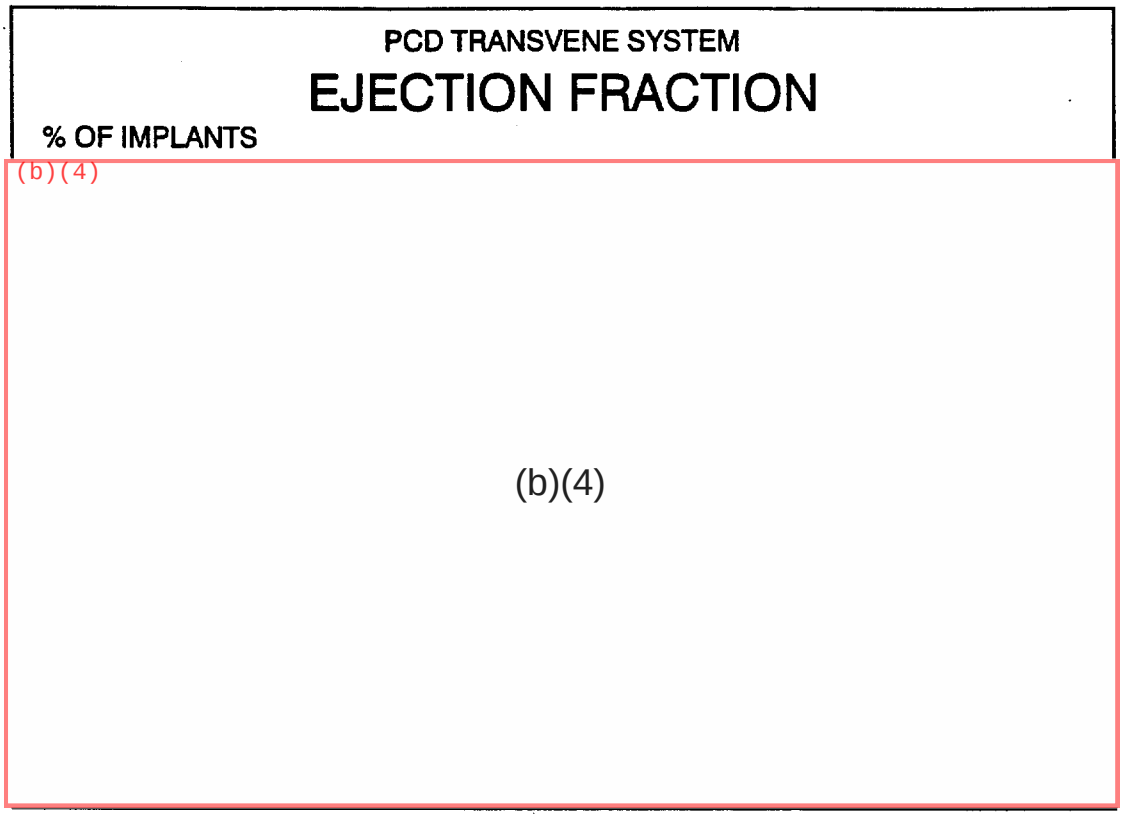
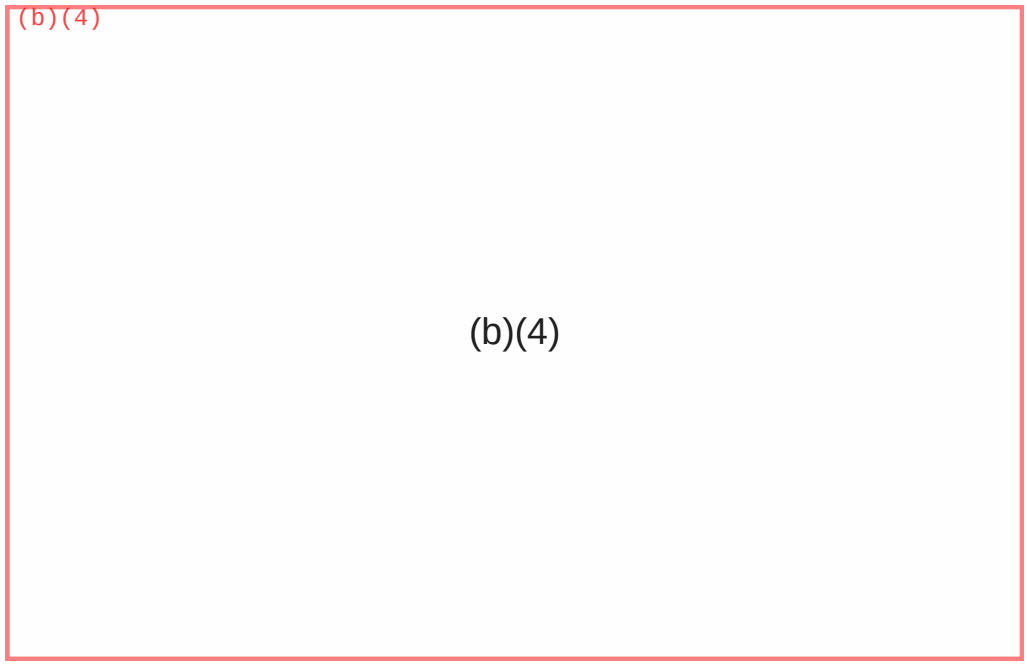


Figure 2: Ejection Fraction

E. New York Heart Association (NYHA) Functional Status



This indicates that most patients are able to perform the activities of daily living without symptoms of congestive heart failure.

PCD™ Transvene™ System NYHA Classification N = 736	
(b)(4)	(b)(4)

Table V-5: NYHA Classification - 6/24/92

F. Preimplant Antiarrhythmic Drug Testing

(b)(4)

(b)(4)

PCD™ Transvene™ System Drug Testing Prior to Implant	
(b)(4)	(b)(4)

Table V-6: Antiarrhythmic Drug Testing Prior to Implant - 6/24/92

G. Pre-Implant Electrophysiologic Evaluation

(b)(4)

(b)(4)

PCD™ Transvene™ System
Pre-Implant Electrophysiological Evaluation of Sustained VT
by Primary Indication

(b)(4)

(b)(4)

Table V-7: Pre-Implant Electrophysiologic Evaluation of Sustained VT- 6/24/92

(b)(4)

(b)(4)

H. Antiarrhythmic Drugs at Implant

(b)(4)

(b)(4)

PCD™ Transvene™ System Antiarrhythmic Drugs at the Time of PCD™ System Implant	
Drug Class	**Number of Patients**
(b)(4)	

(b)(4)

Table V-8: Antiarrhythmic Drugs at Implant - 6/24/92

I. Patients with Bradycardia in Past Medical History

(b)(4)

(b)(4)

PCD™ Transvene™ System
Bradycardia Pacing Post Therapy

(b)(4)

(b)(4)

Table V-9: Post Therapy Pacing - 6/24/92

15

J. Summary: Patient Data

PCD™ Transvene™ System **Patient Data Summary** N = 757	
Primary Indication **SCD** **VT** **SCD/VT**	 281 37.1% 377 49.8% 99 13.1%
Mean Age	59.4 years
Male **Female**	610 80.6% 147 19.4%
History of Coronary Artery Disease	559 73.8%
Mean Ejection Fraction	35.6%
NYHA Classification I or II	609 80.4%
Antiarrhythmic Drugs Prior to Implant	588 77.7%
VT Induced at Pre-Implant EP Study	546 72.1%
VT Demonstrated to be Pace Terminable at Pre-Implant EP Study	266 48.7%
History of Bradycardia	120 15.9%
Pacing Following Termination of an Induced Tachyarrhythmic Episode	122 17.2% (% of Induced Patients)

Table V-10: Patient Data Summary - 6/24/92

K. Conclusions: Patient Data

The patient population receiving the PCD™ Transvene™ System is the patient population described in the study protocol.

VI. Implant Data

(b)(4)

(b)(4)

A. Implant Procedure Summary

(b)(4)

(b)(4)

1.

2. (b)(4)

(b)(4)

(b)(4)

1. (b)(4)

(b)(4)

PCD™ Transvene™ System
Pace/Sense Parameters
Recommended Implant Values

(b)(4)

(b)(4)

(b)(4)

Table VI-

2.

(b)(4)

3.

(b)(4)

(b)(4)

110

B. Venous Entry Site

(b)(4)

(b)(4)

PCD™ Transvene™ System Venous Entry Site			
	RV Leads Model 6884/6966/SP2100	CS/SVC Leads Model 6881/6963	All Transvene™ Leads
(b)(4)			

(b)(4)

Table VI-2: Venous Entry Site - 6/24/92

(b)(4)

(b)(4)

C. Pace/Sense Data

(b)(4)

(b)(4)

1. Implant Pace/Sense Parameters

(b)(4)

(b)(4)

PCD™ Transvene™ System Implant Pace/Sense Parameters				
	Pacing Parameters		Sensing Parameters	
	Implant Pacing Threshold	Implant Pacing Resistance	Implant R-Wave Amplitude	Implant Slew Rate
(b)(4)				

(b)(4)

Table VIC-3: Implant Pacing Parameters - 6/24/92

(b)(4)

(b)(4)

PCD™ Transvene™ System Implant Pacing Parameters								
	Implant Pacing Threshold (V @ 0.5ms)				Implant Pacing Resistance (ohms)			
	RV-RV	RV-CS	RV-SQ	RV-SVC	RV-RV	RV-CS	RV-SQ	RV-SVC
(b)(4)								

(b)(4)

Table VIC-4: Implant Pacing Parameters by Pathway - 6/24/92

(b)(4)

(b)(4)

2. P and T wave Sensing Testing

(b)(4)

(b)(4)

PCD™ Transvene™ System Implant P and T Wave Sensing			
	Total N = 762	Model 7217B N = 744	Model 7216A N = 18
(b)(4)			

(b)(4)

Table VIC-5: P/T Wave Sensing - 6/24/92

(b)(4)

(b)(4)

D. Defibrillation Testing

1. Lead System Testing

(b)(4)

(b)(4)

(b)(4)

(b)(4)

PCD™ Transvene™ System
Lead System Testing

(b)(4)

(b)(4)

Table VID-1: Lead System Evaluation Summary - 6/24/92

2. Implanted Lead Systems

(b)(4)

(b)(4)

PCD™ Transvene™ System Implanted Lead Systems	
Lead System	**Implant Frequency**
(b)(4)	

(b)(4)

Table VID-2: Implanted Lead System - 6/24/92

(b)(4)

(b)(4)

PCD™ Transvene™ System Location of the Subcutaneous Patch Electrode						
Intercostal Space	Mid Clavicular Line	Anterior Axillary Line	Mid Axillary Line	Posterior Axillary Line	Subscapular	Total
(b)(4)						

(b)(4)

Table VID-3: Location of the Subcutaneous Patch Electrode - 6/24/92

(b)(4)

(b)(4)

PCD™ Transvene™ System
Number of Configurations Tested Prior to Implant

(b)(4)

(b)(4)

Table VID-4: Number of Configurations Tested Prior to Implant

(b)(4)

(b)(4)

PCD™ Transvene™ System
Number of Lead System Configurations Evaluated

(b)(4)

(b)(4)

Table VID-5: Number of Lead System Configurations Tested - 6/24/92

(b)(4)

(b)(4)

PCD™ Transvene™ System
Implantation of the First Lead System Evaluated

(b)(4)

(b)(4)

(b)(4)

(b)(4)

PCD™ Transvene™ System
Implanted Lead Systems

(b)(4)

(b)(4)

3. Lowest Energy of Defibrillation (LED)

(b)(4)

(b)(4)

PCD™ Transvene™ System
Lowest Energy of Defibrillation

(b)(4)

(b)(4)

4. Defibrillation Threshold (DFT)

(b)(4)

(b)(4)

PCD™ Transvene™ System
Defibrillation Threshold (DFT)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

5. Patients not Meeting Implant Criteria

(b)(4)

(b)(4)

E. Data Summary - Implant Data

(b)(4)

(b)(4)

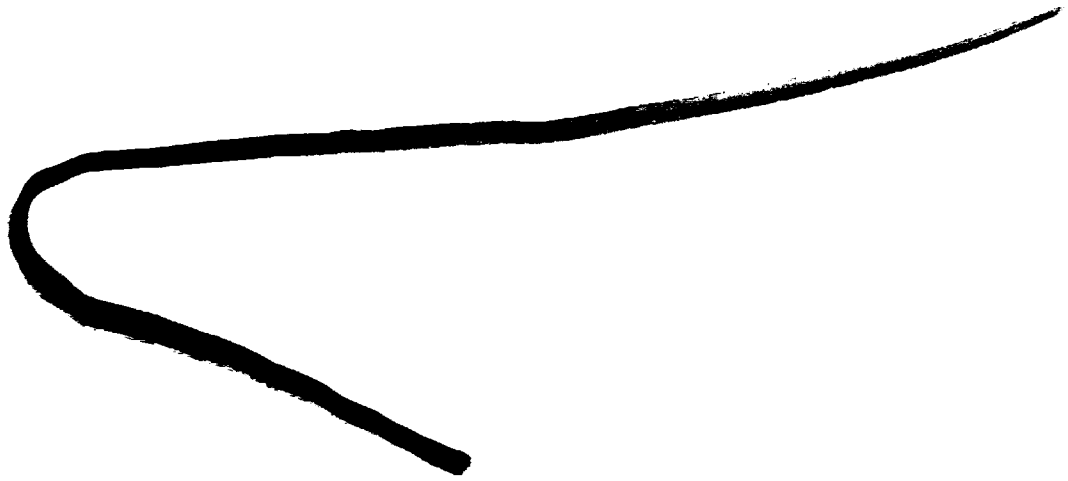
(b)(4)

(b)(4)

F. Conclusions - Implant Data

Five-hundred-forty-three (543) of the 854 patients evaluated for a Transvene™ system met the implant criteria. Seven-hundred-fifty-seven (757) received a Transvene™ system or 88.6% of the patients evaluated. Seven-hundred-thirteen (713) patients or 94.2% of the 757 patients receiving the Transvene™ system had an LED $\leq$ 24 Joules.

Follow-up Data



VII. Follow-up Data

A. (b)(4)

(b)(4)

B. Follow-up Data - Quantity

(b)(4)

(b)(4)

PCD™ Transvene™ System
Follow-up Quantity

(b)(4)

(b)(4)

Table VII-1: Follow-up Time - Months - 6/24/92

Table VII-2 shows the follow-up time by type of data form.

PCD™ Transvene™ System
Follow-up Quantity by Data Form Type

(b)(4)

(b)(4)

Table VII-2: Follow-up Quantity - Data Form Type - 6/24/92

C. Induced and Spontaneous VT Episode Experience

The primary benefits from the use of the PCD™ System are the detection and termination of life-threatening ventricular arrhythmias. The use of pacing therapies for the treatment of ventricular tachycardia reduces patient trauma associated with higher energy cardioversion pulses and extends the longevity of the PCD™ pulse generator. The PCD™ System allows the titration of therapies for patients with ventricular tachycardia while providing critical defibrillation backup.

The purpose of this section is to describe VT detection and therapy. Information and experience obtained from both induced and spontaneous episodes of VT will demonstrate the safe and effective operation of the PCD™ for detection and treatment of ventricular tachycardias.

The criteria for detecting episodes of ventricular tachycardia are independent of the detection criteria for ventricular fibrillation. Up to four independently programmable ventricular tachycardia (VT) therapies may be chosen and automatically delivered from among two overdrive pacing modes; burst and ramp, and synchronous cardioversion.

Cardioversion pulses can be delivered by three methods:

- Single Pulse - a single pulse is delivered between two electrodes with a single current pathway.

- Simultaneous Pulse - two pulses are delivered simultaneously via two current pathways of three electrodes. Two of the electrodes act as the anodes (positive) while the third acts as a common (negative) cathode for both pulses.

- Sequential Pulse - two pulses are delivered in a sequential fashion (one pulse is delivered, followed by a short delay, and then the second pulse is delivered) over two different pathways, between three electrodes. Again, two of the electrodes act as the anodes while the third acts as the common electrode for both pulses.

The clinical study was designed to evaluate the operation, safety, and effectiveness of the PCD™ System components in detecting

and treating episodes of ventricular tachycardia and ventricular fibrillation.

The objectives of the clinical study that are addressed in this section are:

- to evaluate the ability of the PCD™ Device to properly detect episodes of VT and to evaluate the ability of the system to appropriately discriminate between VT/VF;

- to determine the efficacy of the PCD™ Device with Transvene™ lead systems in treating VT.

Ventricular tachycardia is detected by the PCD™ using two primary detection parameters, tachycardia detection interval (TDI) and number of intervals to detect (VT NID). In addition, two optional parameters, the "Onset Criteria" and the "Interval Stability Criteria", may be utilized in special situations. The "Onset Criteria" is designed to differentiate between sinus tachycardia and ventricular tachycardia. The "Stability Criteria" is designed to differentiate between ventricular tachycardia and atrial arrhythmias with a rapid ventricular response.

1. Tachycardia Detection Interval (TDI)

   The programmable tachycardia detection interval (TDI) allows the physician to choose the range of intervals between the programmed TDI and the fibrillation detection interval (FDI) that are detected as VT. If the VT detection criteria are all fulfilled, the rhythm will be treated by one of the three (3) programmable VT therapy types; Ramp, Burst or Cardioversion. Intervals longer than or equal to the programmed TDI but shorter than the minimum programmed pacing rate are considered as normal sensed events. Sensed intervals shorter than the FDI are applied towards the VF detection criteria.

   Table VIIC-1 shows the distribution of the last known programmed tachycardia detection interval (TDI) for those patients with VT detection programmed ON at last known follow-up. Note that this excludes patients that died (22), those patients that had their device explanted (14), and patients with VT detection programmed OFF (219). Patients with VF only as their primary indication often have

VT detection programmed OFF if they do not have a VT to treat. The most common TDI's programmed are between

(b)(4)

(b)(4)

PCD™ Transvene™ System
Tachycardia Detection Interval
at Last Known Follow-Up

(b)(4)

(b)(4)

Table VIIC-1: Tachycardia Detection Interval (TDI) at Last Known Follow-up - 6/24/92

(b)(4)

(b)(4)

2. Number of Intervals to Detect (VT NID)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

PCD™ Transvene™ System
Number of Intervals to Detect VT
at Last Known Follow-Up

(b)(4)

(b)(4)

Table VIIC-2: Number of Intervals to Detect VT (NID) at Last Known Follow-up - 6/24/92

134

3. VT Therapy Programming

(b) (4)

(b)(4)

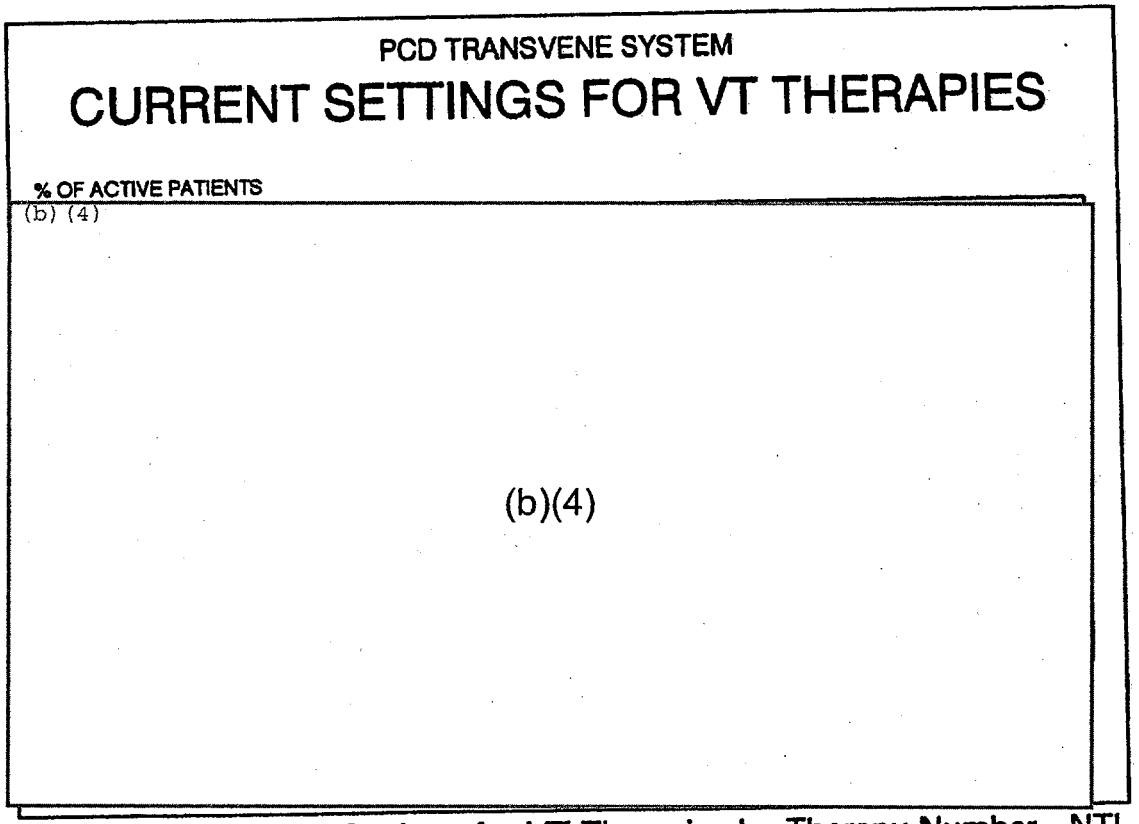


Figure 3: Current Settings for VT Therapies by Therapy Number - NTL System

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4. Stability and Onset Criterion

An implantable cardioverter defibrillator such as the PCD™ Device attempts to distinguish clinical ventricular tachyarrhythmias from both sinus and other non-ventricular tachyarrhythmias such as rapid atrial fibrillation or flutter. The Stability algorithm is intended to prevent inappropriate VT detection when rapid ventricular contractions with irregular intervals caused by atrial fibrillation would otherwise fulfill the Interval Criterion. The Onset algorithm is intended to avoid inappropriate VT detection during an episode of sinus tachycardia with gradually increasing rates.

Prior to implant of the PCD™ system, the patient undergoes a complete evaluation of his arrhythmia status. This usually includes a cardiovascular history, electrophysiology study, holter monitoring, and exercise testing. Through this testing the investigator can determine if the patient is likely to have a non-ventricular arrhythmia that could be inappropriately detected as ventricular tachycardia and result in the delivery of a anti-tachycardia pacing therapy or cardioversion.

The physician has several clinical options when dealing with such patients prior to the use of the Onset or Stability algorithms. In the case of patients whose maximum sinus rate overlaps with the VT rate the physician can program the Tachycardia Detection Interval (TDI) to ensure that only VT is detected and treated by the PCD™ Device. In addition, the physician may elect to place the patient on beta blocker therapy to lower the patient's maximum sinus rate during exercise. If the patients maximum sinus rate continues to overlap the VT rate, the use of the Onset algorithm may be the best method of avoiding inappropriate VT detection. In patients with rapid ventricular responses to atrial fibrillation the physician can elect to treat the atrial fibrillation with antiarrhythmic therapy. If there is still a problem with inappropriate detection and therapy delivery, the use of the Stability algorithm may be warranted.

(b)(4)

(b)(4)

(b)(4)

(b)(4)

PCD™ Transvene™ System Interval Stability Criterion Uses by Patient Indication	
Indication	Number of Patients
(b)(4)	

(b)(4)

Table VIIC-3: Stability Uses by Patient Indication - 6/24/92

(b)(4)

(b)(4)

PCD™ Transvene™ System
Interval Stability Criterion
At Last Known Follow-up (n = 459 pts)

(b)(4)

(b)(4)

Table VIIC-4: Interval Stability Criterion - 6/24/92

The indications for use of the Stability algorithm included previous history of atrial fibrillation or if atrial fibrillation/flutter has caused inaappropriate detection nd delivery of therapy.

(b)(4)

(b)(4)

PCD™ Transvene™ System
Onset Criterion

(b)(4)

(b)(4)

Table VIIC-5: Onset Uses by Patient Indication - 6/24/92

(b)(4)

(b)(4)

PCD™ Transvene™ System Onset Criterion
(b)(4)
(b)(4)

Table VIIC-6: Onset Criterion Programmed Values - 6/24/92

The indications for use of the Onset algorithm in the patient population include overlap of maximum sinus rate and VT rate and delivery of inappropriate therapy secondary to sinus tachycardia.

(b)(4)
(b)(4)

5. Induced Episodes of Ventricular Tachycardia

(b)(4)
(b)(4)

(b)(4)

(b)(4)

PCD™ Transvene™ System
Induced VT Episodes
by Follow-up

(b)(4)

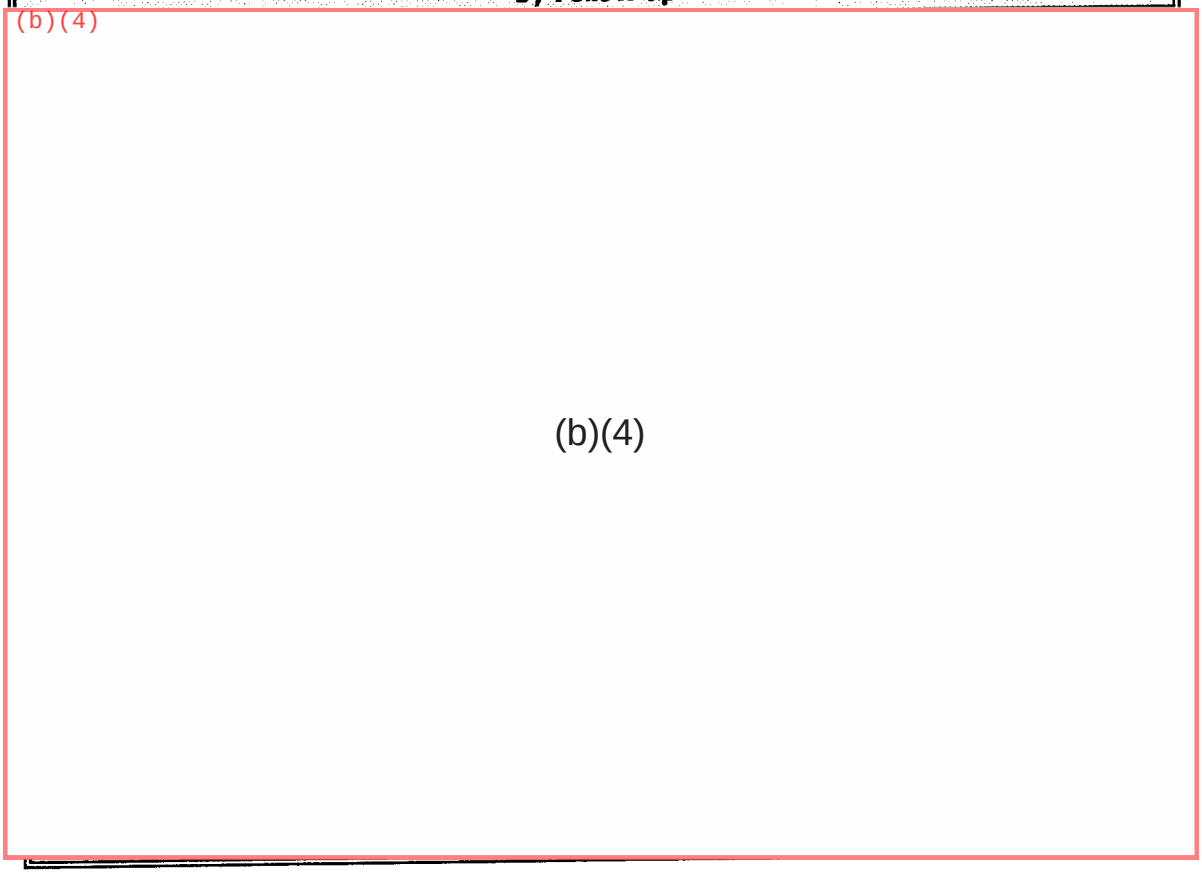


Table VIIC-7: Induced Episodes of VT at Follow-up - 6/24/92

(b)(4)

(b)(4)

a. Accelerations

(b)(4)

(b)(4)

(b)(4)

(b)(4)

PCD™ Transvene™ System
Acceleration
VT to Faster VT

(b)(4)

(b)(4)

Table VIIC-8: Accelerations from VT to Faster VT - 6/24/92

142

PCD™ Transvene™ System
Acceleration
VT to V-Flutter

(b)(4)

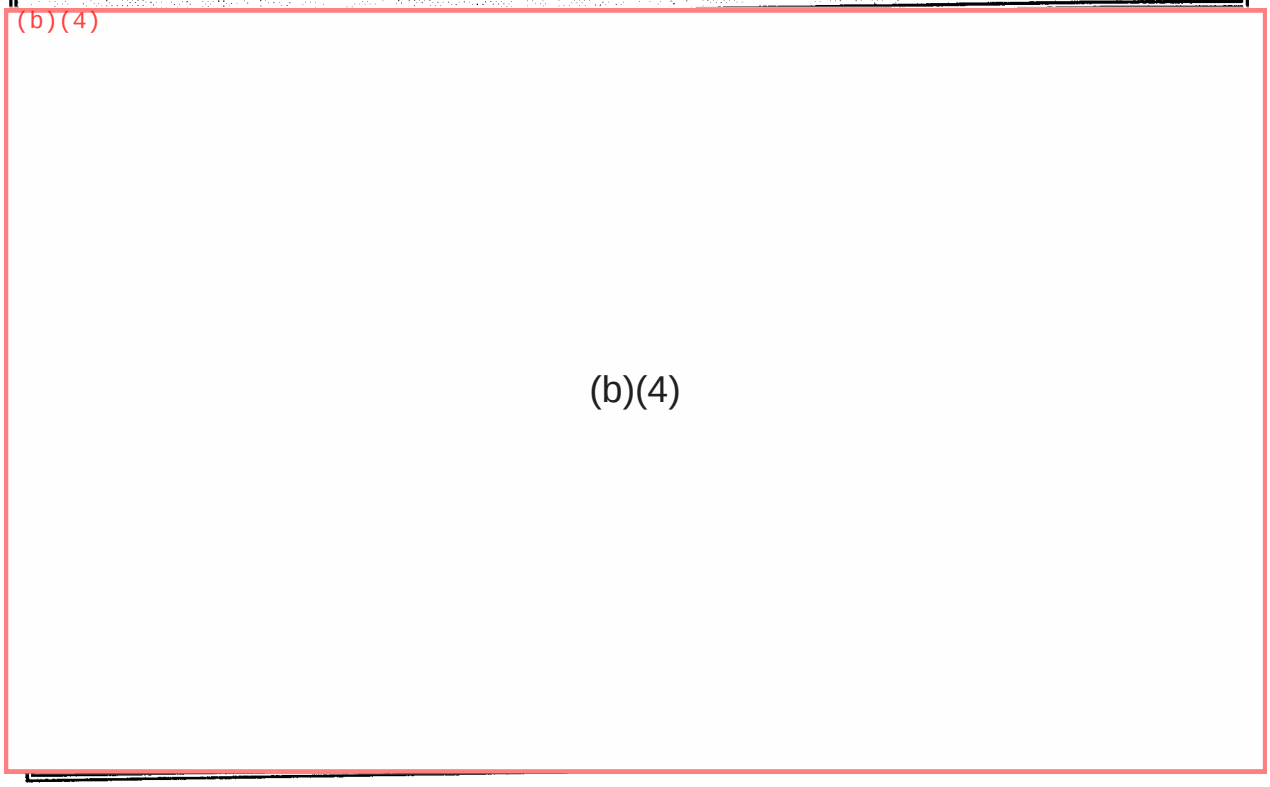


Table VIIC-8a: Accelerations from VT to V-Flutter - 6/24/92

(b)(4)

(b)(4)

PCD™ Transvene™ System
Acceleration
VT to VF

(b)(4)

(b)(4)

Table VIIC-9: Accelerations from VT to VF - 6/24/92

(b)(4)

(b)(4)

6. Spontaneous VT Episode Experience

(b)(4)

(b)(4)

PCD™ Transvene™ System
Spontaneous VT Episodes
by Follow-up Interval

(b)(4)

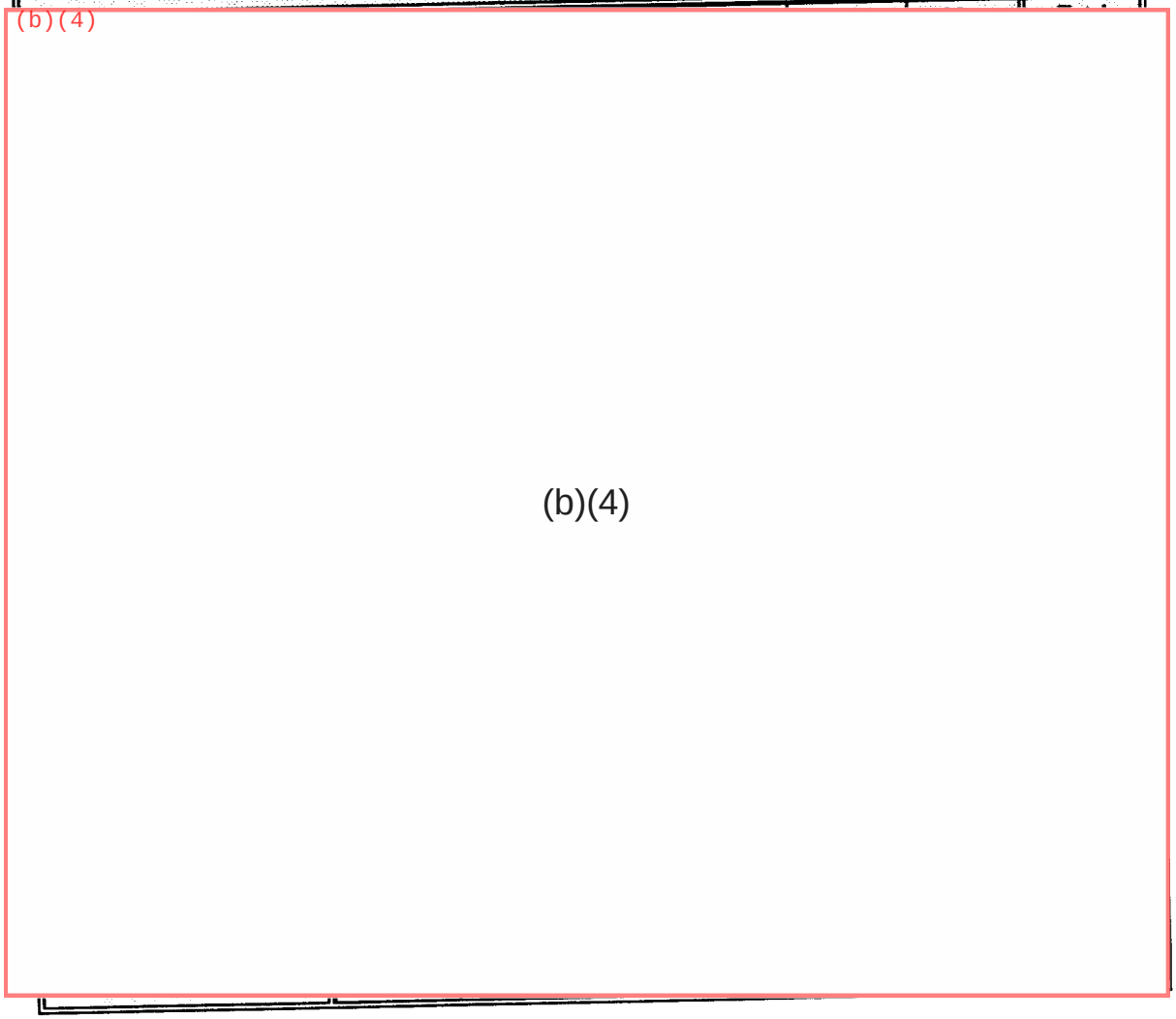


Table VIIC-10: Spontaneous VT Episode and Therapy Experience by Follow-up Interval - 6/24/92

(b)(4)

(b)(4)

(b)(4)

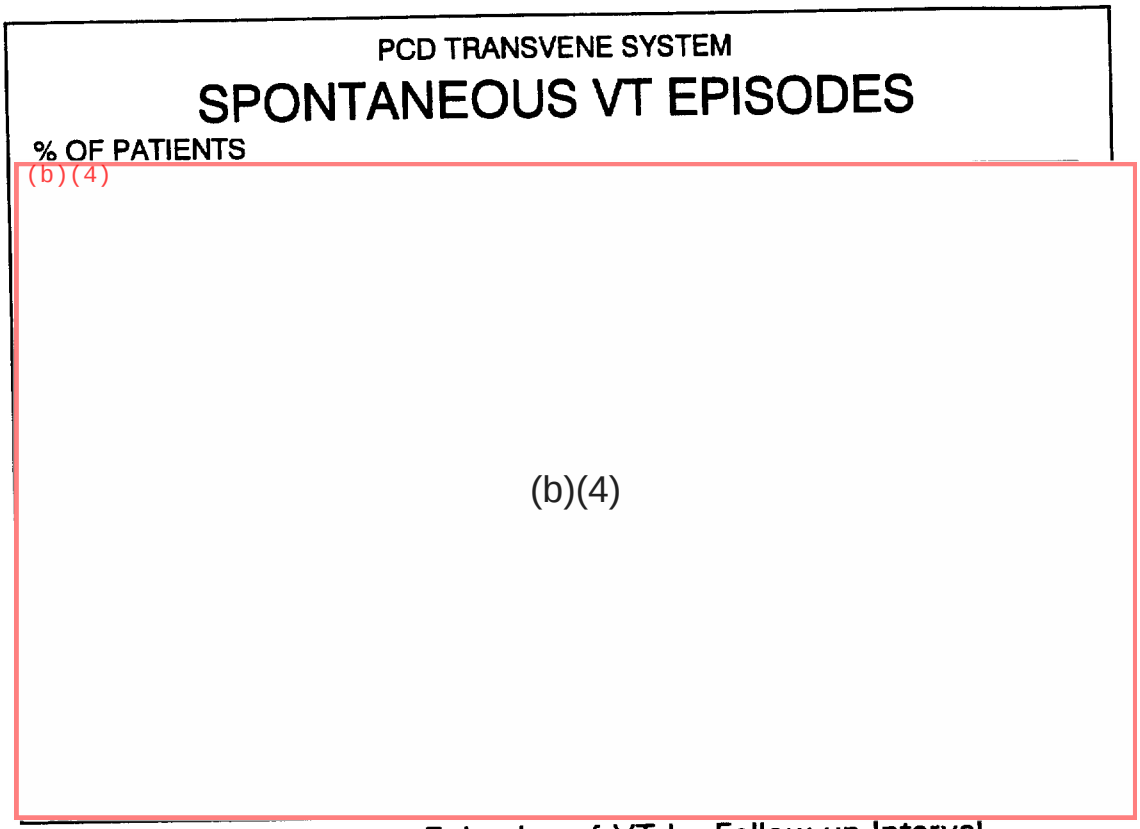


Figure 4: Spontaneous Episodes of VT by Follow-up Interval

(b)(4)

(b)(4)

PCD TRANSVENE SYSTEM

PATIENTS WITH SPONTANEOUS VT EPISODES

CUMULATIVE NUMBER OF PATIENTS OVER TIME

(b)(4)

(b)(4)

Figure 5: Cumulative Number of Patients with Spontaneous VT Episodes by Follow-Up Interval

(b)(4)

(b)(4)

PCD TRANSVENE SYSTEM

PATIENTS WITH SPONTANEOUS VT EPISODES

CUMULATIVE NUMBER OF PATIENTS OVER TIME WITH 6+ MO FOLLOW-UPS

(b)(4)

(b)(4)

Figure 6: Cumulative Number of Patients with $\geq$6 Months of Follow-Up with Spontaneous VT Episodes

(b)(4)

(b)(4)

PCD TRANSVENE SYSTEM

DISTRIBUTION OF SPONTANEOUS VT EPISODES

CUMULATIVE % OF PATIENTS WITH 6+ MO FOLLOW-UPS

(b)(4)

(b)(4)

Figure 7: Cumulative % of Patients with $\geq$6 Months Follow-Up with a Spontaneous Episode of VT

(b)(4)

(b)(4)

PCD TRANSVENE SYSTEM

DISTRIBUTION OF SPONTANEOUS VT EPISODES

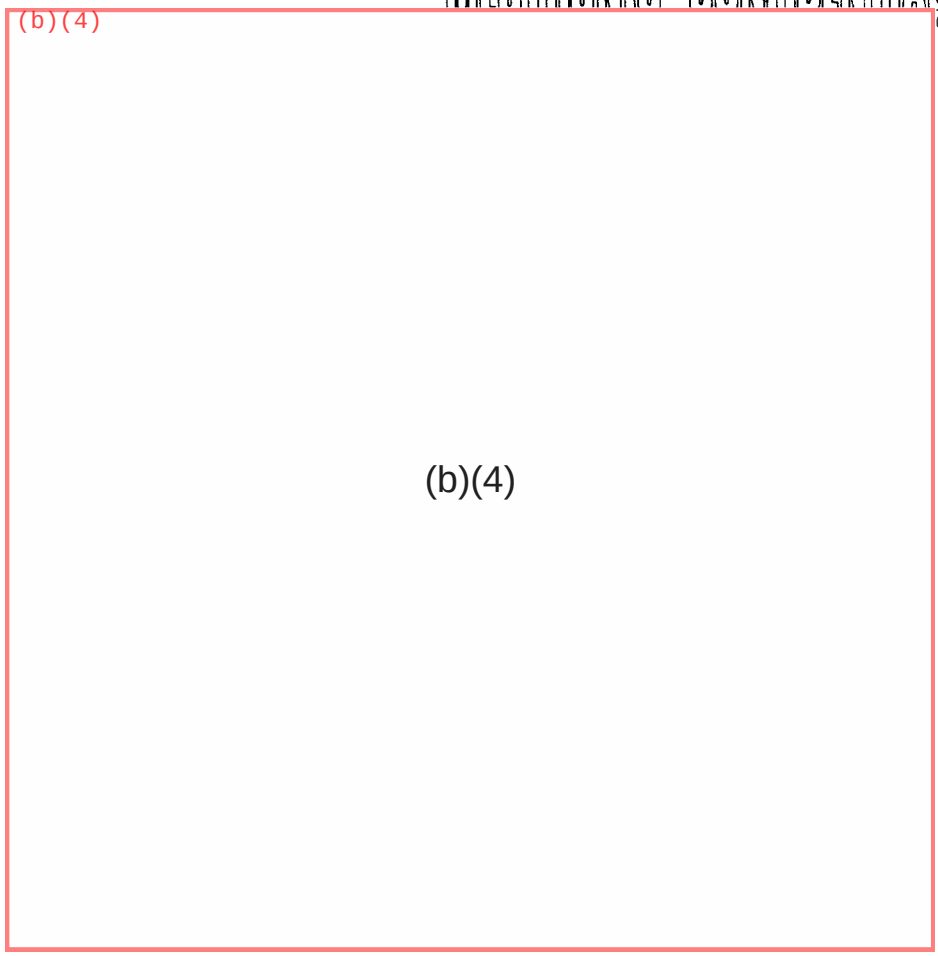
CUMULATIVE % OF PATIENTS WITH 6+ MO FOLLOW-UPS AND SPONTANEOUS VT EPISODES

(b)(4)

(b)(4)

Figure 8: Distribution of Spontaneous VT Episodes in a Cumulative % of Patients with $\geq$6 Months Follow-Up and Spontaneous VT Episodes

(b)(4)



PCD™ Transvene™ System
Spontaneous VT Episodes
Therapeutic Efficacy

	# Episodes	# Success	% Success
(b)(4)			

(b)(4)

Table VIIC-11: Spontaneous VT Episode Therapeutic Efficacy by Lead System - 6/24/92

(b)(4)

(b)(4)

(b)(4)

(b)(4)

7. Spontaneous Episodes of VT - by Primary Indication

(b)(4)

(b)(4)

154

PCD™ Transvene™ System
Spontaneous VT Episodes
Therapeutic Efficacy by Primary Indication

	# Success	# Episodes	% Success
(b)(4)			

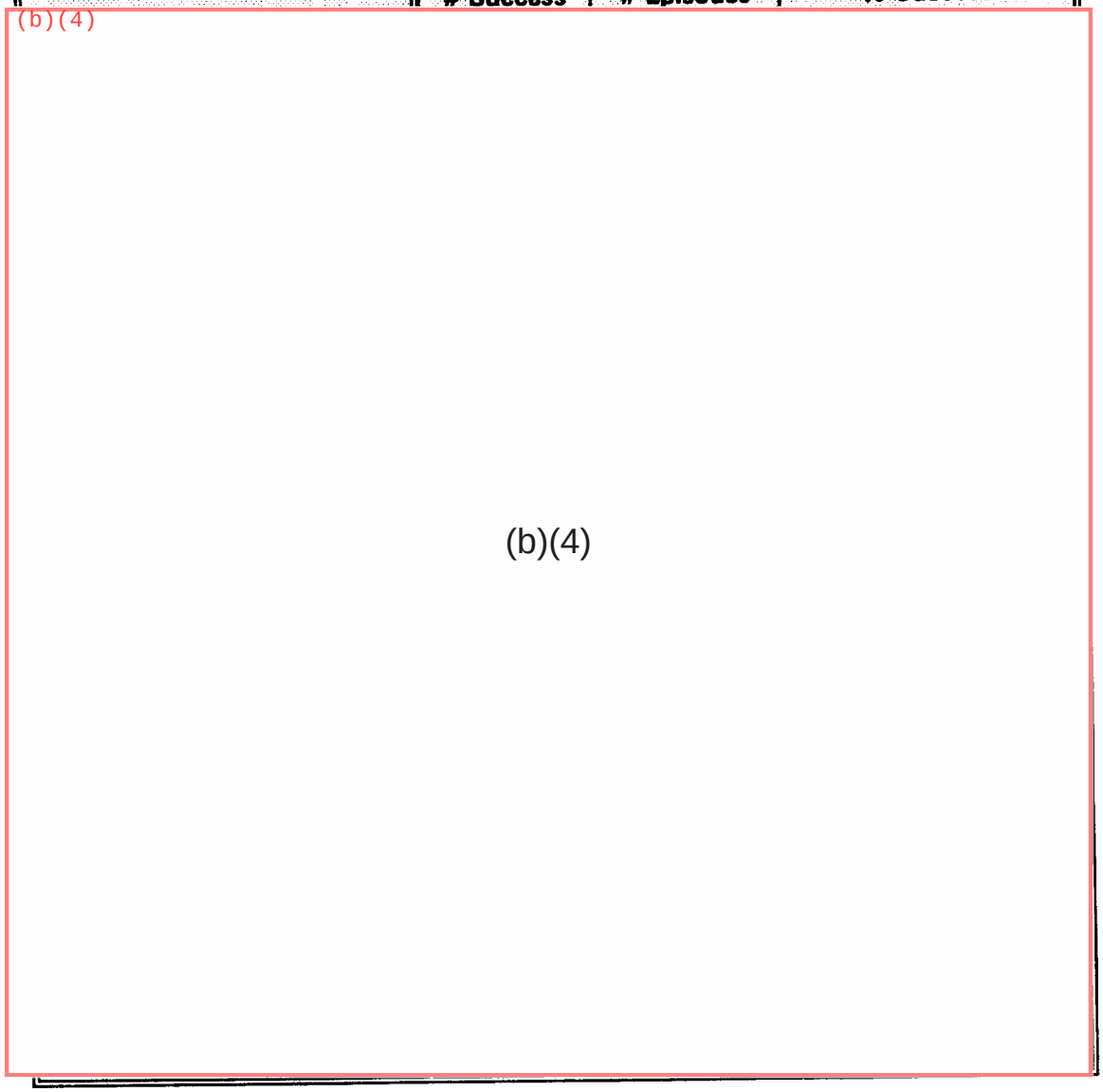


Table VIIC-12: Spontaneous VT Episode Therapeutic Efficacy by Primary Indication - 6/24/92

8. Spontaneous Episodes of VT - Ineffective Therapies

(b)(4)

(b)(4)

PCD™ Transvene™ System
Ineffective VT Therapies

	Number of Episodes	Number of Patients
(b)(4)		

(b)(4)

Table VIIC-13: Ineffective VT Therapies - 11/27/91

(b)(4)

(b)(4)

(b)(4)

(b)(4)

9. Patients with > 100 spontaneous VT Episodes

(b)(4)

(b)(4)

10. Predictors of Having a Spontaneous Episode of VT

(b)(4)

(b)(4)

(b)(4)

(b)(4)

PCD™ Transvene™ System
Predictors of Having Spontaneous VT

(b)(4)

(b)(4)

Table VIIC-14: Predictors of having Spontaneous VT

11. Induced and Spontaneous VT Episode Experience - Summary

a.

b.

c.

(b)(4)

(b)(4)

(b)(4)

d.

e.

f.

g.

(b)(4)

h.

g.

12. Induced and Spontaneous VT Episode Experience - Conclusions

The evaluation of induced and spontaneous VT episode experience indicates that the PCD™ Transvene™ System's VT detection and therapy functions have performed safely and effectively in the indicated patient population.

D. Induced and Spontaneous VF Episode Experience

(b)(4)

(b)(4)

1. Fibrillation Detection Interval (FDI)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

PCD™ Transvene™ System
Fibrillation Detection Interval
at Last Known Follow-Up

(b)(4)

(b)(4)

Table VIID-1: Fibrillation Detection Interval (FDI) at Last Known Follow-up - 6/24/92

2. Number of Intervals to Detect VF (VF NID)

(b)(4)

(b)(4)

PCD™ Transvene™ System
Number of Intervals to Detect VF
at Last Known Follow-Up

(b)(4)

(b)(4)

Table VIID-2: VF NID at Last Known Follow-Up - 6/24/92

3. Programmed Sensitivity

(b)(4)

(b)(4)

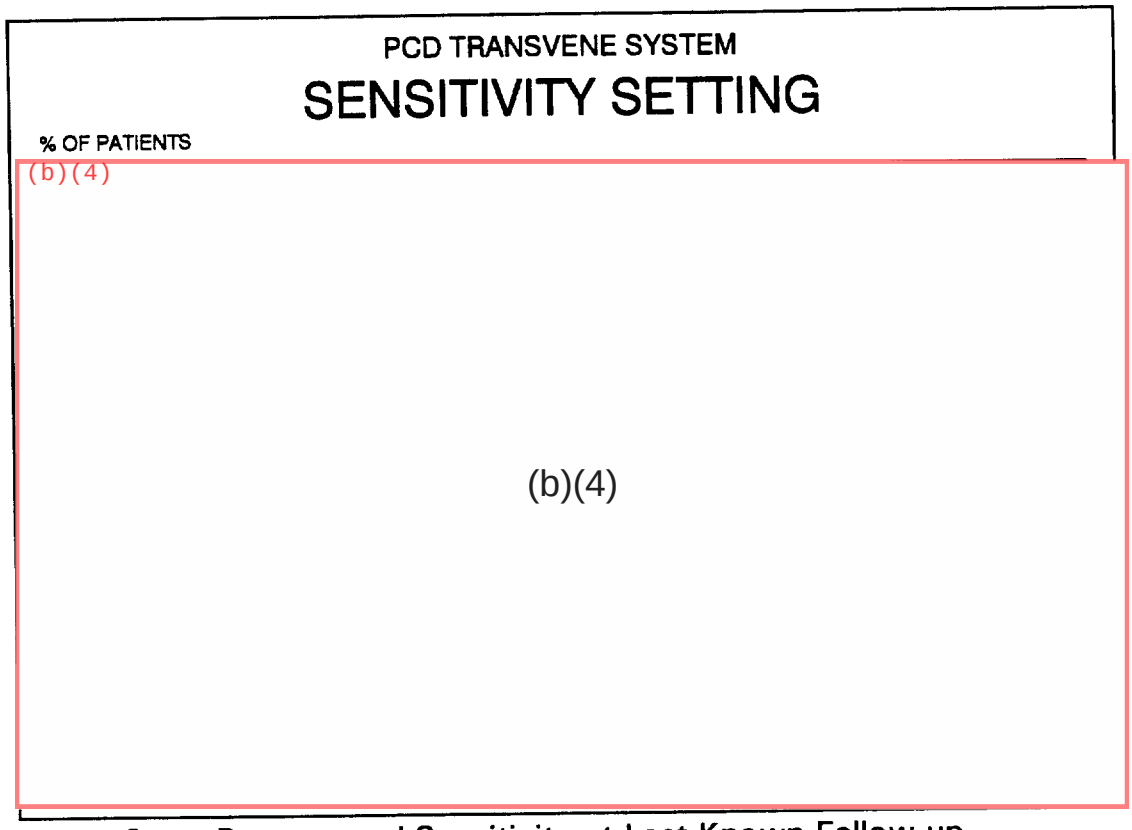


Figure 9: Programmed Sensitivity at Last Known Follow-up

4. Defibrillation Energy Settings

Figure 10 contains the current settings for the defibrillation energy (mean joules) for each programmable therapy. Most of the patients in this study have 34 joules as the most frequently programmed value for defibrillation therapy.

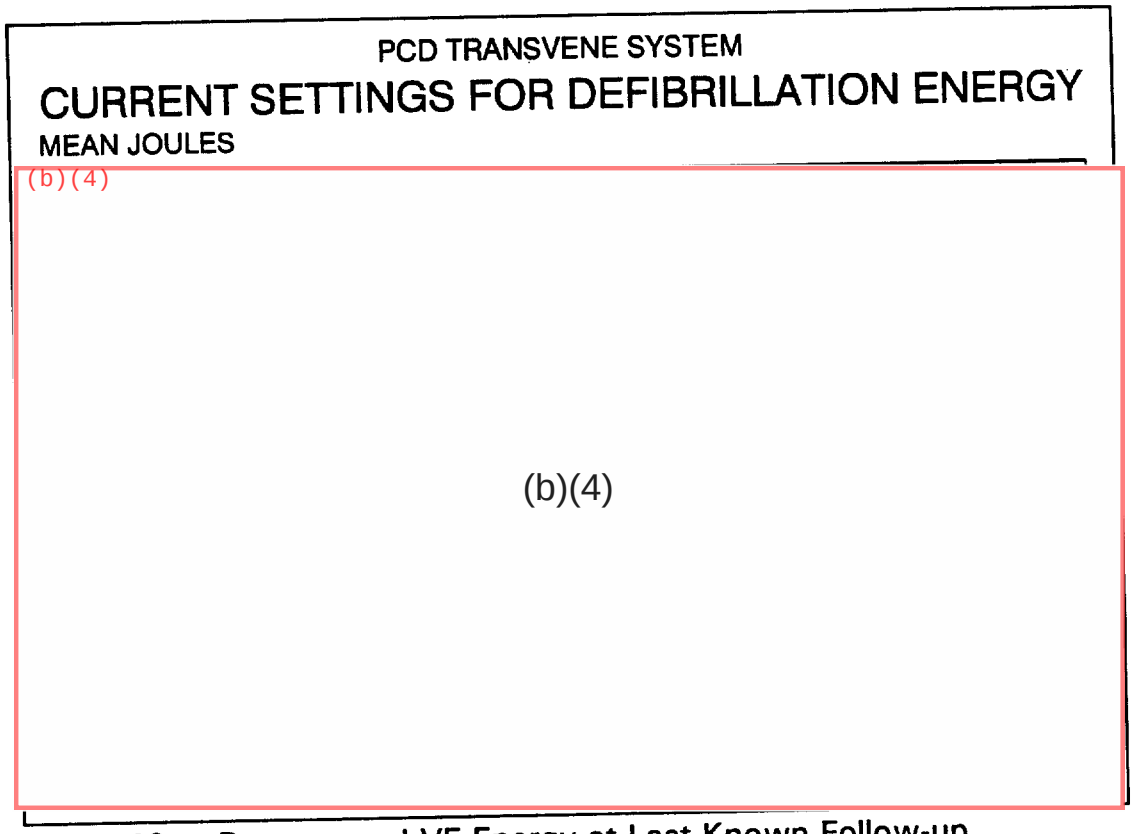


Figure 10: Programmed VF Energy at Last Known Follow-up

163

(b)(4)

(b)(4)

PCD TRANSVENE SYSTEM

CURRENT PROGRAMMED DEFIBRILLATION ENERGY

FOR VF THERAPY #1

% OF IMPLANTS

(b)(4)

(b)(4)

Figure 11: Programmed Energy for VF Therapy #1 at Last Known Follow-up - NTL System

(b)(4)

(b)(4)

PCD TRANSVENE SYSTEM

CURRENT PROGRAMMED DEFIBRILLATION ENERGY

FOR VF THERAPY #2

% OF IMPLANTS

(b)(4)

(b)(4)

Figure 12: Programmed Energy for VT Therapy #2 - NTL System

165

5. Induced VF Episode Experience

(b)(4)

(b)(4)

PCD™ Transvene™ System
Induced VF Episodes
by Follow-up

(b)(4)

(b)(4)

Table VIID-3: Induced Episodes of VF at Follow-up - 6/24/92

a. Lowest Energy of Defibrillation (LED)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

PCD™ Transvene™ System
Lowest Energy of Defibrillation
Number Obtained at Follow-up

(b)(4)

(b)(4)

Table VIID-4: Number of LED Values Obtained at Follow-up Studies - 6/24/92

(b)(4)

(b)(4)

PCD™ Transvene™ System
Lowest Energy of Defibrillation
Obtained at Follow-up
[Average energy (joules)/number of patients]

(b)(4)

(b)(4)

Table VIID-5: Lowest Energy of Defibrillation (LED) Obtained at Follow-up - 6/24/92

b. Chronic Defibrillation Thresholds (DFT)

(b)(4)

(b)(4)

PCD™ Transvene™ System
Chronic Defibrillation Threshold

(b)(4)

(b)(4)

Table VIID-6: Defibrillation Threshold (DFT) Obtained at Follow-up - 6/24/92

(b)(4)

(b)(4)

PCD TRANSVENE SYSTEM

DFT MEASUREMENTS

PATIENTS WITH 6 MONTH OR 12 MONTH FOLLOW-UPS

MEAN DFT

(b)(4)

(b)(4)

Figure 13: DFT Measurements of Patients with 6 Month or 12 Month Follow-up

(b)(4)

(b)(4)

PCD™ Transvene™ System Chronic Defibrillation Threshold				
Patient I.D.	Implant	PHD	1 Month	3 Month
(b)(4)				

(b)(4)

Table VIID-6: Patients with a DFT Obtained at Implant, PHD (b)(4) and (b)(4) Month Follow-up - 6/24/92

(b)(4)

(b)(4)

PCD TRANSVENE SYSTEM

DFT MEASUREMENTS

FOR PATIENTS WITH IMPLANT TO 3 MONTH FOLLOW-UP

MEAN DFT

(b)(4)

(b)(4)

Figure 14: DFT Measurements at Implant, PHD (b)(4) Month, and (b)(4) Months

6. Number of Spontaneous Episodes of VF and Therapy Experience

(b)(4)

(b)(4)

124

PCD™ Transvene™ System
Spontaneous Episodes of VF
by Follow-up Interval

(b)(4)

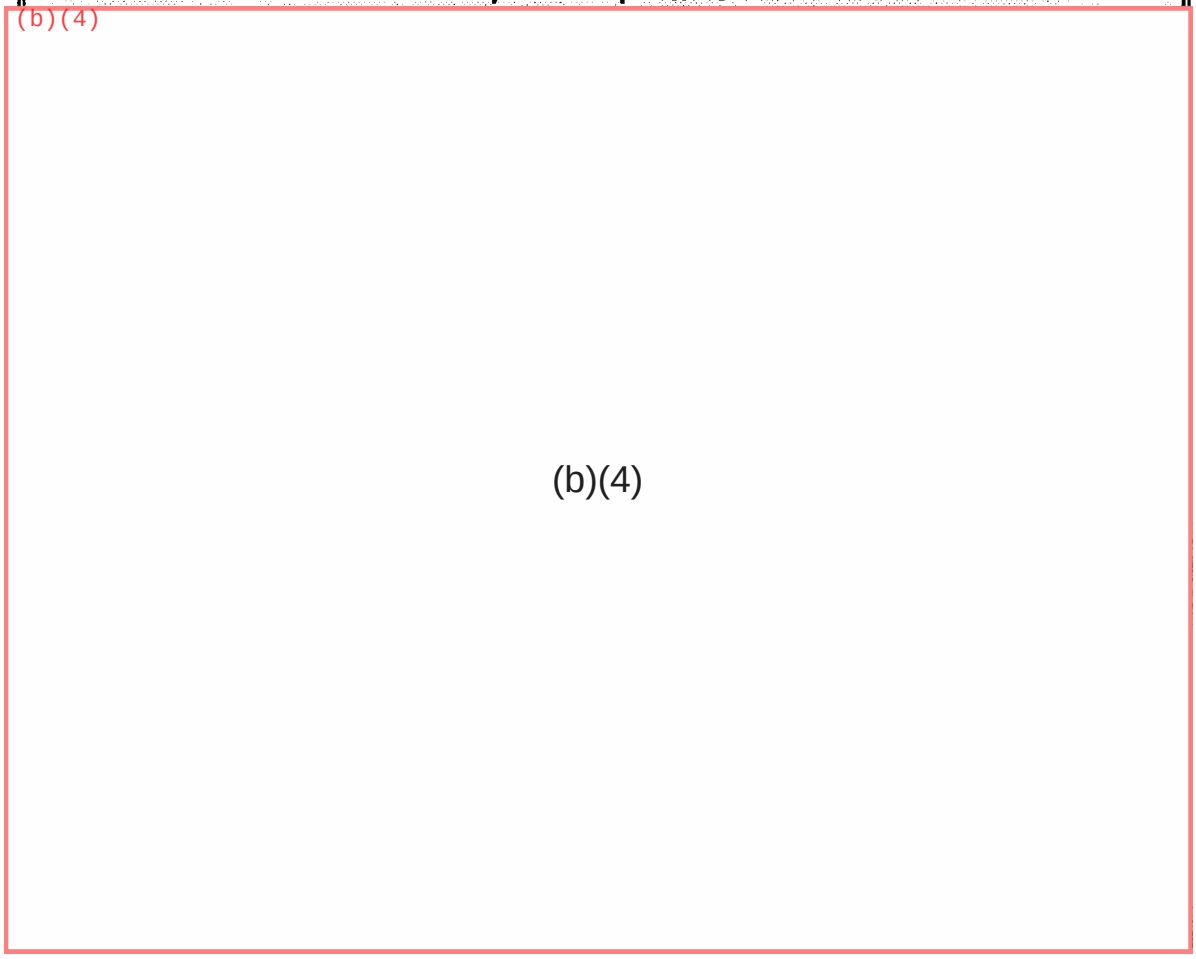


Table VIID-7: Spontaneous VF Episodes and Therapeutic Experience by Follow-up Interval - 6/24/92

(b)(4)

(b)(4)

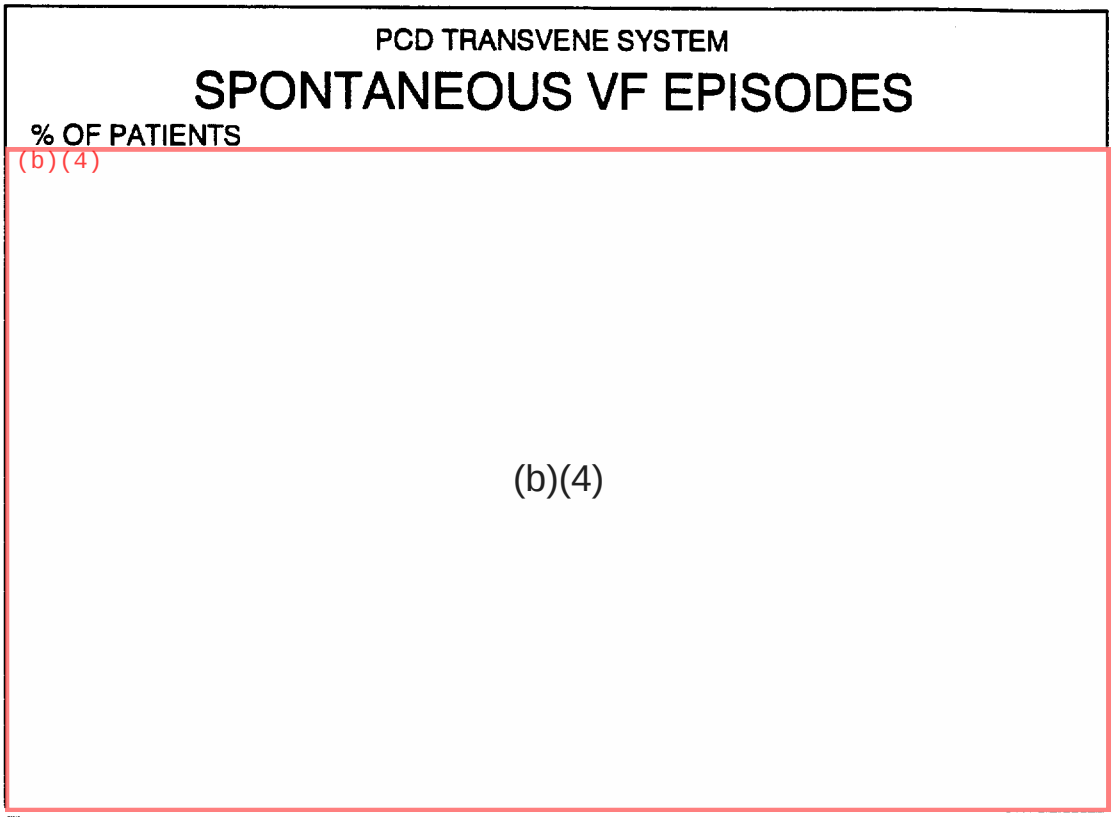


Figure 15: Percent of Patients and Number of Episodes of Spontaneous VF Episodes by Follow-up Interval

(b)(4)

(b)(4)

PCD TRANSVENE SYSTEM

PATIENTS WITH SPONTANEOUS VF EPISODES

CUMULATIVE NUMBER OF PATIENTS OVER TIME

(b)(4)

(b)(4)

Figure 16: Cumulative Number of Patients with Spontaneous VF Episodes by Follow-Up Interval

(b)(4)

(b)(4)

PCD TRANSVENE SYSTEM

PATIENTS WITH SPONTANEOUS VF EPISODES

CUMULATIVE NUMBER OF PATIENTS OVER TIME WITH 6+ MO FOLLOW-UPS

(b)(4)

(b)(4)

Figure 17: Cumulative Number of Patients with $\geq$6 Months of Follow-Up with Spontaneous Episodes

(b)(4)

(b)(4)

PCD TRANSVENE SYSTEM

DISTRIBUTION OF SPONTANEOUS VF EPISODES

CUMULATIVE % OF PATIENTS WITH 6+ MO FOLLOW-UPS

(b)(4)

(b)(4)

Figure 18: Cumulative % of Patients with $\geq$6 Months Follow-Up with a Spontaneous Episode of VF

(b)(4)

(b)(4)

PCD TRANSVENE SYSTEM

DISTRIBUTION OF SPONTANEOUS VF EPISODES

CUMULATIVE % OF PATIENTS WITH 6+ MO FOLLOW-UPS AND SPONTANEOUS VF EPISODES

(b)(4)

(b)(4)

Figure 19: Distribution of Spontaneous VF Episodes as a Cumulative % of Patients with $\geq$6 Months of Follow-up and Spontaneous VF Episodes

(b)(4)

(b)(4)

190

(b)(4)

(b)(4)

PCD™ Transvene™ System Spontaneous VF Episodes Therapeutic Efficacy			
	# Episodes	# Success	% Success
(b)(4)			

(b)(4)

Table VIID-8: Spontaneous VF Episode Therapeutic Efficacy - 6/24/92

7. Spontaneous Episodes of VF by Primary Indication

(b)(4)

(b)(4)

PCD™ Transvene™ System Spontaneous VF Episodes Therapeutic Efficacy by Primary Indication			
	# Success	# Therapies	% Success
(b)(4)			

Table VIID-9: Spontaneous VF Episodes Therapeutic Efficacy by Primary Indication - 6/24/92

8. Spontaneous Episodes of VF - Ineffective Therapies

(b)(4)

(b)(4)

PCD™ Transvene™ System Ineffective VF Therapies		
	Number of Episodes	Number of Patients
(b)(4)		

(b)(4)

Table VIID-10: Ineffective VF Therapies - 6/24/91

(b)(4)

(b)(4)

9. Patients with >50 episodes of VF

(b)(4)

(b)(4)

10. Predictors of Having a Spontaneous Episode of VF

(b)(4)

(b)(4)

PCD™ Transvene™ System
Predictors of Having Spontaneous VF

(b)(4)

(b)(4)

Table VIID-11: Predictors of Having Spontaneous VF - 6/24/92

188

11. Induced and Spontaneous VF Episode Experience - Summary

a. (b)(4)

b.

c.

d.

e.

f. (b)(4)

g.

h. (b)(4)

(b)(4)

12. Induced and Spontaneous VF Episode Experience - Conclusions

The evaluation of induced and spontaneous VT episode experience indicates that the PCD™ Transvene™ System's VF detection and therapy functions have performed safely and effectively in the indicated patient population.

E. Overall VT and VF Episode Experience

1. VT Episode Experience

(b)(4)

(b)(4)

(b)(4)

(b)(4)

2. VF Episode Experience

(b)(4)

(b)(4)

(b)(4)

(b)(4)

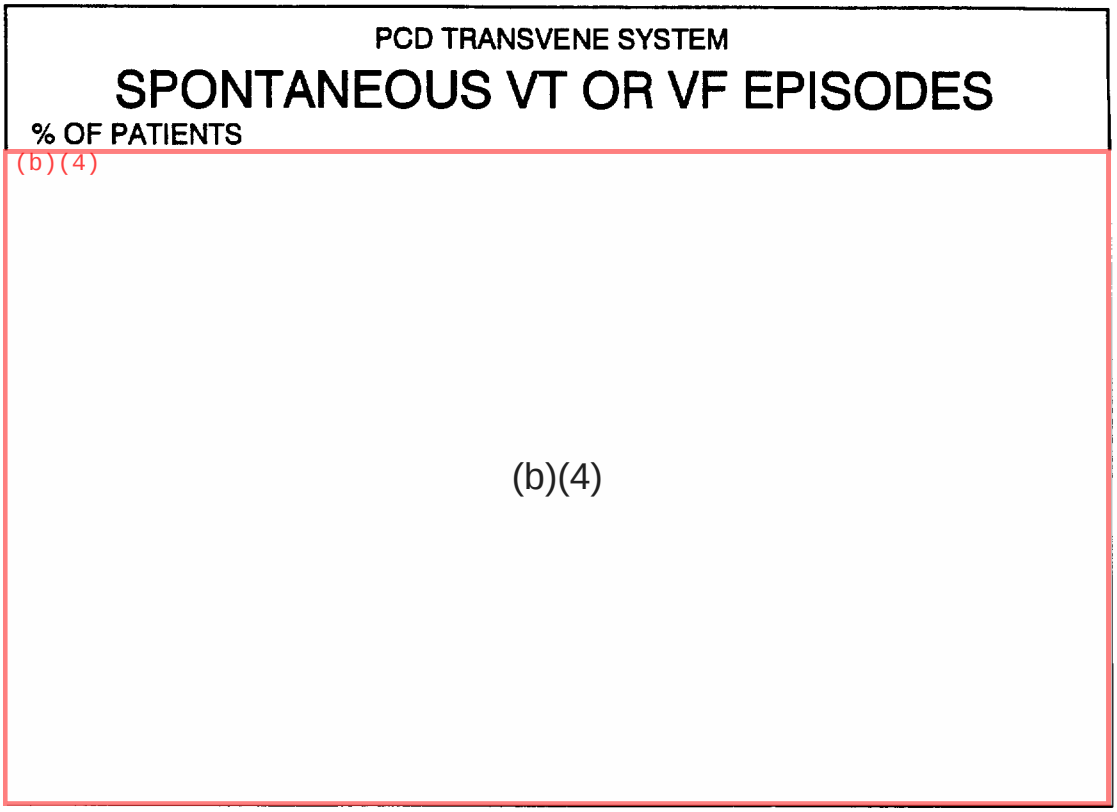


Figure 20: Spontaneous VT or VF Episodes

18

(b)(4)

(b)(4)

PCD TRANSVENE SYSTEM

PATIENTS WITH SPONTANEOUS VT OR VF EPISODES

CUMULATIVE NUMBER OF PATIENTS OVER TIME

(b)(4)

(b)(4)

Figure 21: Cumulative Number of Patients with Spontaneous VT or VF Episodes by Follow-Up Interval

(b)(4)

(b)(4)

PCD TRANSVENE SYSTEM

PATIENTS WITH SPONTANEOUS VT OR VF EPISODES

CUMULATIVE NUMBER OF PATIENTS OVER TIME WITH 6+ MO FOLLOW-UPS

(b)(4)

(b)(4)

Figure 22: Cumulative Number of Patients with ≥6 Months of Follow-up with Spontaneous VT or VF Episodes

(b)(4)

(b)(4)

PCD TRANSVENE SYSTEM

DISTRIBUTION OF SPONTANEOUS VT OR VF EPISODES

CUMULATIVE % OF PATIENTS WITH 6+ MO FOLLOW-UPS

(b)(4)

(b)(4)

Figure 23: Cumulative % of Patients with $\geq$6 Months Follow-Up with a Spontaneous Episode of VT or VF

(b)(4)

(b)(4)

PCD TRANSVENE SYSTEM

DISTRIBUTION OF SPONTANEOUS VT OR VF EPISODES

(b)(4)

(b)(4)

Figure 24 Cumulative Number of Patients with ≥6 Months of Follow-Up with Spontaneous VT or VF

3. Holter Monitored Patients

(b)(4)

(b)(4)

PCD™ Transvene™ System
Spontaneous VT Episodes
Patients with Episodes Recorded on Holter by Primary Indication

(b)(4)

(b)(4)

Table VIIE-1: Number of Patients with Spontaneous VT Episodes Recorded on Holter by Patient Indication - 6/24/92

Table VIIE-2 contains the number of VT episodes by follow-up interval captured for this one patient. Also included in the table is the efficacy of the VT therapies.

PCD™ Transvene™ System
Spontaneous VT Episodes
Recorded on Holter by Follow-up Interval

(b)(4)

(b)(4)

Table VIIE-2: Spontaneous VT Episodes Recorded on Holter by Follow-Up Interval - 6/24/92

(b)(4)

(b)(4)

Table VIIE-3 contains the number of patients that experienced a spontaneous VF episode while they were Holter monitored. This information is presented by patient indication.

PCD™ Transvene™ System
Spontaneous VF Episodes
Patients with Episodes Recorded on Holter
by Primary Indication

(b)(4)

(b)(4)

Table VIIE-3: Number of Patients with Spontaneous VF Episodes Recorded on Holter - 6/24/92

(b)(4)

(b)(4)

PCD™ Transvene™ System
Spontaneous VF Episodes
Recorded on Holter by Follow-Up Interval

(b)(4)

(b)(4)

Table VIIE-4: Spontaneous VF Episodes Recorded on Holter by Follow-Up Interval -6/24/92

Table VIIE-5 contains the number of VF episodes by patient indication and Model number.

PCD™ Transvene™ System
Spontaneous VF Episodes
Recorded on Holter by Patient Indication

(b)(4)

Table VIIE-5: Number of VF Episodes by Patient Indication Captured on Holter - 6/24/92

(b)(4)

(b)(4)

F. Programmed Parameters

(b)(4)

(b)(4)

1. Ventricular Tachycardia (VT) Detection and Therapy Programmed Parameters

a. Tachycardia Detection Interval (TDI)

(b)(4)

(b)(4)

Table VIIF-1 shows the distribution of the last known programmed tachycardia detection interval (TDI) for those patients with VT detection programmed ON (excluding deaths and explants)

PCD™ Transvene™ System Tachycardia Detection Interval	
TDI Range	**Number of Patients**
(b)(4)	

(b)(4)

Table VIIF-1 : Tachycardia Detection Interval (TDI) - 6/24/92

(b)(4)

(b)(4)

b. Number of Intervals to Detect (NID) VT

(b)(4)

(b)(4)

PCD™ Transvene™ System Number of Intervals to Detect VT	
NID	Number of Patients
(b)(4)	

(b)(4)

Table VIIF-2: Number of Intervals to Detect VT (NID) - 6/24/92

(b)(4)

(b)(4)

c. Programmed Ventricular Tachycardia (VT) Therapy Type by Therapy Number

(b)(4)

(b)(4)

PCD TRANSVENE SYSTEM

CURRENT SETTINGS FOR VT THERAPIES

% OF ACTIVE PATIENTS

(b)(4)

(b)(4)

Figure 27: Programmed VT Therapies by Therapy Number at Last Known Follow-up - Transvene™ System

2. Ventricular Fibrillation Detection and Therapy Programmed Parameters

a. Sensitivity

(b)(4)

(b)(4)

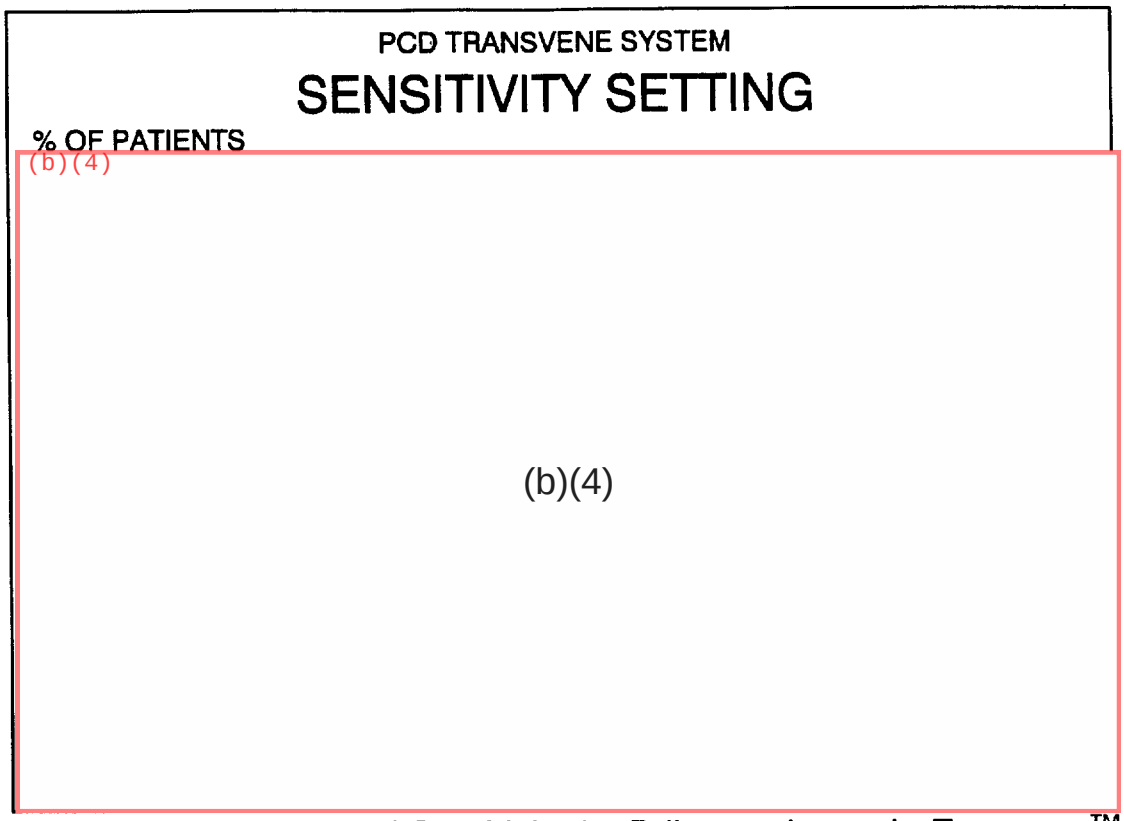


Figure 28: Programmed Sensitivity by Follow-up Interval - Transvene™ Lead System

b. Fibrillation Detection Interval (FDI)

(b)(4)

(b)(4)

PCD™ Transvene™ System Fibrillation Detection Interval	
FDI Range	Number of Patients
(b)(4)	

(b)(4)

Table VIIF-3: Fibrillation Detection Interval (FDI) - 6/24/92

(b)(4)

(b)(4)

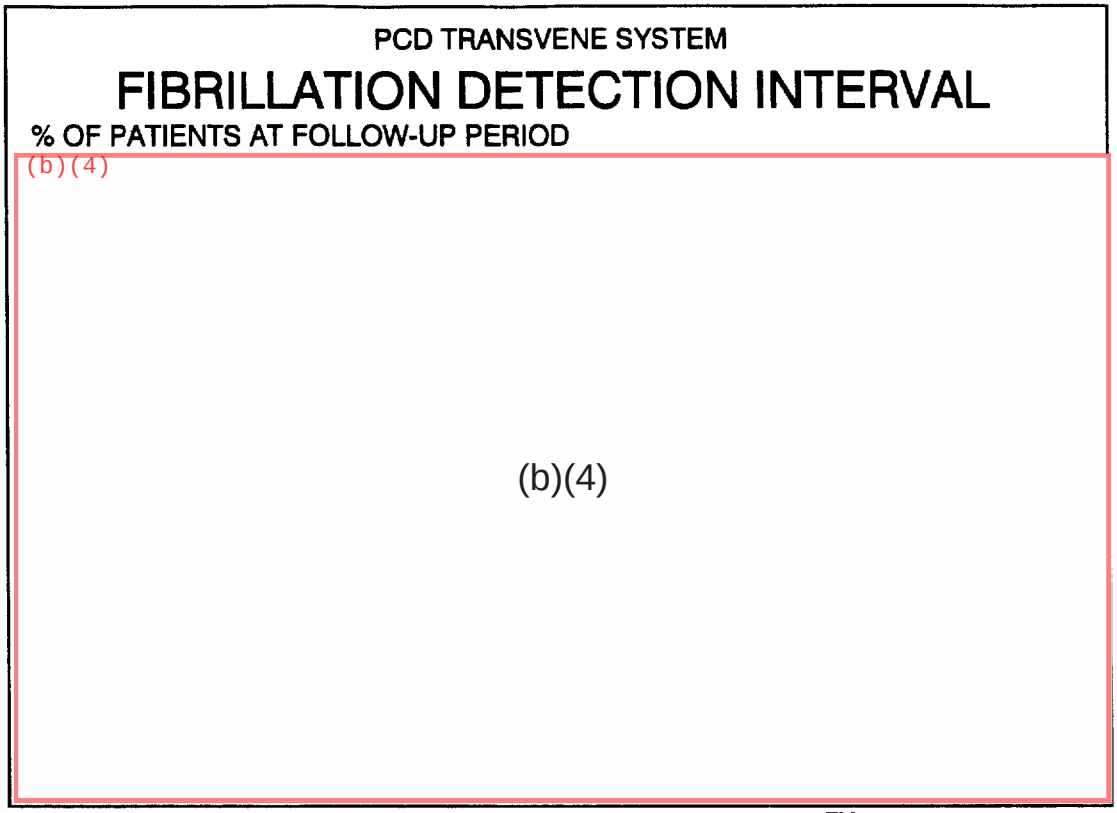


Figure 29: Fibrillation Detection Interval - Transvene™ Lead System

c. Number of Intervals to Detect VF

(b)(4)

(b)(4)

PCD™ Transvene™ System Number of Intervals to Detect VF	
NID	Number of Patients
(b)(4)	

(b)(4)

Table VIIF-4: Number of Intervals to Detect VF (NID) - 6/24/92

(b)(4)

(b)(4)

PCD TRANSVENE SYSTEM

NUMBER OF INTERVALS TO DETECT VF

% OF PATIENTS AT FOLLOW-UP PERIOD

(b)(4)

(b)(4)

Figure 30: Number of Intervals to Detect VF by Follow-up Interval - Transvene™ Lead System

d. Programmed Defibrillation Energy

(b)(4)

(b)(4)

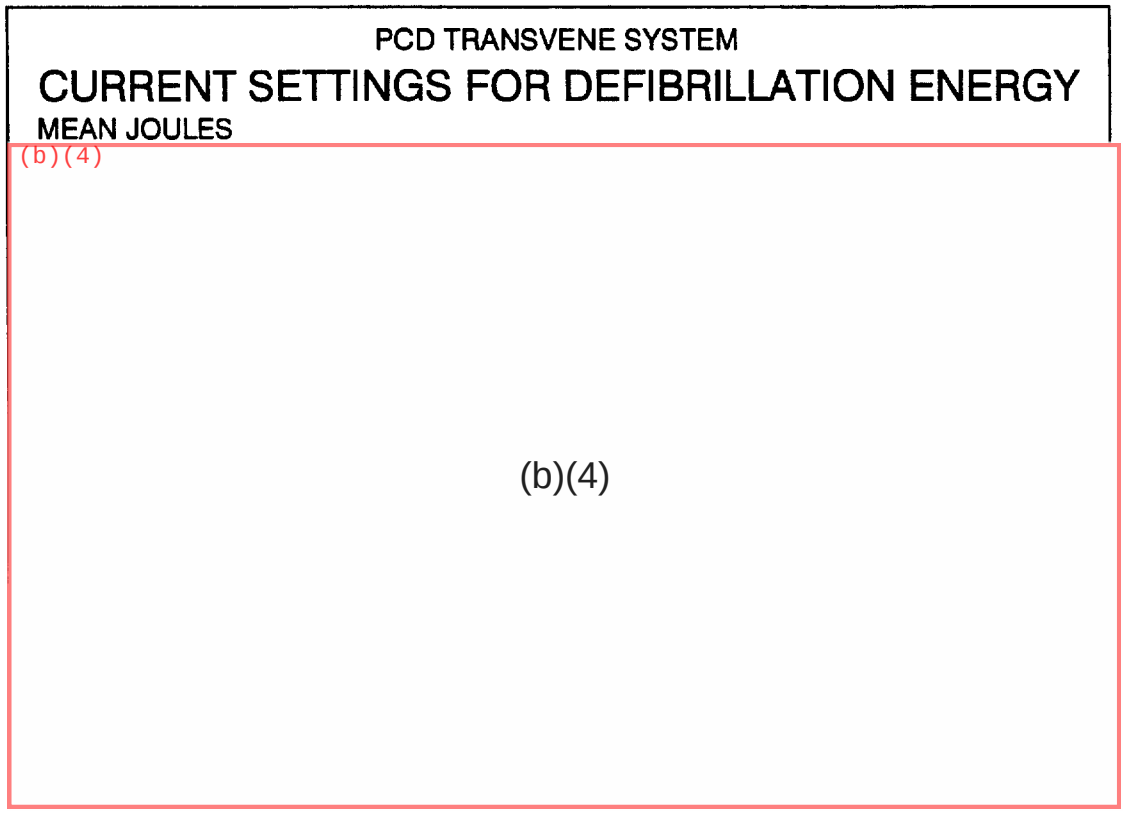


Figure 31: Programmed Defibrillation Energy

(b)(4)

(b)(4)

PCD TRANSVENE SYSTEM

CURRENT PROGRAMMED DEFIBRILLATION ENERGY

FOR VF THERAPY #1

% OF IMPLANTS

(b)(4)

(b)(4)

Figure 32: Programmed Energy of VF Therapy #1 - Transvene™ Lead System

(b)(4)

(b)(4)

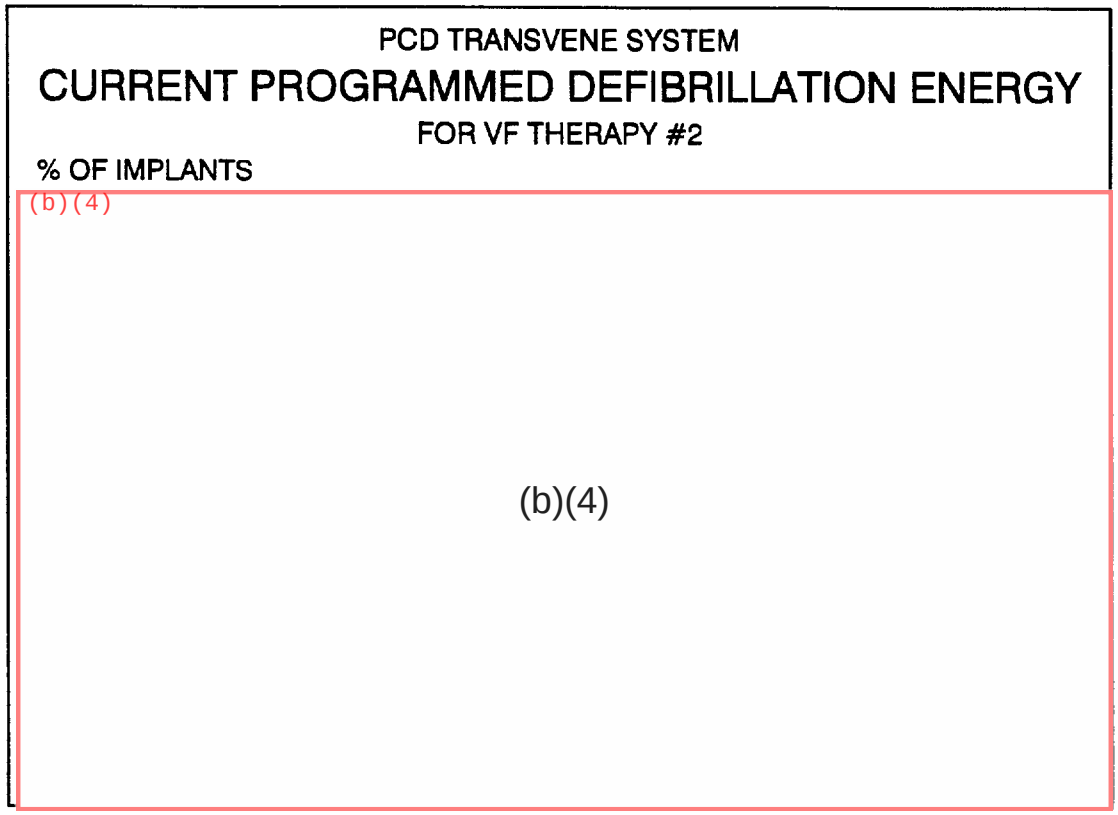


Figure 33: Programmed Defibrillation Energy of VF Therapy #2 - Transvene™ Lead System

(b)(4)

(b)(4)

3. Reprogrammings

(b)(4)

(b)(4)

PCD™ Transvene™ System
Reprogramming Summary

(b)(4)

(b)(4)

Table VIIF-5: Summary of PCD™ System Reprogramming - % of Patients with Parameter Reprogramming at Follow-up Evaluation - 6/24/92

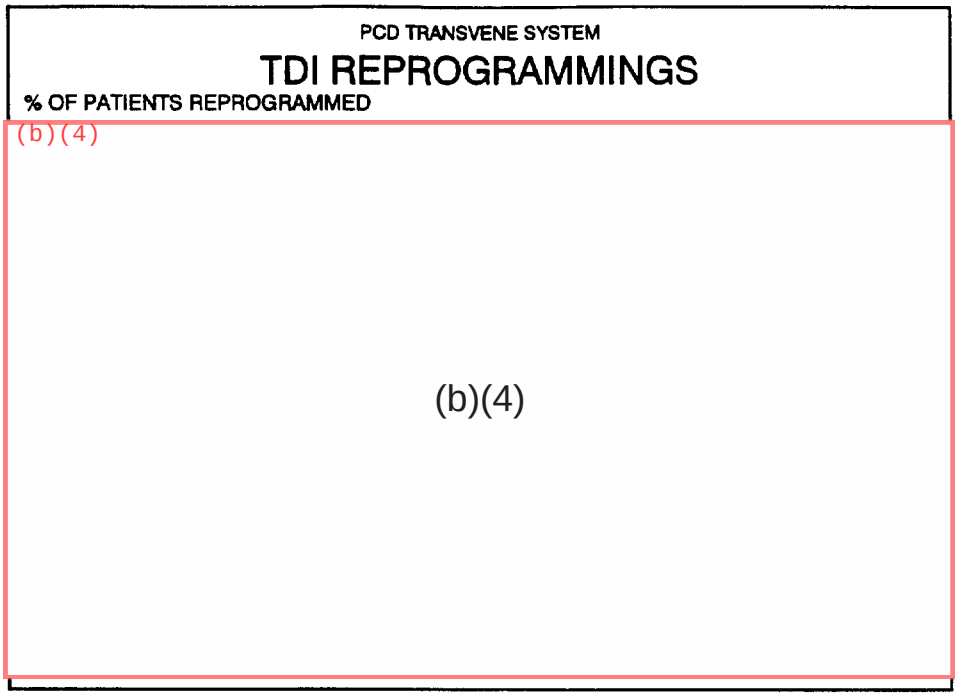


Figure 34: Reprogrammings of the Tachycardia Detection Interval

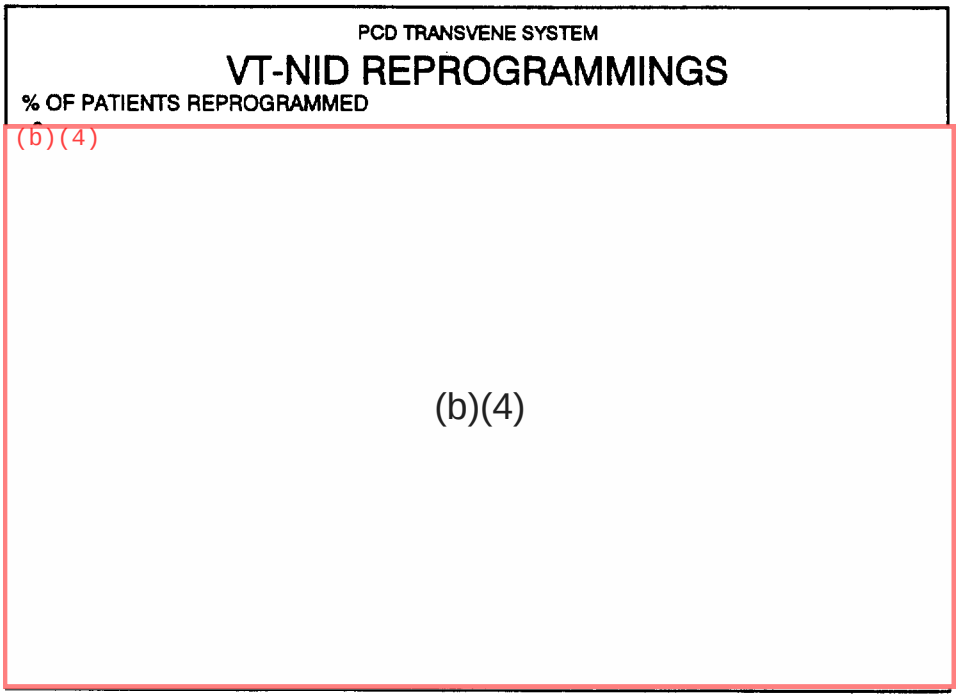


Figure 35: Reprogrammings of the Number of Intervals to Detect VT

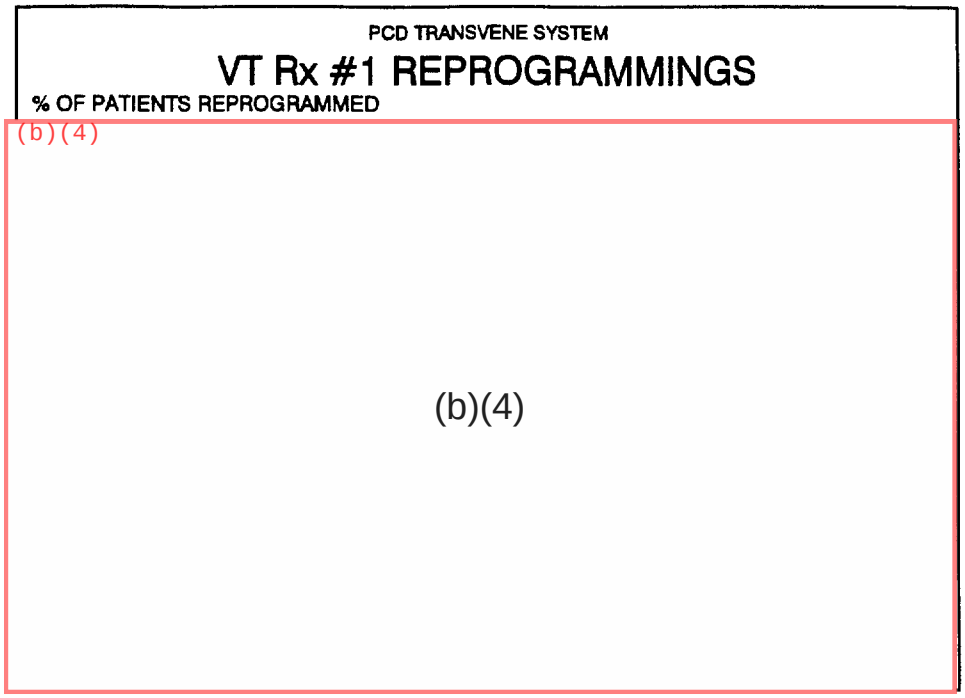


Figure 36: Reprogrammings of VT Therapy #1

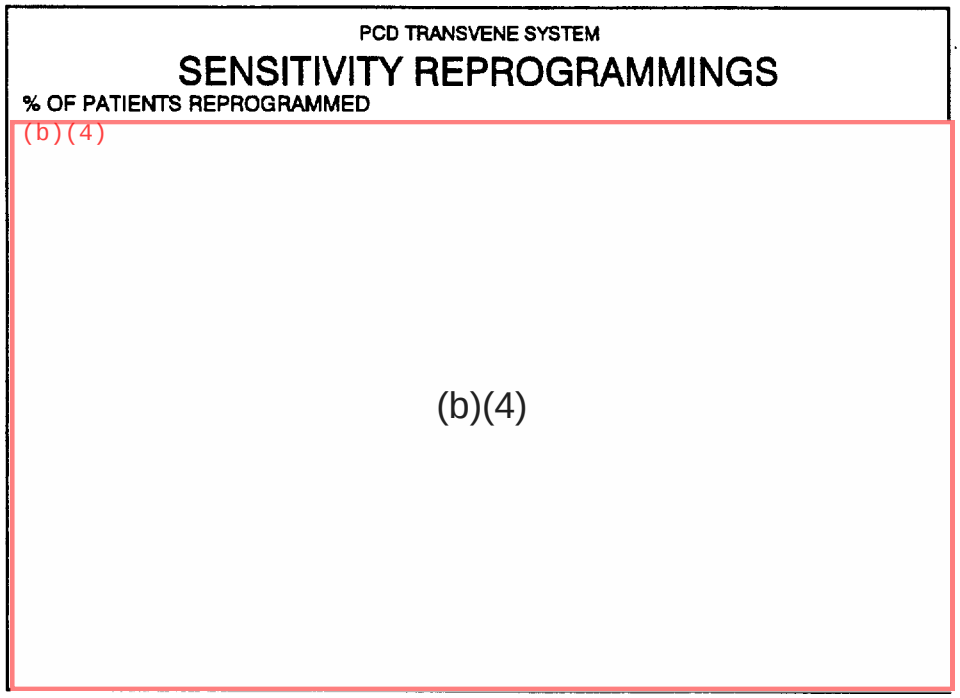


Figure 37: Reprogrammings of Sensitivity

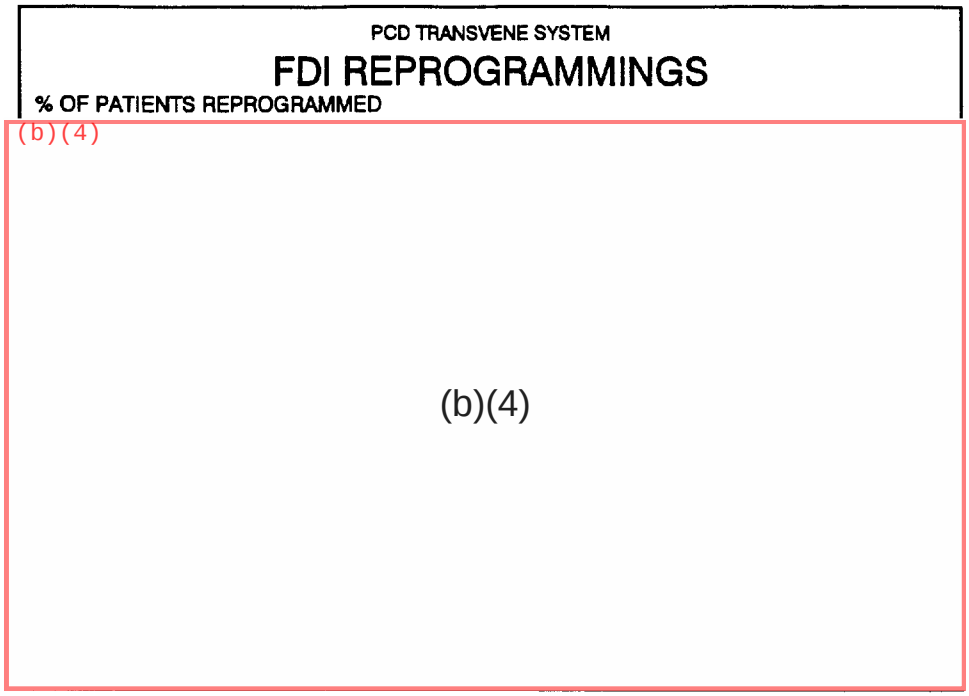


Figure 38: Reprogrammings of the Fibrillation Detection Interval

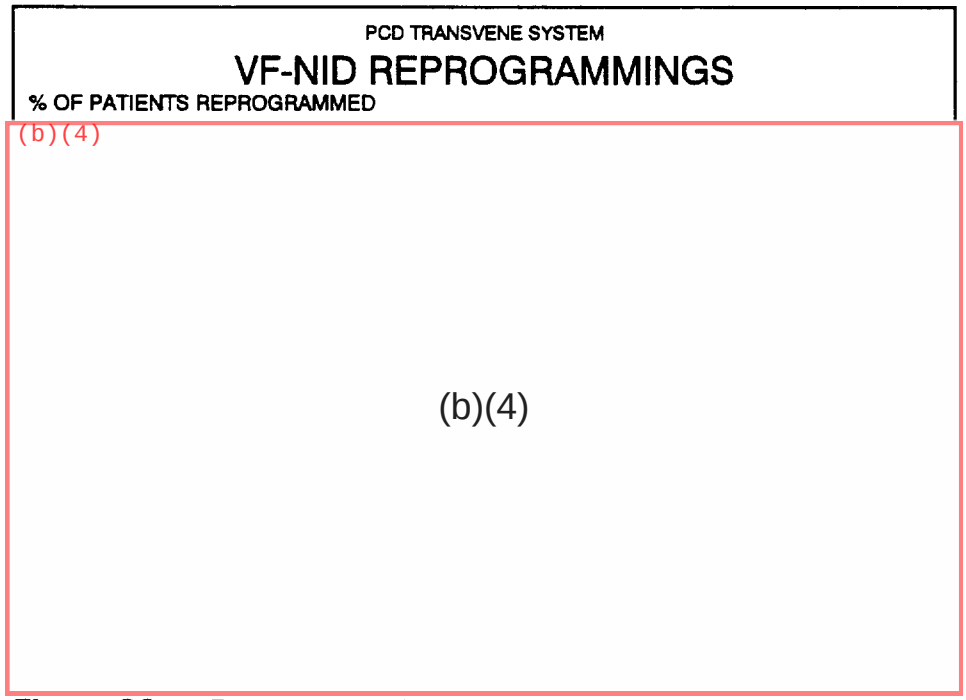


Figure 39: Reprogrammings of the Number of Intervals to Detect VF

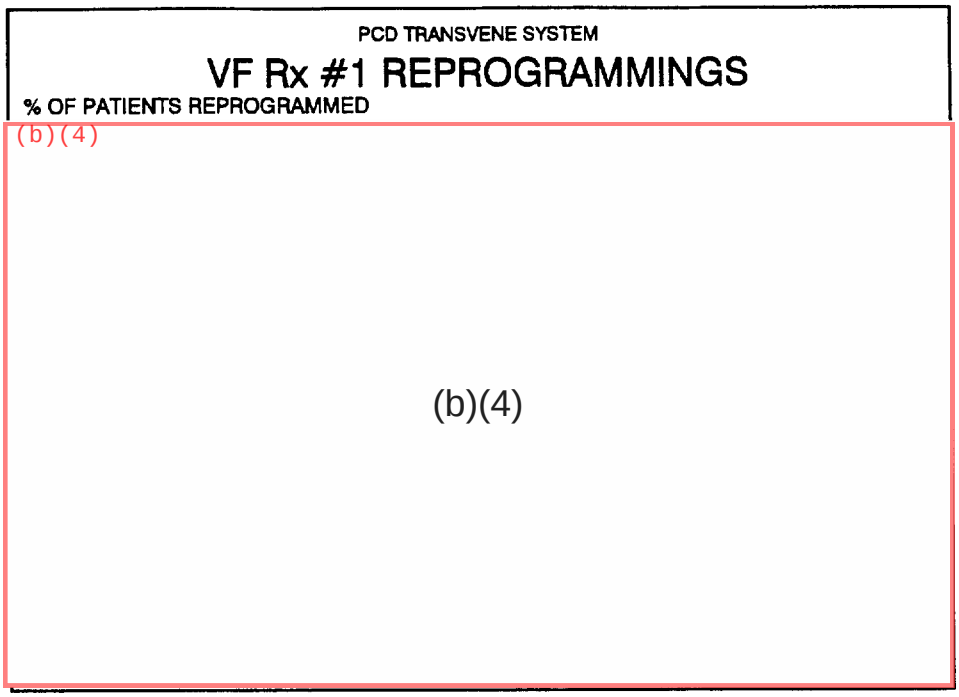


Figure 40: Reprogrammings of VF Therapy #1

4. Programming Summary

a.

b.

c.

d.

e.

f.

(b)(4)

(b)(4)

g. (b)(4)

h. (b)(4)

i.

5. Programming Conclusions

Reprogrammings tend to occur early in the follow-up period indicating that parameter values selected as a result of early evaluation remain appropriate for the reported implant duration in this patient population. The programming ranges available in the PCD™ system are appropriate.

G. Chronic Pace/Sense Evaluation

1. (b)(4)

(b)(4)

PCD™ Transvene™ System
Electrogram Amplitude
at Last Follow-up Evaluation

(b)(4)

(b)(4)

Table VIIG-1: Electrogram Amplitude at Follow-up Evaluation - 6/24/92

(b)(4)

(b)(4)

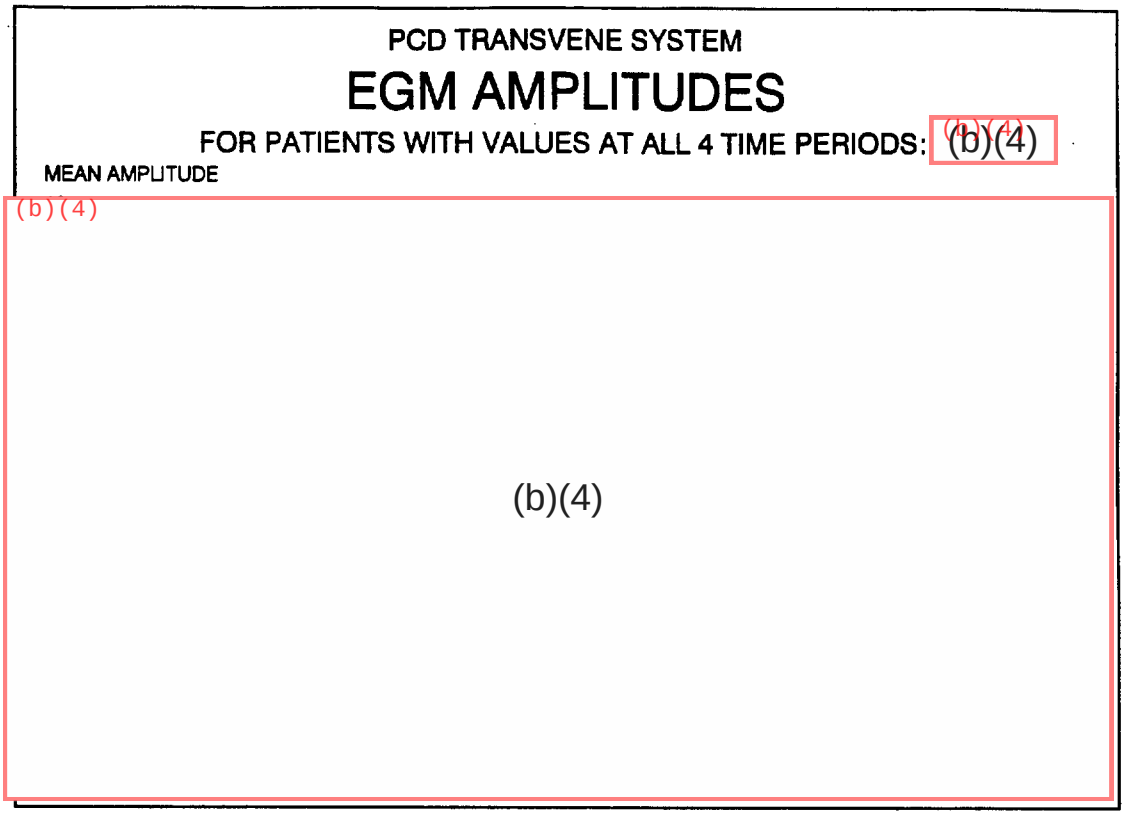


Figure 41: Chronic Electrogram Amplitude

2. Pacing Thresholds

(b)(4)

(b)(4)

PCD™ Transvene™ System
Pacing Pulse Width Threshold
at Last Follow-up Evaluation

(b)(4)

(b)(4)

Table VIIG-2: Pacing Threshold at Last Known Follow-up - 6/24/92

(b)(4)

(b)(4)

PCD TRANSVENE SYSTEM

PULSE WIDTH THRESHOLDS

FOR PATIENTS WITH VALUES AT ALL 4 TIME PERIODS: N=214

MEAN PULSE WIDTH

(b)(4)

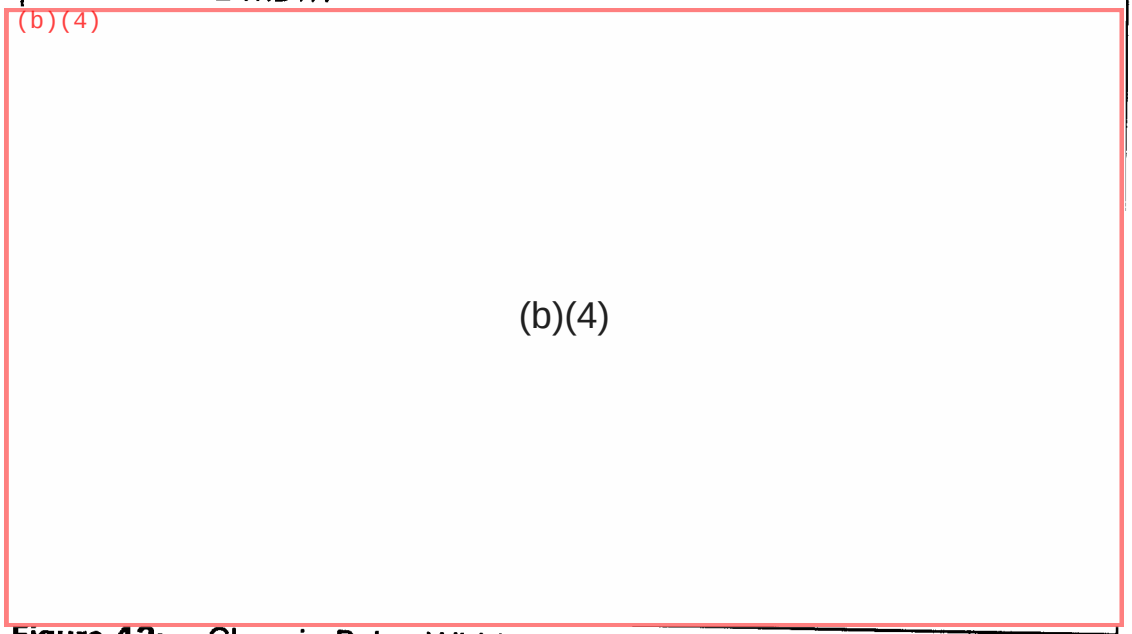


Figure 42: Chronic Pulse Width Threshold

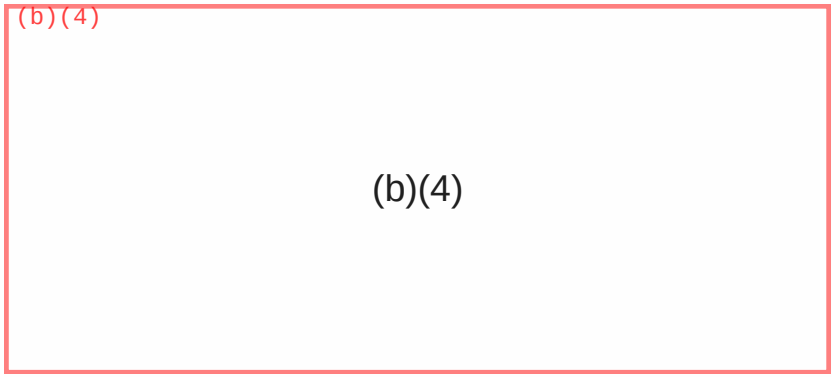
3. Chronic Pace/Sense Evaluation - Summary

a.

b.

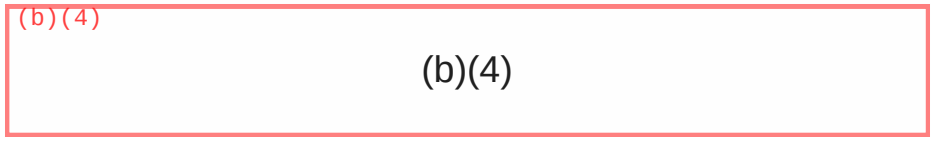
c.

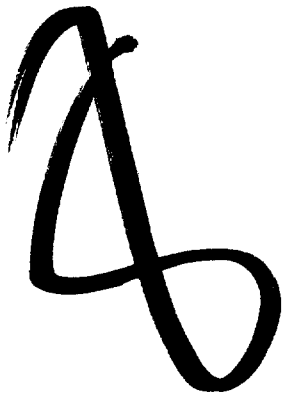
(b)(4)



4. Chronic Pace/Sense Evaluation - Conclusions

(b)(4)





VIII. Specific Patient Populations

A. Analysis by Age Groups

(b)(4)

(b)(4)

PCD™ Transvene System
Data Summary by Age Groups

(b)(4)

(b)(4)

Table VIIIA: Data Summary: Age Groups Clinical Results

B. Previous Pulse Generators

1. Introduction

(b)(4)

(b)(4)

(b)(4)

(b)(4)

2. Bradycardia Pulse Generators

(b)(4)

(b)(4)

PCD Transvene System
Retained Pulse Generators

(b)(4)

(b)(4)

Table VIII B-1: PCD Transvene System Retained Pulse Generators - 6/24/92

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

3. Patients with Previous ICD Epicardial Systems

(b)(4)

(b)(4)

4. Patients with Multiple PCD Transvene Implant Procedures

(b)(4)

(b)(4)

PCD Transvene System Patients with Multiple Implant Procedures	
Reason	Number of Patients
(b)(4)	

(b)(4)

Table VIII B-2: PCD Transvene System: Multiple Implant Procedures - 6/24/92

(b)(4)

(b)(4)

(b)(4)

(b)(4)

5. Summary

(b)(4)

(b)(4)

(b)(4)

(b)(4)

6. Conclusion

Clinical experience indicates that the current labelling provides appropriate recommendations for the implant of bradycardia pacemakers, including dual chamber devices, with the PCD Transvene System. In addition, implant and follow-up data on these patients indicates that a bipolar bradycardia pacemaker can be safely implanted in conjunction with the PCD Transvene System.

C. Patients Not Meeting Implant Criteria

1. Section Overview

The PCD Transvene System offers a simpler and safer implantation technique for an implantable cardioverter defibrillator system. In addition, the PCD Transvene System decreases the potential perioperative and long term mortality associated with current epicardial system implantation approaches.

There is a class of patients who cannot tolerate the thoracotomy required for the utilization of the epicardial patch lead defibrillation lead system and who are at high risk of sudden cardiac death. Because of the surgical risks and postsurgical complications associated with the implant of an epicardial lead system, implantation in the following patient groups may not be desirable or possible:

(1) patients in whom there is no indication for concomitant cardiovascular surgery at the time of ICD implant;

(2) patients with severe pulmonary disease who can not tolerate prolonged anesthesia or an open chest procedure;

(3) patients with severe congestive heart failure (ejection fraction < 40%) who are at increased risk for perioperative mortality post a thoracotomy procedure;

(4) patients who may eventually require open chest procedures for treatment of their coronary artery disease or cardiac transplant.

For these patients, the PCD Transvene System is the only therapy available. The PCD Transvene System simplifies and greatly reduces the risk associated with lead introduction, making therapy available to these patient groups. Because there is no need to open the chest of these patients, options for future therapy remain available; e.g. CABG is associated with decreased morbidity and mortality if there has been no prior open chest surgery.

However, it is expected that nonthoracotomy lead systems will have higher mean implant defibrillation thresholds as compared to traditional epicardial lead systems. In an epicardial lead system, the lead system has a larger electrode surface area which would theoretically decrease defibrillation requirements.

The smaller electrode surface areas of the PCD Transvene System defibrillation leads might reduce the proportion of patients in whom the implant criteria could be met. Not meeting the implant criteria may reduce the chronic effectiveness of the lead system. Recent studies indicated that only 70% of patients evaluated may be candidates for a nonthoracotomy defibrillation lead system (Wilber, D, et al. Clinical Advances in Nonepicardial Implantable Defibrillator Lead Systems. The Journal of Invasive Cardiology. Vol.3, No.6,November/December 1991).

For purposes of the PCD Transvene System, the implant criteria was defined as successful VF termination at least 3 times in 4 attempts with the final lead configuration with an output energy of 18 Joules or less. The determination of a defibrillation threshold was not necessary.

A defibrillation threshold (**DFT**) was defined as the energy at the lowest successful defibrillation attempt, provided the patient had a failure below the lowest success or a success at $\leq$ 5J. The lowest energy of defibrillation (**LED**) was defined as the lowest programmed energy that successfully defibrillated the patient. In both cases, conversion of ventricular tachycardia or ventricular flutter to sinus rhythm was **not** included in the determination of the DFT or LED.

(b)(4)

(b)(4)

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(b)(4)

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• **Patient Group Overview**	Description of patients screened for a PCD Transvene System
• **Patients Screened for PCD Transvene System**	Clinical characteristics and clinical outcome of patients screened for PCD Transvene System
• **Patients Not Meeting Implant Criteria**	Description of reasons for not meeting implant criteria, clinical characteristics and outcome of patient group
• **One Year Actuarial Survival**	Survival analysis for patients screened for a PCD Transvene System and received a PCD Transvene System.

2. Patient Group Overview

Patients Screened for a PCD Transvene System

(b)(4)

(b)(4)

(b)(4)

(b)(4)

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(b)(4)

(b)(4)

3. *Patients Screened For PCD Transvene System Implant*

(b)(4)

(b)(4)

(b)(4)

(b)(4)

PCD Transvene System Screened for PCD Transvene System versus Screened for PCD Epicardial System		
Patient Characteristics		
Data	**Transvene System**	**Epicardial System**
Number of Patients	854	645
Device Months Follow-Up	4771 months	6638 months
Mean Follow-Up Time	5.6 months	10.3 months
Maximum Follow-Up Time	28.6 months	33.3 months
Male **Female**	698 (81.7%) 156 (18.3%)	548 (85.1%) 96 (14.9%)
Mean Age	59.3 yrs	59.9 yrs
Primary Indication* **SCD** **VT** **SCD/VT**	 314 (36.8%) 429 (50.2%) 111 (13.0%)	 181 (28.1%) 353 (54.7%) 111 (17.2%)
Cardiovascular History **CAD** **Cardiomyopathy**	 74.4% (N=635) 31.1% (N=266)	 76.7% (N=495) 30.1% (N=194)
Mean Ejection Fraction	35.2% (N=781)	34.2% (N=606)
NYHA Class **Class I** **Class II** **Class III** **Class IV**	 245 (29.5%) 444 (53.4%) 129 (15.5%) 13 (1.6%)	 199 (31.4%) 310 (48.9%) 123 (19.4%) 2 (0.3%)

* **Statistically Significant**

Table VIII C-1: PCD Transvene System Screened versus PCD Epicardial Screened: Patient Characteristics - 6/24/92

(b)(4)

(b)(4)

(b)(4)

(b)(4)

PCD Transvene System Screened for PCD Transvene System versus Screened for PCD Epicardial System
Implant Data

(b)(4)

(b)(4)

Table VIII C-2: PCD Transvene System Screened versus PCD Epicardial Screened: Implant Data - 6/24/92

(b)(4)

(b)(4)

(b)(4)

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PCD Transvene System Screened for PCD Transvene System versus Screened for PCD Epicardial System
Spontaneous VT/VF Episode Efficacy

(b)(4)

(b)(4)

* Statistically Significant

Table VIII C-3: PCD Transvene System Screened versus PCD Epicardial Screened: Clinical Outcome - 6/24/92

(b)(4)

(b)(4)

4. Patients Receiving PCD Transvene System & Did Not Meet Implant Criteria

(b)(4)

(b)(4)

PCD Transvene System Reasons for Not Meeting Implant Criteria Physician Justification	
Reason	**Number of Patients**
(b)(4)	

(b)(4)

Table VIII C-4: PCD Transvene System: Physician Justification for Not Meeting Implant Criteria - 6/24/92

(b)(4)

AL333

(b)(4)

151

(b)(4)

(b)(4)

PCD Transvene System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Patient Characteristics		
Data	**Meeting Criteria**	**Not Meeting Criteria**
Number of Patients	543	214
Mean Follow-Up	6.2 months	4.0 months
Male*	422 (77.7%)	188 (87.9%)
Female	121 (22.3%)	26 (12.1%)
Mean Age	59.4 yrs	59.6 yrs
Indication*		
SCD	209 (38.5%)	72 (33.6%)
VT	278 (51.2%)	99 (46.3%)
SCD/VT	56 (10.3%)	43 (20.1%)
Cardiovascular History		
CAD	396 (72.9%)	165 (77.1%)
Cardiomyopathy	173 (31.9%)	65 (30.4%)
Mean EF*	36.3%	33.7%
NYHA Class		
I	164 (30.9%)	53 (25.8%)
II	278 (52.4%)	114 (56.6%)
III	82 (15.4%)	34 (16.6%)
IV	7 (1.3%)	4 92.0%)
Number ON Drugs at Implant	223 (41.1%)	97 (45.3%)
Number ON Amiodarone	78 (14.4%)	38 (17.8%)

* **Statistically Significant**

Table VIII C-5: PCD Transvene System: Patients Not Meeting Implant Criteria versus Patients Meeting Implant Criteria - Comparison of Patient Characteristics - 6/24/92

(b)(4)

(b)(4)

(b)(4)

(b)(4)

PCD Transvene System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Implant Data		
Data	Meeting Criteria	Not Meeting Criteria
(b)(4)		

(b)(4)

Table VIII C-6: PCD Transvene System: Patients Not Meeting Implant Criteria versus Patients Meeting Implant Criteria - Comparison of Implant Data - 6/24/92

(b)(4)

(b)(4)

PCD Transvene System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Implant Data		
Data	Meeting Criteria	Not Meeting Criteria

(b)(4)

(b)(4)

Table VIII C-7: PCD Transvene System: Patients Not Meeting Implant Criteria versus Patients Meeting Implant Criteria - Comparison of Clinical Outcome - 6/24/92

(b)(4)

(b)(4)

(b)(4)

(b)(4)

PCD Transvene System Patients Not Meeting Implant Criteria Survival Analysis versus PCD Epicardial System Patients Not Meeting Implant Criteria Survival Analysis		
	PCD Transvene System Not Meeting Implant Criteria	PCD Epicardial System Not Meeting Implant Criteria
(b)(4)	(b)(4)	

* Statistically Significant

Table VIII C-8: PCD Transvene System: Patients Not Meeting Implant Criteria - PCD Transvene System vs PCD Epicardial System - 6/24/92

(b)(4)

(b)(4)

Lowest Energy of Defibrillation < 24 Joules

(b)(4)

(b)(4)

(b)(4)

(b)(4)

PCD Transvene System Patients Not Meeting Implant Criteria 10J Safety Margin Provided
(b)(4) (b)(4)

Table VIII C-9: PCD Transvene System: Patients Not Meeting Implant Criteria with 3/4 Successes at $\leq$ 24 Joules Clinical Experience - 6/24/92

Difficult to Induce VF

(b)(4)

(b)(4)

284

Patient Condition

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Conclusion

(b)(4)

(b)(4)

(b)(4)

(b)(4)

5. *One Year Actuarial Survival*

(b)(4)

(b)(4)

PCD Transvene System
Patients Screened
Patient Death Classifications

(b)(4)

(b)(4)

Table VIII C-10: PCD Transvene System - Patients Screened Patient Deaths - 6/24/92

(b)(4)

(b)(4)

PCD Transvene System
Patients Received PCD Transvene System
Met Implant Criteria and Did Not Meet Implant Criteria
Patient Death Classifications

(b)(4)

(b)(4)

Table VIII C-11: PCD Transvene System - Patients Received PCD Transvene System Death Classifications - 6/24/92

(b)(4)

(b)(4)

(b)(4)

(b)(4)

PCD Transvene System
Patients Screened for PCD Transvene/Received a PCD Epicardial System
Met Implant Criteria and Did Not Meet Implant Criteria
Patient Death Classificatione

(b)(4)

(b)(4)

Table VIII C-12: PCD Transvene System: Patients Screened PCD Transvene/Received PCD Epicardial System Death Classifications - 6/24/92

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

PCD Transvene System
Patients Screened for PCD Transvene System
One Year Actuarial Survival

(b)(4)

(b)(4)

Table VIII C-13: PCD Transvene System - One Year Actuarial Survival for Patients Screened - 6/24/92

(b)(4)

(b)(4)

PCD Transvene System Patients Received Transvene System One Year Actuarial Survival	
(b)(4)	
(b)(4)	

Table VIII C-14: PCD Transvene System: One Year Actuarial Survival for Patients who Received PCD Transvene System - 6/24/92

PCD Transvene System Patients Screened Transvene System/Received Epicardial System One Year Actuarial Survival	
(b)(4)	
(b)(4)	

Table VIII C-15: PCD Transvene System: One Year Actuarial Survival for Patients Screened Transvene/Received Epicardial System - 6/24/92

6. Patients Not Meeting Implant Criteria - Conclusion

(b)(4)
(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

D. Ejection Fraction

(b)(4)

(b)(4)

PCD™ Transvene System Data Summary by Ejection Fraction				
	≤ 35%	36 - 59%	≥ 60%	All Patients
# of Patients	396	236	56	757
Number, % Male Number, % Female	336 84.9% 60 15.1%	186 78.8% 50 21.2%	37 66.1% 19 33.9%	610 80.6% 147 19.4%
Mean Age	62.0 yrs	58.7 yrs	45.6 yrs	59.4 yrs
Primary Indication: SCD VT SCD/VT	 130 32.8% 207 52.3% 59 14.9%	 91 38.6% 117 49.6% 28 11.8%	 38 67.9% 15 26.8% 3 5.3%	 281 37.1% 377 49.8% 99 13.1%
Coronary Artery Disease	325 82.1%	171 72.5%	19 33.9%	561 74.1%
Mean Ejection Fraction	25.5% (N=396)	44.9% (N=236)	67.3% (N=56)	35.6% (N=688)
Defibrillation Pathway: Sequential Simultaneous Single	 305 76.8% 89 22.4% 3 0.8%	 170 71.7% 65 27.2% 4 1.7%	 36 63.1% 20 35.1% 1 1.8%	 574 75.3% 178 23.4% 10 1.3%
Mean LED	16.1J (N=371)	16.0J (N=221)	14.9J (N=54)	16.0J (N=703)
Mean DFT	15.0J (N=151)	14.7J (N=111)	14.1J (N=32)	14.8J (N=316)
Spontaneous VT: # of Patients # of Episodes % Success	 120 3010 98.5%	 66 1932 99.1%	 11 213 98.6%	 226 5430 98.7%
Spontaneous VF: # of Patients # of Episodes % Success	 115 567 99.8%	 52 260 98.8%	 9 26 96.2%	 198 973 99.1%
1 Year SCD Survival	100.0%	100.0%	100.0%	99.8%

Table VIIID: Data Summary: Ejection Fraction - 6/24/92

E. Antiarrhythmic Drug Use

(b)(4)

(b)(4)

PCD™ Transvene™ System
Antiarrhythmic Drug Therapy By Follow-up Interval

(b)(4)

(b)(4)

Table VIIIE-1: Antiarrhythmic Drug Therapy by Follow-up Interval - 6/24/92

(b)(4)

(b)(4)

PCD™ Transvene™ System Patients on Antiarrhythmic Medication at the Time of Implant		
	Patients on Antiarrhythmic Medication at the Time of Implant	All Patients
(b)(4)		

(b)(4)

Table VIIIE-2: Patients on Antiarrhythmic Medication at the Time of Implant - 6/24/92

F. Model 7217B vs Model 7216A PCD Transvene System Experience

(b)(4)

(b)(4)

PCD™ Transvene System Data Summary 7217B vs 7216A			
	Model 7216A	Model 7217B	All Patients
(b)(4)			

(b)(4)

Table VIIIF: Data Summary: Model 7216A vs Model 7217B - 6/24/92

G. Patients with Non-Standard Lead Systems

(b)(4)

(b)(4)

PCD™ Transvene™ System
"Nonstandard" Defibrillation Lead Systems

(b)(4)

(b)(4)

Table VIIIG-1: "Nonstandard" Defibrillation Lead Systems

(b)(4)

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(b)(4)

PCD™ Transvene™ System Data Summary: Non-Standard Lead Systems		
	Non-Standard Lead Systems	All Patients
(b)(4)		

(b)(4)

Table VIIIG-2: Data Summary: Non-Standard Lead Systems - 6-24-92

H. Primary Indication

(b)(4)

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PCD™ Transvene System
Data Summary by Primary Indication

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(b)(4)

Table VIIIH: Data Summary by Primary Indication - 6/24/92

I. U.S. vs International

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(b)(4)

PCD™ Transvene System Data Summary: U.S. vs International			
	U.S.	International	All Patients
# of Patients	445	312	757
Mean Months F/U Max Months F/U Total Months F/U	4.6 26.9 2060.5	6.9 28.6 2185.9	5.6 22.8 4246.4
Number, % Male Number, % Female	351 78.9% 94 21.1%	259 83.0% 53 17.0%	610 80.6% 147 19.4%
Mean Age	61.1 yrs	57.0 yrs	59.4 yrs
Primary Indication: SCD VT SCD/VT	166 37.3% 240 53.9% 39 8.8%	115 36.9% 137 43.9% 60 19.2%	281 37.1% 377 49.8% 99 13.1%
Coronary Artery Disease	347 78.0%	214 68.6%	561 74.1%
Mean Ejection Fraction	33.6% (N=410)	38.5% (N=278)	35.6% (N=688)
Defibrillation Pathway: Sequential Simultaneous Single	321 71.8% 188 26.4% 8 1.8%	253 80.3% 60 19.1% 2 0.6%	574 75.3% 178 23.4% 10 1.3%
Mean LED	15.2J (N=426)	17.2J (N=277)	16.0J (N=703)
Mean DFT	13.9J (N=196)	16.1J (N=120)	14.8J (N=316)
Spontaneous VT: # of Patients # of Episodes % Success	126 3124 98.7%	100 2306 98.8%	226 5430 98.7%
Spontaneous VF: # of Patients # of Episodes % Success	101 431 99.8%	97 543 98.5%	198 973 99.1%
1 Year Survival: Sudden Cardiac Non-Sudden Cardiac All Cardiac Non-Cardiac Overall Number of Deaths Perioperative	99.7% 97.1 96.8 99.1 94.7 15 5	100.0% 97.0% 97.0% 99.5% 96.5% 7 0	99.8% 96.8 96.6 99.4 95.3 22 5

Table VIII-I: Data Summary: U.S. vs International - 6/24/92

IX. System Performance

A. PCD Device

1. Overview

Devices implanted for the treatment of recurrent ventricular tachyarrhythmias should perform safely and reliably in the indicated patient population. Device longevity and explant analysis were evaluated to assess the PCD device performance.

There have been a total of 41 (5.4%) devices explanted due to patient death, pocket infection, cardiac transplant or low battery voltage measurement and PCD Device performance issues.

There have been no patient deaths related to PCD malfunction. Based on the data presented in this section, the PCD device has performed safely and reliably in the indicated patient population.

2. Introduction

The data from a total of 762 implants in 757 patients of the PCD Transvene Systems been accumulated as of June 24, 1992. These implants have been followed for a mean of 5.6 months with a range of 0 -28.6 months. The cumulative implant duration for the total patient population is 4246.4 months.

Table IX A-1 shows the number of implants, device months experience and incidence of early device explant for reasons other than patient death, infection or cardiac transplant.

PCD™ Transvene™ System PCD Performance	
	All Implants
Data Cutoff	6/24/92
Number of Implants	762
Mean Follow-Up Months	5.6 months
Device Months of Implantation	4246.4 months
Early Device Explant	0.5%

Table IX A-1: Overview of PCD Transvene System Performance - 6/24/92

There were four devices explanted for reasons other than death, infection or transplant. These devices are discussed in detail in Section 4., Explanted Device Analysis.

As part of both the clinical protocol and required device follow-up, device battery performance was evaluated via telemetered battery voltage and charge time data.

There have been no reported patient deaths secondary to a malfunction of the PCD device or implanted Transvene lead system.

The clinical performance of the PCD System, as reported in the following sections, demonstrates that the Model 7217B PCD device when implanted with the Transvene System performed safely in the indicated patient population.

3. Explanted Unit Analysis

In the 762 implants, a total of 41 units (5.4%) were explanted secondary to patient deaths, infection, heart transplant, low battery voltage measurement and PCD Device performance issues. Table IX A-2 provides an overview of the units explanted, and returned to Medtronic for analysis and reason for explant.

PCD™ Transvene™ System Reasons for PCD Device Explant	
Reason	**All Models**
Number of Implants	762
Patient Death	15
Infection	17
Cardiac Transplant	5
Low Battery Voltage Measurement	1
PCD Device Performance Issues	3
Total	41

Table IX A-2: Reasons for PCD Device Explant - 6/24/92

The investigational plan requests that if the patient expires during the course of the clinical study that the PCD device be explanted and returned to Medtronic for analysis. There were 22 reported patient deaths and 15 devices were explanted and returned to Medtronic for analysis. In the remaining 7 deaths, the patients expired and were buried before the devices could be explanted.

Results of analysis performed on the 41 explanted devices is presented in Table IX A-3.

PCD™ Transvene™ System Final Analysis on Explanted PCD Devices (N = 762)	
Within Normal Specifications	16
Hermetic Leakage at IC	1
Random Component Failure	2
Shorted on Pulse 2 Output	1
Analysis Pending	21
Total	41

Table IX A-3: Final Analysis on Explanted PCD Devices - 6/24/92

Of the 41 devices explanted, final analysis on 16 units indicated that the devices were functioning within normal specifications. Final analysis is not available on 21 units which have been explanted. The reason for explant in these units includes patient death (6), infection (13) and cardiac transplant (2). It should be noted that none of these devices were explanted secondary to concern over the function of the implanted PCD Transvene System.

Four PCD Devices were explanted for the following device performance issues:

- explanted due to a Power On Reset (POR) condition that was not related to the delivery of external defibrillation or cautery (N = 1);
- explanted for lower than expected battery voltage for time in service (N = 1);
- explanted secondary to failure to appropriately synchronize and deliver cardioversion therapy for an induced VT episode (N = 1); and
- explanted post inappropriate delivery of VF therapy during a manual capacitor charge time (N = 1).

These devices are discussed in detail in the discussion that follows.

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4. Summary

a. Data on a total of 762 PCD Transvene System implants with a mean implant duration of 5.6 months and a cumulative implant duration of 4246.4 months is reported.

b. PCD device battery performance has been effectively monitored utilizing battery voltage obtained via telemetry and charge time and the data obtained supports the longevity projections.

c. There have been a total of 41 (5.4%) units explanted during the duration of the study as of June 24, 1992. The majority of these units were explanted due to patient death, pocket infection or cardiac transplant. One device was explanted secondary to lower than expected battery voltage for time in service. Three devices were explanted secondary to PCD Device performance issues.

d. The identified reason for low battery voltage in the PCD Transvene System experience was due to hermetic leakage at the input to one the integrated circuits which lead to a voltage drop across a resistor where the voltage measurement is taken. The actual battery voltage was normal in this device.

5. Conclusion

The PCD device longevity has been appropriately monitored via battery voltage and charge time. There have been no patient deaths related to PCD malfunction. Based on the data presented in this section, the PCD device when implanted with the Transvene System has performed safely and reliably in the indicated patient population.

B. Lead Durability and Integrity

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(b)(4)

PCD™ Transvene™ System
Transvene™ Leads: Experience and Complications

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(b)(4)

Table IX B-1: PCD Transvene™ Lead Experience and Complications - 6/24/92

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X. Comparison to AICD Epicardial System Clinical Experience

A. Overview

The efficacy and safety of implantable cardioverter defibrillator (ICD) therapy for recurrent ventricular tachycardia (VT) and ventricular fibrillation (VF) has been well established. The current market released device provides defibrillation therapy for VF or hemodynamically unstable VT. However, this type of therapy may not be optimal for patients with stable, well tolerated VT that is amenable to antitachycardia pacing due to the pain associated with cardioversion shock therapy. The need to incorporate programmability, multiple detection and therapeutic options and a desire to avoid thoracic surgery has lead to the development of tiered therapy devices such as the PCD Transvene System.

These tiered therapy devices combine features of bradycardia support pacing, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. Tiered therapy devices should provide enhanced clinical benefit as measured by complication rates and avoidance of cardioversion shocks. The one year actuarial survival rates should be comparable between the PCD Transvene System and the AICD Epicardial System.

The current AICD Epicardial System is implanted only with a defibrillation lead system requiring a thoracotomy. The PCD Transvene System allows the implantation of an implantable cardioverter defibrillator (ICD) system without the potential increased perioperative morbidity and mortality associated with a thoracotomy. This allows the application of ICD therapy in patients who may not otherwise be candidates for this type of therapy. Though the PCD Transvene System will have complications and observations that are specific to the lead system, the overall performance should be equivalent to that reported with the current AICD Epicardial System.

This section provides a comparison of the PCD Transvene System clinical experience to that of the reported AICD Epicardial System clinical experience. The following areas will be discussed:

- Patient characteristics
- Clinical performance
- Survival analysis

For purposes of comparison, the Ventak-P Epicardial System patient population described in the Summary of Safety and Effectiveness Data (PMA Application Number P890061) dated May 2, 1991 will be used. A copy of this summary was obtained through the Freedom of Information Act.

B. Comparison of Patient Characteristics

In comparing the clinical experience with the PCD Transvene System to the reported Ventak-P Epicardial System clinical experience, it is important to determine that the patients who received the device are comparable.

The patient characteristics of the patients receiving the PCD Transvene System were compared to the patients discussed in the Ventak-P Summary of Safety and Effectiveness Data and are presented in Table X B-1. There were no differences between the two patient groups.

PCD™ Transvene™ System
Comparison of Patient Characteristics
PCD versus AICD

	PCD	Ventak-P
Number of Patients	757	292
Mean Follow-Up Time	5.6 months	6.8 months
% Males **% Females**	610 (81%) 147 (19%)	231 (79%) 61 (21%)
Mean Age	59.4 years	61.5 years
Primary Indication: **SCD** **VT** **SCD/VT**	 281 (37%) 377 (50%) 99 (13%)	 49 (16%) 169 (59%) 73 (25%)
Coronary Artery Disease	561 (74%)	228 (78%)
Mean Ejection Fraction	35.6%	34%
Drug Therapy at Implant	42%	45.0%
Concomitant Surgery	0%	18.0%

Table X B-1: Comparison of Patient Characteristics, PCD versus Ventak-P 6/24/92

The two patient groups are comparable in mean age and mean ejection fraction. Both groups had moderately depressed left ventricular function demonstrated by the mean ejection of 35.6% for the PCD Transvene System patient group and 34% for the Ventak-P Epicardial System patient group.

Analysis indicated that no statistical differences between the PCD Transvene System and Ventak-P Epicardial System patient populations except in the category of patient indication. There are more patients that had Sudden Cardiac Death as their primary indication in the PCD Transvene population than in the AICD population ($p = 0.001$).

C. Comparison of Clinical Performance

Areas of clinical performance that were compared were implant defibrillation thresholds, incidence of spontaneous VT/VF events, incidence of complications and patient survival. These specific areas were selected in order to evaluate the system performance in the two patient populations.

Implant Defibrillation Thresholds

For the purposes of the PCD Transvene System clinical study, determination of defibrillation threshold was not mandatory. However, the preferred method of evaluating defibrillation efficacy was to determine the defibrillation threshold using a testing sequence of 18J, 15J, 10J, 5J with a failure at any level causing a return to 18 J for the remaining attempts. For the purposes of this report a defibrillation threshold was defined as the energy at the lowest successful defibrillation attempt, provided a patient had a failure below their lowest defibrillation success or a success at $\leq$ 5J. The rhythm treated must have been VF to be included in the analysis.

It should be noted, that it was expected that the PCD Transvene System would have a higher mean defibrillation threshold as compared to a traditional epicardial defibrillation lead system. In a traditional system, The increased electrode surface area would theoretically decrease defibrillation requirements.

A total of 316 patients had a defibrillation threshold determined at the time of PCD device implant. The mean defibrillation threshold (DFT) for all lead systems was 14.8J. The

recommendation for VF Therapy #1 is to program the stored energy to twice the implant DFT or 18 Joules, whichever is greater. Thus an adequate defibrillation safety margin was provided when following the VF therapy programming recommendations.

In the Ventak-P Epicardial System, the mean defibrillation threshold at implant was 13.4J. Thus the two systems had similar defibrillation thresholds at implant despite the fact that one system utilized an epicardial defibrillation lead system while the other utilized a transvenous defibrillation lead system.

This data indicate that the PCD Transvene System had comparable implant defibrillation threshold performance when compared to the reported Ventak-P Epicardial System clinical experience.

Incidence of Spontaneous VT/VF Episodes

The incidence of spontaneous VT/VF episodes in the Ventak-P Epicardial System and PCD Transvene System patient population was evaluated by utilizing the stored episode information provided in both devices.

In the Ventak-P device, the total number of shocks delivered to the patient is provided via interrogation of the device. The PCD device provides information on the total number of VT and VF episodes detected by the PCD device and the total number of VT and VF episodes successfully treated by the PCD device as well as the number of VT/VF episodes where the PCD device was ineffective. In addition, the last 20 intervals of the last episode satisfying detection criteria along with the first 10 intervals after the last therapy delivered are recorded by the device. This data assists the physician in evaluating the frequency of VT/VF episodes, the efficacy of the PCD device programmed parameters and the need for reprogramming.

In the Ventak-P Epicardial System experience of 292 patients with a mean follow-up of 6.8 months, 137 (46.9%) received a device countershock in response to a spontaneous ventricular tachyarrhythmia episode as defined by the Ventak-P Device detection criteria.

In the PCD Transvene System experience of 757 patients with a mean follow-up of 5.6 months, 311 patients (41%) have received device therapy in response to a spontaneous ventricular tachyarrhythmia episode.

A total of 5430 spontaneous VT and 973 spontaneous VF episodes have been recorded by the PCD device episode counters. Of the 5362 successfully treated spontaneous VT episodes, 92% were treated with one of the programmed antitachycardia pacing therapies incorporated in the PCD device. The clinical benefit of tiered therapy is the reduction of delivery of high energy shocks for the treatment of stable recurrent ventricular tachycardia that may be responsive to antitachycardia pacing.

Incidence of Complications

For purposes of the PCD System clinical study relevant medical events were classified as either **clinical complications** or **clinical observations**. The classification was based on the following definitions:

Complication: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

Observation: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

Table X C-1 provides a comparison of reported complications and observations. The AICD clinical experience data is from the Winkle, et al Long Term Outcome with Automatic Implantable Cardioverter-Defibrillator; JACC, May 1989; 13(6); 135-161. This article was selected because it provides a detailed clinical complication experience on a large patient population, 270 patients. Note that the percentage reported in the PCD Transvene System includes **both** complications and observations. In the following table, the complications are reported for the categories of Fail to Cardiovert/Defibrillate, Pocket Infection, and Erosion. Observations are reported in the Inappropriate/Problematic VT/VF Therapy Delivery category.

PCD™ Transvene™ System Comparison of Complication/Observation Rates PCD versus AICD		
Category	**PCD%**	**AICD%**
Fail to Cardiovert/Defibrillate	0.8%	4.1%
Inappropriate/Problematic VT/VF Therapy Delivery	8.2%*	20%
Pocket Infection	2.0%	2.2%
Erosion	0.3%	0.7%

* Includes Observations only; there were no Complications in this category.

Table X C-1: Comparison of Complication/Observation Rates: PCD Transvene System vs AICD Epicardial System - 6/24/92

The incidence of failure to cardiovert and/or defibrillate was lower in PCD Transvene System patient population. The instances of failure to cardiovert and/or defibrillate in the PCD Transvene System patient population were associated with increased defibrillation requirements during induced episodes, none of which resulted in patient death. In six cases, the implanted system was modified to provide adequate defibrillation efficacy, in four cases the patient's drug therapy was modified and in the final two cases, reprogramming provided for adequate defibrillation efficacy.

The failures to cardiovert/defibrillate reported in the Winkle, et al article were associated with patch dislodgement, patch crinkling, lead conductor fracture and elevated defibrillation thresholds.

The incidence of inappropriate/problematic VT/VF therapy delivery was lower in the PCD Transvene System patient population. This is to be anticipated since the device incorporates independently programmable detection algorithms for VT and VF. The reasons for inappropriate VT/VF therapy delivery included sinus tachycardia being detected as VT or VF and atrial fibrillation with rapid ventricular response being detected as VT or VF.

The circumstances reported in Winkle, et al were nonsustained VT, VT, sinus tachycardia, atrial fibrillation with rapid ventricular response, sensing lead fracture and pacemaker interaction. The patients with VT complained of receiving multiple shocks with limited or no symptoms. The incorporation of antitachycardia pacing in the PCD device decreases the need for delivery of cardioversion shocks for the termination of stable VT and increases patient acceptance of ICD therapy.

In the Winkle, et al experience all patients with pocket infection had the devices explanted. In the PCD Transvene System experience, the incidence of device explant secondary to pocket infection was 2.0% which was comparable to Winkle's article.

Thus, the incidence of complications and observations was similar to that of the AICD Epicardial System in the categories of ineffective VT/VF therapies, infection requiring explant and erosion. The incidence of inappropriate delivery of therapy is lower in the PCD Transvene System experience than in the AICD Epicardial System experience, which is clinically significant.

This analysis indicates that the PCD Transvene System offers the potential clinical advantages in removing the need for a thoracotomy for implantation and the associated morbidity.

D. Comparison of One Year Actuarial Survival

The Ventak-P Epicardial System produced by Cardiac Pacemaker, Inc, has obtained market approval from the U.S. FDA to date. While there are important differences in the function of the Ventak-P Epicardial System and the PCD Transvene System, there is a natural desire for comparison of the clinical outcome, particularly the impact of these devices on death rate.

A total of 22 deaths (2.9%) were reported in the PCD Transvene System patient population. Of the 18 cardiac deaths, 15 were non-sudden cardiac and 3 were sudden cardiac. Four deaths were classified as noncardiac. Five of the 22 total deaths occurred within the perioperative period (death less than 30 days post implant) with a resultant perioperative mortality of 0.7%.

In the Ventak-P Epicardial System patient population a total of 19 deaths (6.5%) were reported. Of the 12 cardiac deaths, 4 were classified as sudden cardiac and 8 were classified as non-sudden

cardiac. Six of the deaths were classified as noncardiac and the cause of one was unknown. Eight of the deaths occurred within the perioperative period with a resultant perioperative mortality of 2.7%. The PCD Transvene System population had a lower perioperative mortality, 0.7% vs 2.7% (b)(4)

For purposes of this comparison, only the **overall** actuarial survival rate includes perioperative deaths. All other calculations in both the PCD Transvene System and Ventak-P Epicardial System group exclude perioperative deaths.

For the Ventak-P Epicardial System, patient deaths were **censored** if the Ventak-P device had been either electively deactivated for various reasons prior to the patient's death, thus preventing the device from attempting to convert the arrhythmia or if the pulse generators were known to be nonfunctional and awaiting replacement. For purposes of this comparison, two patient deaths were **censored** in the PCD Transvene System patient population because the devices were deactivated at the time of patient death.

This PCD Transvene System sudden cardiac death survival of 100% at one year is comparable to that of the Ventak-P Epicardial System sudden cardiac death survival rate of 98.6 %. More importantly, the overall one year actuarial survival for the PCD Transvene System was 95.6% as compared to 90.8% for the Ventak-P Epicardial System. This difference was primarily due to the improvement in the reported perioperative mortality in the PCD Transvene System patient population. [Note: Confidence interval analysis was performed indicating that there was a statistical difference in the reported **Overall** mortality.]

This comparison of actuarial survival rates indicates that the projected sudden cardiac death survival of patients receiving a PCD Transvene System is comparable to that reported for the Ventak-P Epicardial System. Thus, the incorporation of programmable VT/VF detection and therapy algorithms has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

In addition, the elimination of a surgical thoracotomy for implant in the PCD Transvene System has improved the perioperative mortality and overall one year survival when compared to the Ventak-P Epicardial System.

E. Summary

The efficacy and safety of implantable cardioverter defibrillator (ICD) therapy for recurrent ventricular tachycardia (VT) and ventricular fibrillation (VF) has been well established. The Ventak-P Epicardial System provides only one type of therapy for the treatment of both recurrent VT and VF. The PCD Transvene System incorporates tiered therapy which combines features of bradycardia support pacing, antitachycardia pacing,low energy cardioversion as well as defibrillation therapy to allow titration of therapy to patient specific ventricular tachyarrhythmias.

In addition, the PCD Transvene System eliminates the need for a thoracotomy for implantation thus increasing the number of patients who may be considered for the therapy and improving both perioperative and overall one year survival.

A comparison of Ventak-P Epicardial System clinical experience and PCD Transvene System clinical experience indicates that the devices are being used in patients with similar cardiovascular disease history.

The mean DFT value at implant of the PCD Transvene System falls well below the maximum output (34J) of the PCD device and is comparable to that reported with the Ventak-P Epicardial System.

The percentage of patients receiving therapy from the PCD Transvene System is comparable to that reported in the Ventak-P Epicardial System experience. However, greater than 90% of the VT episodes are treated by antitachycardia pacing in the PCD Transvene System experience versus cardioversion shocks in the Ventak-P Epicardial System experience. This reduction in shocks is a clinical benefit to the patients.

The reported incidence of most complications is comparable between the two systems. The incorporation of programmable VT/VF detection has decreased the delivery of inappropriate therapy for sinus tachycardia and/or atrial fibrillation with a rapid ventricular response. The incorporation of programmable VT/VF detection and therapy algorithms has not resulted in an increase in reported complications.

The reported Sudden Cardiac Death survival rates in the two patient groups is comparable (PCD Transvene System - 100%; Ventak-P System - 98.6%). This indicates that the programmable features within the PCD Transvene System have improved the types of therapy available for the treatment of recurrent VT and VF without adversely affecting sudden cardiac death survival.

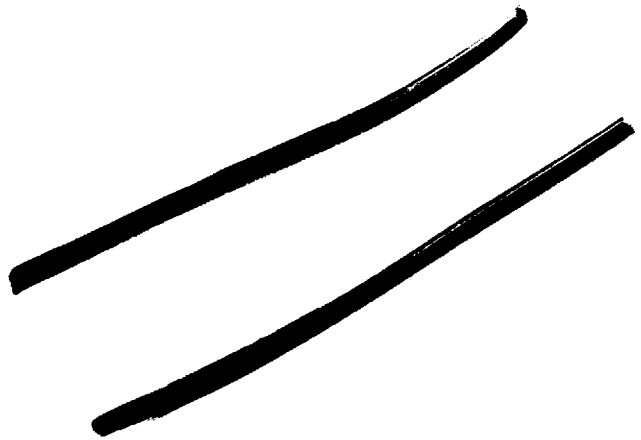
More importantly, the overall one year actuarial survival for the PCD Transvene System was 95.6% as compared to 90.8% for the Ventak-P Epicardial System. This difference was primarily due to the improvement in the reported perioperative mortality in the PCD Transvene System patient population.

F. Conclusion

The PCD Transvene System incorporates additional detection and therapy features as compared to currently market released system and has been used in a comparable patient population. In that patient population the PCD Transvene System has allowed for fewer shocks to be delivered because of the antitachycardia pacing features, fewer cases of inappropriate therapy delivery due to programmable detection and a identical sudden cardiac death survival rate.

In addition, the elimination of a thoracotomy for implant in the PCD Transvene System has improved the perioperative mortality and overall one year survival when compared to the Ventak-P Epicardial System.

XI. Comparison to PCD
Epi. Clinical Results



XI. Comparison to PCD Epicardial System Clinical Experience

A. Overview

The PCD Epicardial System, is a tiered therapy device that, combines features of bradycardia support pacing, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. This system has incorporated programmability and multiple detection and therapeutic options that allows the titration of device therapy to a patient's specific clinical arrhythmia history.

The PCD Epicardial System requires a thoracotomy for implantation because of the need to insert epicardial patch leads. This exposes the patient to surgical risk and potentially limits the type of patient who may be considered for implant of the system. The need for a simpler and safer implantation technique is widely recognized. The incorporation of a nonthoracotomy lead system, such as the PCD Transvene System, should decrease the potential perioperative and long term mortality and morbidity associated with current epicardial system implantation approaches. One measure of the positive impact of the PCD Transvene System is hospital stay post implant. There was a statistically significant ($p = 0.001$) improvement for patients receiving a PCD Transvene System (mean hospital stay - 7.2 days) versus patients receiving a PCD Epicardial System (mean hospital stay - 10.3 days).

The PCD Epicardial System and PCD Transvene System are identical except for the implanted defibrillation lead system. Thus the performance of the PCD device, and associated support equipment, is similar in the two systems and therefore a comparison of clinical experience should focus on those areas where the lead system implanted may impact clinical outcome.

This section provides a comparison of the PCD Transvene System clinical experience to the reported PCD Epicardial System clinical experience. The following areas will be discussed:

- Patient characteristics
- Implant Data
- Spontaneous VT/VF Episode Efficacy
- Complications and Observations
- Survival analysis

This analysis will show that the incorporation of a nonthoracotomy defibrillation lead system has maintained the type

of therapy available for the treatment of recurrent VT/VF and decreased the potential mortality and morbidity associated with epicardial implant approaches while maintaining the positive impact of ICD therapy on VT/VF episode efficacy and patient survival.

B. Comparison of Patient Characteristics

In comparing the clinical experience with the PCD Transvene System to the PCD Epicardial System clinical experience, it is important to determine that the patients who received the device are comparable.

The characteristics of the patients receiving the PCD Transvene System were compared to the characteristics of the 742 patients who received the PCD Epicardial System as of 5/14/92.

PCD™ Transvene™ System
Comparison of Patient Characteristics

	PCD Transvene System	PCD Epicardial System
Number of Patients	757	742
Mean Follow-Up Time	5.6 months	9.7 months
% Males* % Females	610 80.6% 147 19.4%	637 85.8% 105 14.2%
Mean Age	59.4 years	59.6 years
Primary Indication* SCD VT SCD/VT	 281 37.1% 377 49.8% 99 13.2%	 214 28.8% 405 54.6% 123 16.6%
Cardiovascular History Coronary Artery Disease Cardiomyopathy	 561 74.1% 238 13.1%	 569 76.7% 222 29.9%
Mean Ejection Fraction	35.6%	34.0%
Number of Drugs Failed*	2.3	3.0

* Statistically Significant

Table XI B-1: PCD Transvene System Comparison to PCD Epicardial System - 6/24/92

Both groups had moderately depressed left ventricular function demonstrated by the mean ejection of 35.6% for the PCD Transvene System patient group and 34.0% for the PCD Epicardial patient group.

Analysis indicated that the PCD Transvene System patient population had a higher percentage of patients whose indication for implant was sudden cardiac death ($p = 0.002$) and higher percentage of females ($p = 0.007$). It is not expected that this difference will result in a different clinical outcome in the PCD Transvene System patient population as compared to the PCD Epicardial System. This difference in patient indication is a reflection of the physicians use of the PCD Transvene System.

It is interesting to note, that there was a statistical difference in the number of antiarrhythmic drugs tested between the two patient groups ($p = 0.001$). The PCD Transvene System patient group failed a mean of 2.3 antiarrhythmic drugs prior to implant while the PCD Epicardial System patient group failed a mean of 3.0 antiarrhythmic drugs. This difference is a reflection of the distribution of indication for implant between the two patient groups. The PCD Transvene System patient group had a higher incidence of patients whose primary indication for implant was sudden cardiac death. These patients have a higher probability of having experienced a sudden cardiac death episode but being non-inducible during electrophysiologic testing thus drug testing is not feasible.

C. Implant Data Comparison

In both systems, lead system testing was performed to verify that one of the specified lead systems was capable of properly detecting and treating episodes of ventricular fibrillation and, when appropriate ventricular tachycardia. This testing included pacing and sensing thresholds during sinus rhythm, evaluation of VF electrogram amplitudes and defibrillation efficacy evaluation. The implant criteria for both systems was identical and were:

1. Successful VF termination at least 3 times in 4 attempts with an output energy of 18 Joules or less and

2. A 2:1 VF sensing safety margin

Pace/Sense Performance

In both the PCD Transvene and PCD Epicardial Systems, sensing is performed in a standard bipolar configuration and pacing is performed in the integrated bipolar configuration. The pace/sense implant criteria for both systems was:

Pacing Threshold:	$\leq$ 1.5V @ 0.5 ms
R-Wave Amplitude:	$\geq$ 5 mV
Slew Rate:	$\geq$ 0.75 volt/sec
Resistance:	200 - 880 ohms

Table XI C-1 provides a comparison of the mean pace/sense values obtained at the time of implant for the PCD Transvene and Epicardial Systems. It should be noted that the pace/sense values presented for the PCD Epicardial System are for the Model 7217B PCD Device.

PCD™ Transvene™ System
Performance Comparison
Implant Pace/Sense Parameters

Parameter	PCD Transvene System	PCD Epicardial System
Pacing Threshold*	0.87 V (0.1-3.6V)	0.98 V (0.2-5.3 V)
R Wave Amplitude*	14.2 mV (1.3-32 mV)	13.5 mV (2.2-37.2 mV)
Slew Rate*	1.66 v/S (0.25-9.8 v/S)	1.38 v/S (0.15-7.2 v/S)
Resistance*	575 ohms (264-1381 ohms)	438 ohms (157-1206)

* Statistically Significant

Table XI C-1: PCD Transvene System: Comparison of Implant Pace/Sense Parameters - 6/24/92

The implant pace/sense parameters obtained for the PCD Transvene System indicates that the lead system provided adequate pacing and safety margins. There was a statistically significant difference in all of the implant pace/sense parameters ($p = 0.001$). However, this difference had no clinical impact on the pacing and sensing performance of the PCD Transvene System.

Electrogram amplitudes were evaluated at follow-up evaluations of both systems to evaluate the performance of the pace/sense lead system and assure adequate safety margin for detection of both baseline rhythms and ventricular tachyarrhythmias. In addition, pacing thresholds were also evaluated at follow-up evaluations to assure an adequate safety margin for capture during both bradycardia and antitachycardia pacing therapies. A comparison of the chronic pace/sense performance for the two systems is presented in Table XI C-2. It should be noted that there was no statistical difference in the chronic pace/sense performance of the two systems.

PCD™ Transvene™ System Performance Comparison Chronic Pace/Sense Parameters		
Parameter	**PCD Transvene System**	**PCD Epicardial System**
Electrogram Amplitude	9.6 mV (0.2 - 25 mV)	9.6 mV (0.5-2.5 mV)
Pulse Width Threshold	0.24 ms (0.03-1.59 ms)	0.28 ms (0.03-1.59 ms)

Table XI C-2: PCD Transvene System: Comparison of Chronic Pace/Sense Parameters - 6/24/92

The incidence loss of capture due requiring lead system modification in the PCD Transvene System was 0.8% while the incidence in the PCD Epicardial System was 2.0%. There were no reports of undersensing requiring lead modification in the PCD Transvene System while the incidence in the PCD Epicardial System was 0.8%.

This comparison of implant and chronic pace/sense performance indicates that the performance of the PCD Transvene System is similar to that reported with the PCD Epicardial System. The PCD Transvene System provides appropriate acute and chronic safety margins for sensing of sinus rhythm and ventricular tachyarrhythmia as well as appropriate safety margins for pacing therapy.

Implant Defibrillation Thresholds

For the purposes of both systems, determination of defibrillation threshold was not mandatory. However, the preferred method of

evaluating defibrillation efficacy was to determine the defibrillation threshold using a testing sequence of 18J, 15J, 10J, 5J with a failure at any level causing a return to 18 J for the remaining attempts.

A defibrillation threshold was defined as the energy at the lowest successful defibrillation attempt, provided a patient had a failure below their lowest defibrillation success or a success at $\leq$ 5J. The rhythm treated must have been VF to be included in the analysis.

Table XI C-3 provides a comparison of defibrillation thresholds determined at implant for the PCD Transvene and PCD Epicardial Systems.

PCD™ Transvene™ System
Performance Comparison
Implant Defibrillation Thresholds

System	Mean DFT
PCD Transvene System*	14.8J
PCD Epicardial System	9.8J

* Statistically Significant

Table XI C-3: PCD Transvene System: Comparison of Implant DFT - 6/24/92

The PCD Transvene System did have a statistically significantly higher mean implant defibrillation threshold ($p = 0.0001$). It should be noted, that it was expected that the PCD Transvene System would have a higher mean defibrillation threshold as compared to a traditional epicardial defibrillation lead system. In a traditional epicardial system, the increased electrode surface area would theoretically decrease defibrillation requirements.

The recommendation for VF Therapy #1 is to program the stored energy to twice the implant DFT or 18 Joules, whichever is greater. With the PCD Transvene System an adequate defibrillation safety margin was provided when following the VF therapy programming recommendations.

As indicated previously, the defibrillation implant criteria for both systems was 3/4 successful terminations of VF at 18 Joules or less. In the PCD Epicardial System, 12.4% (92/742) of the

patients received the system without meeting the defined implant criteria. In the PCD Transvene System, 28.3% (214/757) of the patients received the system without meeting the defined implant criteria.

Though the incidence of not meeting implant criteria was higher in the PCD Transvene System ($p = 0.001$) it was clinically justified. The reasons for not meeting implant criteria included deteriorating patient condition, failure to induce VF or 3/4 successes at less than 24 Joules. The investigator's felt in every case that the testing performed at the time of implant, though it did not meet the recommended implant criteria, did provide an adequate defibrillation safety margin when programming VF Therapy #1. The investigator's also felt that these patients medical condition precluded a PCD Epicardial System with a thoracotomy approach. The advantage of not performing a thoracotomy to implant the PCD Epicardial System outweighed the risk of not meeting the recommended implant defibrillation criteria.

The long term clinical efficacy of the two systems was evaluated by the incidence of clinical cases of failure to successfully defibrillate a spontaneous episode of VF despite delivery of all four programmed therapies. In addition, the incidence of modification of the implanted lead system in order to improve defibrillation efficacy in the two systems was evaluated.

In the PCD Transvene System, there were a total of 973 spontaneous episodes of VF detected by the PCD Device in 198 patients. The incidence of unsuccessful termination of an apparent "true" episode of ventricular fibrillation despite the delivery of all four therapies was 0.1% (1/973).

In the PCD Epicardial System, there were a total of 1694 spontaneous episodes of VF detected by the PCD Device in 258 patients. The incidence of unsuccessful termination of an apparent "true" episode of ventricular fibrillation despite the delivery of all four therapies was 0.5% (9/1694).

The incidence of increased defibrillation requirements requiring modification of the implanted defibrillation lead system was similar in the two systems. The reported incidence in the PCD Transvene System was 0.8% while in the PCD Epicardial System the incidence was 0.6%.

This comparison of implant and chronic defibrillation performance indicates that the performance of the PCD Transvene System is similar to that reported with the PCD Epicardial System. The PCD Transvene System provides appropriate acute and chronic safety margins for defibrillation therapy and has not required an increased need for modification of the lead system to maintain defibrillation efficacy when compared to the PCD Epicardial System. Finally, the PCD Transvene System has effectively treated spontaneous episodes of VF without an increase in the incidence of ineffective therapies.

D. Programmed Parameter Status

In comparing the programmed status of PCD Transvene and PCD Epicardial System patients, three areas of difference were identified -number of patients with VF detection/therapy only enabled, range of VF Therapy #1 defibrillation energies and programmed defibrillation pathways. The use of the remaining PCD Device parameters was similar in the two patient groups.

Table XI D-1 provides the PCD Device programmed status for the two patient populations. There was a higher percentage of patients with VF Detection/Therapy only programmed ON in the PCD Transvene System patient population (29.0%) as compared to the PCD Epicardial System (20.1%). This difference is reflective of the indication for implant in the two patient groups. The PCD Transvene System patient population had a higher incidence of patients who were sudden cardiac death survivors without recurrent VT (37.1%) versus the PCD Epicardial System (28.8%).

There was also a difference in the number of inactive patients in the two patient groups. "Inactive Patients" includes patients no longer active in the study due to patient death, explant due to infection or explant due to heart transplant. The PCD Epicardial System had 105 patients (14.2%) who were no longer active in the study while the PCD Transvene System had 38 patients (5.0%).
This difference was due to a greater number of patient deaths in the PCD Epicardial System, 88, compared to a total of 22 patient deaths in the PCD Transvene System patient population.

PCD™ Transvene™ System Performance Comparison PCD Device Programmed Status		
Programmed Status	**PCD Transvene System**	**PCD Epicardial System**
VT/VF Detection/Therapy ON	516 (68.2%)	529 (71.5%)
VF Detection/Therapy Only ON	219 (29.0%)	149 (20.1%)
VVI Only*	21 (2.8%)	62 (8.4%)
TOTAL	757	742

* VVI Only reflects patients who are have not undergone the pre-hospital discharge EPS

Table XI D-1: PCD Transvene System: Comparison of PCD Device Programmed Status - 6/24/92

Table XI D-2 provides the distribution of programmed VF Therapy #1 energies for the two patient groups. This difference in programmed VF Therapy #1 defibrillation energies is related to the implant defibrillation thresholds obtained in the two groups. The mean implant DFT for the PCD Transvene System was 9.8J and ranged from 0.6 to 30.0 J Joules. The recommendation for VF Therapy #1 is to program the stored energy to 34 Joules, twice the implant DFT or 18 Joules, whichever is greater. The physicians followed these recommendations and the range values used reflects this. The mean implant DFT for the PCD Epicardial System was 9.8J and ranged from 0.4 to 26.0 Joules. This difference in the mean DFT and range of DFT's allowed the use of lower energy values when following the programming recommendations for VF Therapy #1.

PCD™ Transvene™ System Performance Comparison Programmed VF Therapy #1 Energy Last Known Follow-Up Visit		
VF Therapy #1 Energy Range	**PCD Transvene System**	**PCD Epicardial System**
≤ 5 J	30 (4.0%)	80 (10.8%)
6-10 J	3 (0.4%)	33 (4.5%)
11-18J	81 (10.7%)	121 (16.4%)
20-30J	21 (2.8%)	16 (2.2%)
34J	621 (82.1%)	490 (66.2%)

Table XI D-2: PCD Transvene System: Comparison of Programmed VF Therapy #1 Energy - 6/24/92

The programmed defibrillation pathways for the two patient populations is presented in Table XI D-3. The implanted PCD Transvene Systems are almost exclusively three lead systems and this explains the decreased use of SINGLE pathway. The use of SIMULTANEOUS pathway is higher in the PCD Transvene System and indicates that in a group of patients the incorporation of multiple defibrillation pathways allowed an increase in the ability to meet the PCD Transvene System implant criteria. The majority of the PCD Epicardial System implants used a two patch system resulting in the increased use of the SINGLE pathway.

PCD Transvene System Performance Comparison Programmed Defibrillation Pathway		
Defibrillation Pathway	**PCD Transvene System**	**PCD Epicardial System**
Sequential	574 (75.3%)	251 (33.0%)
Simultaneous	178 (23.4%)	14 (1.8%)
Single	10 (1.3%)	496 (65.2%)

Table XI D-3: PCD Transvene System: Comparison of Programmed Defibrillation Pathway - 6/24/92

The differences in the programmed status of the PCD device in the PCD Transvene System are a reflection of the type of patients who received the device and the defibrillation energy requirements for each lead system. It is important to note that the PCD device performed safely and effectively in both patient populations.

E. Spontaneous VT/VF Episodes Efficacy Comparison

The primary benefits from the use of the PCD System center on the detection and termination of life-threatening ventricular tachyarrhythmias. The additional benefit of the PCD Transvene System is the elimination of the need for a thoracotomy for implantation of the defibrillation lead system and the resultant decrease in potential patient morbidity and mortality associated with a thoracotomy. This clinical benefit should not be gained at the expense of providing effective termination of spontaneous VT and VF episodes. Table XI E-1 provides a comparison of the efficacy of the PCD Transvene and PCD Epicardial System in treating spontaneous episodes of VT and VF.

PCD Transvene System Performance Comparison		
Spontaneous VT Episodes		
	PCD Transvene System	**PCD Epicardial System**
Mean Follow-Up	5.6 months	9.7 months
Number of Episodes	5430	13,706
% Overall Efficacy	98.7%	98.1%
% Unsuccessful Termination	0.4%	1.0%
Spontaneous VF Episodes		
	PCD Transvene System	**PCD Epicardial System**
Mean Follow-Up	5.6 months	9.7 months
Number of Episodes	973	1694
% Overall Efficacy	99.1%	98.6%
% Unsuccessful Termination	0.1%	0.5%

Table XI E-1: PCD Transvene System: Comparison of Spontaneous VT/VF Episode Efficacy - 6/24/92

The overall success rate of the PCD Transvene System in terminating spontaneous episodes of VT or VF is 98.8%. In addition, there have been no reported patient deaths due to ineffective termination of a spontaneous VT/VF episode. This success rate compares very favorably with the overall success rate of the PCD Epicardial System of 98.2%. Therefore, the PCD Transvene System offers the potential of decreased patient morbidity and mortality without decreasing the treatment efficacy of spontaneous VT/VF episodes.

F. Incidence of Complications/Observations

For purposes of the PCD System clinical study relevant medical events were classified as either **clinical complications** or **clinical observations**. The classification was based on the following definitions:

Complication: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

Observation: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

A comparison of the reported complications and observations was made between the PCD Transvene System and the PCD Epicardial System. The PCD Epicardial System patient population used for comparison included clinical experience as of May 14, 1992 with 742 patients and a mean implant duration of 9.7 months. These two patient groups are similar in the patient demographics and indication for implant of the PCD System. In the PCD Transvene System patient population, 18.2% of the patients experienced a clinical complication and 20.8% of the patients experienced a clinical observation. In the PCD Epicardial System, 12.8% of the patients experienced a clinical complication and 25.7% of the patients experienced a clinical observation.

Table XI F-1 and F-2 provide a comparison of the reported complications/observations and their incidence in the two patient populations.

PCD Transvene System versus PCD Epicardial System Reported Complications		
Reported Complications	**PCD Transvene System (N=767)**	**PCD Epicardial System (N=742)**
Increased Defibrillation Requirements	0.8%	0.5%
Inappropriate Therapy	-	1.8%
Pace/Sense Related	0.9%	3.5%
Infection Related - Explant	2.0%	1.9%
Lead Related	6.6%	2.8%
Device Related	0.5%	0.9%

Table XI F-1: Reported Complications: PCD Transvene System versus PCD Epicardial System - 6/24/92

PCD Transvene System versus PCD Epicardial System Reported Observations		
Reported Observations	**PCD Transvene System (N=767)**	**PCD Epicardial System (N=742)**
Ineffective Therapy	0.5%	1.1%
Inappropriate Therapy	8.2%	10.6%
Pace/Sense Related	4.1%	10.2%
Infection Related	5.3%	2.2%
Lead Related	2.2%	1.2%
Device Related	-	-

Table XI F-2: Reported Observations: PCD Transvene System versus PCD Epicardial System - 6/24/92

The PCD Epicardial System requires a thoracotomy for implantation because of the need to insert two or more epicardial patch leads. This exposes the patient to increased surgical risk and potentially limits the type of patient who may be considered for implant of the system. The requirement of thoracotomy contributes significantly to patient morbidity and mortality, patient discomfort, and prolonged hospitalization. Clinically significant complications associated with epicardial implants include atrial fibrillation with additional risk of inappropriate therapy, potential erosion of native coronary arteries or bypass grafts by the epicardial patches and requirement for repeated thoracotomy in seriously ill patients if an infection develops. The PCD Transvene System offers a less invasive, simpler and safer implantation technique and should decrease the incidence of complications and observations associated with epicardial system implants.

Further analysis was performed to evaluate if the incidence of specific complications and observations was different between the two patient populations.

The incidence of inappropriate therapy delivery in the two patient groups was evaluated. Inappropriate therapy delivery is defined as the delivery of either VT or VF therapy for reasons other than spontaneous VT or VF episode. This includes atrial fibrillation with a rapid ventricular response or sinus tachycardia that overlaps with the programmed detection criteria. In addition, inappropriate therapy may be delivered due to oversensing due to hardware issues such as a loose set screw. Specifically a comparison was made between the incidence of atrial fibrillation resulting in inappropriate therapy between the two patient groups and this data is presented in Table XI F-3.

Atrial fibrillation, with a risk of inappropriate shocks and the potential need for concomitant antiarrhythmic drug therapy, is a recognized medical event in patients receiving an ICD System utilizing an epicardial defibrillation lead system. The occurrence of atrial fibrillation in these patients may be related to the thoracotomy procedure required for implant, manipulation of the atrium during the implant procedure or the positioning of the epicardial patch leads near or on the atrium resulting in irritation and induction of atrial fibrillation. The incidence of inappropriate therapy for atrial fibrillation in the PCD Epicardial System was 6.1% while that for that the PCD Transvene System was 4.9%. An decreased incidence of inappropriate therapy results in a

decreased potential risk for acceleration on non VT/VF rhythms as well as increased patient acceptance of ICD therapy. Though the introduction of a transvenous lead system has not totally removed the risk of inappropriate therapy for atrial fibrillation, from this clinical experience it appears that the incidence has been decreased.

PCD Transvene System versus PCD Epicardial System Incidence of Inappropriate Therapy for Atrial Fibrillation				
	PCD Transvene System		PCD Epicardial System	
	Number	Total %	Number	Total %
Inappropriate VF Therapy	9	1.2%	11	1.5%
Inappropriate VT Therapy	28	3.7%	34	4.6%
Overall Incidence	37	4.9%	45	6.1%

Table XII F-3: PCD Transvene System: Incidence of Inappropriate Therapy for Atrial Fibrillation - 6/24/92

The incidence of pocket infection in the two patient groups was also evaluated. In the patient receiving an ICD System with epicardial defibrillation lead systems, if an infection does develop patch explant is usually required resulting in repeated thoracotomy to remove the system.

The incidence of pocket infection that required explant of the PCD System was similar in the two patient groups - **2.0% for the PCD Transvene System versus 1.9% for the PCD Epicardial System.** The incidence of pocket infection that could be successfully treated with antibiotic therapy alone was similar between the PCD Transvene and Epicardial Systems (1.1% versus 2.2%). This similarity in the incidence of pocket infection between the two patient groups is not unexpected. The PCD Transvene System, though it does not required a thoracotomy, can require the evaluation of multiple lead orientations to obtain adequate defibrillation efficacy thus resulting in a prolonged operative procedure.

It should be noted however, that the reported incidence of infection in both patient groups is equivalent to that reported with current market released implantable cardioverter defibrillator system of 2.4% (Ventak-P Summary of Safety and Effectiveness Data, PMA Application Number P890061, May 2, 1991).

The final comparison was made between the incidence of lead dislodgement in the two patient groups. In both systems, the clinical impact of a lead dislodgement is the potential for inappropriate therapy delivery, nondetection of VT/VF or ineffective therapy for an episode of VT/VF. Also in both systems, reoperation is usually required to reestablish a lead system that provides adequate defibrillation efficacy. The incidence of overall lead dislodgement (complications and observations) in the PCD Epicardial System was 0.9% while the overall incidence (complications and observations) in the PCD Transvene System was 5.5%. This difference was not unexpected since in the PCD Epicardial System the patch leads are usually physically sutured either to the epicardium or pericardium resulting in a marked decrease potential for dislodgement.

In the case of the PCD Transvene System, there were typically two and perhaps three transvenous leads implanted. Though the leads are secured by suturing the anchoring sleeve at the venous entry site they are more susceptible to dislodgement due to patient activity, particularly movement of the upper extremities. Though the incidence was higher in the PCD Transvene System, the clinical outcome was identical in the two patient groups - there have been no reported patient deaths secondary to a lead dislodgement in either patient group.

This analysis indicates that the PCD Transvene System offers not only potential clinical advantages in removing the need for a thoracotomy for implantation and the associated morbidity but has not increased morbidity as compared to patients receiving a PCD Epicardial System.

G. Survival Analysis Comparison

Despite their excellent clinical performance, epicardial defibrillation lead system have important limitations. The requirement for direct thoracic access contributes significantly to patient morbidity and mortality, patient discomfort and prolonged hospitalization. The availability of reliable nonthoracotomy lead systems should provide positive clinical impact on these issues while not negatively impacting patient survival. Therefore, a comparison of the one year actuarial survival rates for the PCD Transvene and Epicardial System was performed.

Table XI G-1 provides a summary of the patient deaths reported in the two patient populations by classification. As a reference, the mean follow-up time for the PCD Transvene System patient population was 5.6 months while for the PCD Epicardial System it was 9.7 months.

PCD Transvene System Death Classifications PCD Transvene System versus PCD Epicardial System		
Death Classification	**PCD Transvene System (N=757)**	**PCD Epicardial System (N=742)**
Sudden Cardiac	3	20
Non-Sudden Cardiac	15	41
All Cardiac	18	61
Noncardiac	4	27
TOTAL	22	88

Table XI G-1: Death Classifications: PCD Transvene System versus PCD Epicardial System - 6/24/92

Table XI G-2 provides a comparison of actuarial survival rates between the PCD Transvene and PCD Epicardial patient populations. The actuarial survival projections include perioperative deaths only in the calculation of survival from death due to all causes (shown in table row labelled **Overall**). Perioperative mortality includes those deaths which occur in the first thirty days post implant of the PCD System.

PCD Transvene System Comparison of Actuarial Survival PCD Transvene System versus PCD Epicardial System			(b)(4)
One Year Survival	PCD Transvene System	PCD Epicardial System	
Number of Patients	757	742	
Sudden Cardiac	99.8%	98.7%	
Non-Sudden Cardiac	96.8%	95.7%	(b)(4)
All Cardiac	96.6%	94.4%	
Noncardiac*	99.4%	97.3%	
Overall*	95.3%	87.2%	

* Statistically Significant

Table XI G-2: Comparison of Actuarial Survival: PCD Transvene System versus PCD Epicardial System - 6/24/92

There was a significant increase in overall survival in the patients receiving a PCD Transvene System. As previously noted, the Overall one year actuarial survival includes death from all causes. The overall one year survival for patients receiving the PCD Transvene System was 95.3%. This is significantly improved as compared to the overall one year actuarial survival for the PCD Epicardial System (87.2%) (b)(4) This improvement in overall survival is primarily due to the marked improvement in perioperative mortality, the PCD Transvene System having a 0.7% perioperative mortality versus the a perioperative mortality of 4.7% in the PCD Epicardial System. This improvement in perioperative mortality is primarily due to the elimination of the need for a thoracotomy and its associated morbidity and mortality.

H. Summary

A comparison of PCD Transvene System clinical experience and PCD Epicardial System clinical experience indicates that the devices are being used in patients with similar cardiovascular disease history.

The mean DFT value at implant of the PCD Transvene System falls well below the maximum output (34J) of the PCD device and are comparable to those obtained with the PCD Epicardial System.

The differences in PCD device programmed status in the two groups is a reflection of the patients receiving the PCD Transvene System and the defibrillation requirements of a nonthoracotomy lead system.

However, despite differences in the programmed status, the PCD device performed safely and effectively in both patient groups.

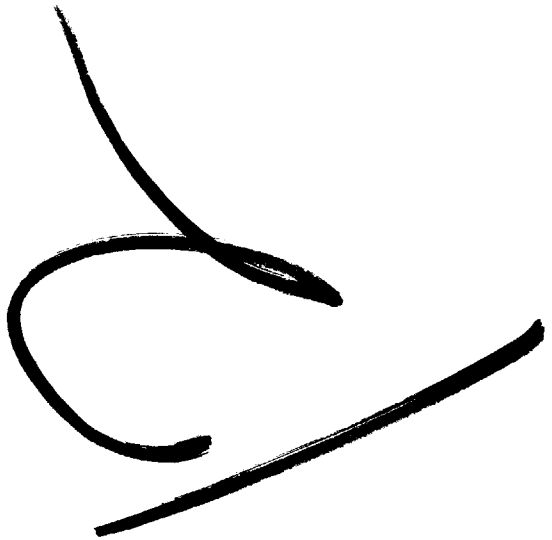
The reported incidence of complications is comparable between the two systems. The reported incidence of observations was statistically lower in the PCD Transvene System.

Finally, the reported Sudden Cardiac Death survival rates in the two patient groups is very similar (PCD Transvene = 99.8%; PCD Epicardial = 98.7%). However, there is statistical improvement in the overall survival in the PCD Transvene System patient population. This is directly related to the decreased perioperative morbidity and mortality associated with the PCD Transvene System.

I. Conclusion

The PCD Transvene System eliminates the need for a thoracotomy for the implantation of defibrillation lead systems. This directly improves the overall patient survival by decreasing the perioperative patient morbidity and mortality when compared to the PCD Epicardial System. This is added benefit however is not gained at the expense the PCD Transvene System efficacy in treating spontaneous VT/VF episodes when compared to the PCD Epicardial System.

observations



XII. Complications and Observations

A. Overview

The introduction of a multiprogrammable implantable cardioverter defibrillator (ICD) devices should assist the physician in resolving the majority of relevant clinical events via modifications in programmed parameters and/or drug therapy rather than via invasive procedures. However, there will continue to be certain relevant clinical events which will require invasive procedures for resolution. The incorporation of these programmable features should not result in an increase in reported clinical complications and/or observations.

The current market released implantable cardioverter defibrillator system requires a surgical thoracotomy for implantation because of the need to insert one or more epicardial patch leads. This exposes the patient to increased surgical risk and potentially limits the type of patient who may be considered for implant of the system. The requirement of surgical thoracotomy contributes significantly to perioperative complications, patient discomfort, and prolonged hospitalization. Clinically significant complications associated with epicardial implants include atrial fibrillation with additional risk of spurious shocks, transient worsening of ventricular arrhythmias, potential erosion of native coronary arteries or bypass grafts by the epicardial patches and requirement for repeated thoracotomy in seriously ill patients if an infection develops. The need for a less invasive, simpler and safer implantation technique is widely recognized. The introduction of a nonthoracotomy lead system should decrease the incidence of complications and observations associated with epicardial system implants.

An analysis of the reported complications and observations was performed and the incidence of these events was compared to that reported with the PCD Epicardial System and that reported in the literature with the market released AICD Epicardial System.

As of June 24, 1992 in the PCD Transvene System patient population, there have been a total of 138 complications identified in 138 patients and 157 observations identified in 157 patients. Thus 18.2% (138/757) of the patients have experienced a clinical event which was defined as a complication and 20.7% (157/757) of the patients have experienced a clinical event which was defined as an observation.

A review of the clinical data that follows indicates that the inclusion of programmable VT/VF detection and therapy parameters into the PCD device has not increased the incidence of reported complications and/or observations. In addition, the PCD Transvene System has performed safely in this patient population with no complications or patient deaths reported due to device malfunction and has not increased the potential risk to the patient.

This section includes the following subsections:

• **Definitions**	Discussion of definitions used to classify each of the complications and observations.
• **Physician Review**	Discussion of purpose of physician review board created to review all reported complications and observations.
• **Event Analysis**	Analysis of reported complications and observations, incidence and resolution.
• **PCD Epicardial System Comparison**	Discussion of PCD Transvene System experience in comparison to the PCD Epicardial System experience
• **AICD Comparison**	Discussion of PCD Transvene System experience in comparison to the published AICD System experience.
• **Event Summary**	For each patient, a detailed summary of the circumstances of the complication and/or observation is provided in Appendix C.

The section concludes with a summary and conclusions which can be drawn from the patient complication/observation clinical experience.

B. Definitions

The complications and observations are divided into various categories as they appear on the Follow-Up Data Form in the Relevant Medical Events section. The events are divided into complications or observations based on the following definitions.

COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device

These definitions were used to categorize the reported clinical events for use in calculation of the reported incidence of complications and observations.

C. Physician Review of Complications

All deaths and significant complications have been, and will continue to be, reviewed by a committee comprised of PCD Transvene System investigators and other physicians. Two committees have been formed, one to review North American clinical events and the other for European clinical events. The members of the two committees is provided in Section XII, Patient Deaths. The primary objective of this committee was to determine whether the PCD Transvene System was related to these complications and, if so, what changes may be required to prevent such events in the future.

D. Clinical Complications and Observations Data Summary

This section provides a summary of the reported complications and observations that have occurred worldwide in patients who have been implanted with a PCD Transvene System.

As of June 24, 1992 there have been a total of 138 complications identified in 138 patients and 157 observations identified in 157 patients. Thus 18.2% (138/757) of the patients have experienced a clinical event which was defined as a complication and 20.7% (157/757) of the patients have experienced a clinical event which was defined as a observation.

Table XII D-1 summarizes how these clinical events were classified.

PCD Transvene System Reported Complications/Observations U.S. versus International		
	Complications	**Observations**
U.S.	77 pts	68 pts
International	61 pts	89 pts
Total	138 pts	157 pts

Table XIID-1: PCD Transvene System Complications/Observations U.S. versus International - 6/24/92

E. Clinical Event Analysis

Reported Incidence of Complications and Observations

As of June 24, 1992 there have been a total of 138 complications identified in 138 patients and 157 observations identified in 157 patients. Thus 18.2% (138/757) of the patients have experienced a clinical event which was defined as a complication and 20.8% (157/757) of the patients have experienced a clinical event which was defined as a observation. Table XII E-1 summarizes how these clinical events were classified.

The percentage is the ratio of the number of Complications or Observations in a given category to the total number of patients (n = 757) in the study population **(NOTED AS Tot%)**.

The reported complications and observations are recognized clinical events that may occur with **any** of the current ICD devices. These complications and observations are discussed in the PCD device and nonthoracotomy leads technical manual.

The reported significant complications have been reviewed by a committee (Clinical Event Review Committee) comprised of PCD investigators and other physicians. The primary objective of this committee was to determine whether the PCD Transvene System was related to these complications and, if so, what changes may be required to prevent such events in the future.

The data in the following sections indicates that the PCD Transvene System has performed safely and effectively in the indicated patient population.

PCD Transvene System Reported Complications/Observations By Category				
Category	Complications		Observations	
	Number	Tot%	Number	Tot%
Increased Defibrillation Requirements	(b)(4)			
Inappropriate VF Therapy Delivery				
Inappropriate VT Therapy Delivery				
Loss of Capture				
Oversensing				
Undersensing				
Skin Erosion				
Pocket Infection				
Seroma				
Hematoma				
Pneumothorax				
Pacemaker Syndrome				
Right Ventricle Perforation				
Subclavian Vein Thrombosis				
Lead Fracture				
Subcutaneous Patch Crinkling				
Total Lead Dislodgement*				
RV Lead Dislodgement*				
CS Lead Dislodgement*				
SVC Lead Dislodgement*				
Early Device Explant				

* Percentage reflects incidence of dislodgement in patients with lead type implanted that occurred at > 30 days

Table XII E-1: PCD Transvene System: Reported Complications/Observations - 6/24/92

Reported Complications and Observations by Follow-Up Interval

An analysis was done on the patient group to determine the distribution of reported complications and observations over time. As a reference, the mean follow-up for the entire patient group is 5.6 months and ranges from implant to 28.6 months. Table XII E-2 provides an analysis of reported clinical events. For purposes of this table the reported complications and observations have been combined.

PCD Transvene System Reported Complications/Observations By Follow-up Interval							
	Follow-Up Interval						
Category	Implant 1 Month	1-3 Month	3-6 Month	6-9 Month	9-12 Month	12+ Month	Total
Increased Defibrillation Requirements	8	1	1	-	-	-	10
Inappropriate VF Therapy	8	2	1	2	-	-	13
Inappropriate VT Therapy	12	15	8	6	5	3	49
Loss of Capture	10	2	-	-	-	1	13
Oversensing	13	6	2	2	1	-	24
Undersensing	-	-	-	-	-	-	-
Skin Erosion	-	2	1	-	-	-	3
Pocket Infection	4	13	4	2	-	-	23
Seroma	12	2	1	1	-	-	16
Hematoma	16	5	-	-	-	-	21
Pneumothorax	3	-	-	-	-	-	3
Pacemaker Syndrome	-	-	1	1	-	-	2
Right Ventricle Perforation	5	-	-	-	-	-	5
Subclavian Vein Thrombosis	-	2	2	-	-	-	4
Lead Fracture	-	-	2	1	-	1	4
Subcutaneous Patch Crinkling	3	4	3	2	-	-	12
RV Lead Dislodgement	15	7	-	-	-	-	22
CS Lead Dislodgement	17	4	2	-	-	-	23
SVC Lead Dislodgement	15	21	6	2	-	-	44
Early Device Explant	1	3	-	-	-	-	4
Clinical Event Total by Follow-up Interval	142	89	34	19	6	5	295
% Patients Completed Follow-Up	18.9%	14.1%	6.9%	6.0%	3.3%	4.4%	

Table XII E-2: PCD Transvene System Reported Complications and Observations by Follow-Up Interval - 6/24/92

Of the reported complications and observations, 48.1% occurred in the first thirty days post implant of the PCD Transvene System. Of the 631 patients who have completed a one month follow-up, 14.1% have experienced either a complication or observation. The majority of these clinical events were associated with the actual implantation of the system itself such as pocket infection and lead dislodgement.

Complications and observations reported at equal to or greater than six months accounted for 10.2% of the reported relevant medical events. Of the 329 patients who have completed a six month follow-up, 6.0% have experienced either a complication or an observation. The majority of these were observations that were resolved either with reprogramming of the PCD device, modification of drug therapy or required no action by the physician for resolution of the clinical event. It should be noted that the "12+ Month" columns reflects all complications and observations reported in patients with implant durations equal to **and** greater that 12 months.

Thus based on this clinical data, the reported incidence of complication and observations with the PCD Transvene System decreases over the implant duration of the system.

Complication and Observation Summary

A brief discussion of each of the complication/observation categories is provided in the following discussion. The technical manuals include discussion of these reported complications and observations. These discussions can be found in the **Programming Considerations and Warnings and Precautions** sections of the PCD Device technical manual as well as the PCD Transvene System manuals. The technical manuals are provided with this submission.

Increased Defibrillation Requirements

There were ten reported cases of failure to defibrillate, six of which were classified as complications and four which were classified as observations.

In the six cases classified as a complication, the patients received a three lead PCD Transvene System and met the required implant criteria of 3/4 successes at 18J. At the prior to discharge electrophysiology study, VF could not be reliably defibrillated at 18J or 34J. In four patients, the PCD Transvene System was explanted and replaced with a three lead epicardial defibrillation system. In the fifth case a hybrid system was implanted which consisted of a Model 6884 right ventricular lead, for pace/sense functions, and two 6897L epicardial patch leads. And in the final patient, a new PCD Transvene System was identified which provided appropriate defibrillation efficacy. In all three cases effective defibrillation was documented.

In the four cases classified as observations, the ineffective defibrillation was observed during an electrophysiology study. In three cases the patient's antiarrhythmic drug regimen was modified (addition of Sotalol) to improve defibrillation efficacy. In the final case, all four VF Therapies were programmed to 34 Joules. There have been no reports of ineffective defibrillation for spontaneous VF in these patients.

Inappropriate VF Therapy Delivery

This medical event was reported in thirteen patients, all of which were classified as observations. In nine cases, inappropriate VF therapy was delivered for atrial fibrillation that had a rapid ventricular response that met the programmed VF detection

criteria. In two cases, inappropriate VF therapy was delivered secondary to sinus tachycardia that was detected as ventricular fibrillation. Modification of the programmed VF detection criteria or the patient's antiarrhythmic drug therapy corrected these two clinical observations.

One patient received inappropriate VF therapy secondary to the sensing of T waves during sinus rhythm with the PCD device programmed to a sensitivity of 0.3 mV. This was resolved with reprogramming of the sensitivity to 1.2 mV. Appropriate VF sensing was documented at this programmed setting.

The final patient received inappropriate VF therapy secondary to nonsustained ventricular tachycardia. In the PCD Device, once "VF" is detected the device is committed to the delivery of defibrillation therapy. This observation was resolved by reprogramming of the FDI and VF NID.

Inappropriate VT Therapy Delivery

This medical event was reported in forty nine patients and was classified as an observation in all cases. Inappropriate VT therapy was delivered for atrial fibrillation with a rapid ventricular response in 28 patients and due to sinus tachycardia in 21 patients. This observation was resolved by reprogramming of the VT detection parameters in 21 patients, with modification of drug therapy in 26 patients and no action was required in one patient. One patient with atrial fibrillation underwent successful AV Node ablation. Post this procedure, appropriate PCD Device function was documented.

In two patients in whom inappropriate VT therapy was delivered for sinus tachycardia, the ONSET algorithm was enabled to improve discrimination between VT and sinus tachycardia. The use of this algorithm resulted in no further delivery of inappropriate therapy for sinus tachycardia.

In three patients in whom inappropriate VT therapy was delivered for atrial fibrillation, the STABILITY algorithm was enabled to improve discrimination between VT and atrial fibrillation. The use of this algorithm resulted in no further delivery of inappropriate therapy for atrial fibrillation.

Loss of Capture

Loss of capture was reported in thirteen patients. Six cases were classified as a complications and required invasive procedures to resolve the loss of capture. In four cases, repositioning of the RV lead was required and in one case, the investigator elected to implant a new RV lead. In the sixth patient, the loss of capture was secondary to a loose connection at the Model 6884 lead connection to the PCD device header. The pocket was reopened, the set screw was tightened and the problem was resolved.

Seven cases were classified as an observation and in four of the cases could be resolved by programming the PCD device to full output (5.4V/1.59 ms). In the remaining three cases, modification of drug therapy was required to resolve the loss of capture.

Oversensing

This medical event was reported in twenty four patients. Oversensing of post VVI pacing was the cause in 13 patients and sensing of T waves in sinus rhythm was the cause in 11 patients. In all cases, the medical event was classified as an observation.

This sensing of T waves did not result in detection of either VT or VF and was resolved with reprogramming of the refractory period (10 patients), sensitivity (5 patients) or no action was taken (9 patients).

Undersensing

There have been no reports of undersensing in the PCD Transvene System.

Skin Erosion

There have been three cases reported, two which were classified as a complication and the remaining case classified as an observation. In the two cases classified as a complication, a skin erosion was noted at the pocket incision site, the pocket was reopened and the area debrided with resolution of the skin erosion. Antibiotic therapy resolved the case classified as an observation.

Pocket Infection

This medical event was reported in twenty three patients. In 15 of the cases, all of which were classified as complications, the pocket infection resulted in explant of the entire implanted PCD Transvene System. Four of the patients has subsequently had a new PCD Transvene System implanted while the remaining patients still have not had a new system implanted.

In 8 cases classified as an observation, the infection was successfully treated with antibiotic therapy.

An analysis of the implant procedures for these patients was performed. In those patients who developed a pocket infection a mean of 9.5 inductions were performed at implant and a mean of 3.0 lead configurations were evaluated at implant. This compares to those patients who did not develop a pocket infection who had a mean of 7.3 inductions performed at implant and a mean of 2.2 lead configurations evaluated at implant. This data indicates that the patients who developed pocket infection had longer implant procedures that may have placed at increased for the development of a pocket infection.

An analysis was performed to determine if other clinical circumstances in addition to a potentially prolonged implant procedure contributed to the development of pocket infection in these patients.

Three patients had a history of diabetes mellitus, one patient was undergoing renal dialysis and one patient had a history of Crohn's disease being treated with steroid therapy. These concomitant diseases processes could contribute to an increase risk for development of infection.

Two patients had a history of prior pocket infection with a previously implanted ICD System and one patient required multiple lead evaluations prior to the implant of the PCD Transvene System. These clinical histories could contribute to an increase risk for development of infection.

Eight patients developed pocket infections after reoperations required for repositioning of the dislodged lead. In seven cases, eventual explant of the entire PCD Transvene System was required and the final patient was successfully treated with

antibiotic therapy and the pocket infection resolved.

It should be noted that the incidence of patients who developed pocket infection and required explant of the PCD Transvene System was 2.0%. In the PCD Epicardial System, the incidence of patients who required explant of the system due to infection was 1.9%. Thus there is no difference between the two patient groups.

Seroma

This medical event was reported in sixteen patients, 11 of which were classified as observations and 5 classified as a complication.

A seroma developed at the pocket site in ten patients, four were classified as complications and six were classified as an observation. A seroma developed at the SQ patch site in five patients, one which was classified as a complication and four which were classified as an observation. Finally, one patient developed a seroma at both the SQ patch and pocket site. This was classified as an observation.

In the cases classified as a complication, aspiration of the fluid which resolved the seroma. In the cases classified as observation, antibiotic therapy was required in two patients and in nine patients the seroma resolved without treatment.

Hematoma

This medical event was reported in twenty-one patients, 17 of which were classified as observations and 4 classified as a complication.

A hematoma developed at the pocket site in 11 patients, one was classified as a complication and 10 were classified as an observation. A hematoma developed at the SQ patch site in six patients, one which was classified as a complication and five which were classified as an observation. In four patients, a hematoma developed at both the SQ patch and pocket site. Two of these cases were classified as complications and two as observations.

In the cases classified as a complication, aspiration of the fluid which resolved the hematoma. In the cases classified as

observation, antibiotic therapy was required in three patients and in 14 patients the hematoma resolved without treatment.

Pneumothorax

This medical event was reported in three patients. In the two patients, in whom this medical event was classified as a complication, a PCD Transvene System was implanted via a left subclavian approach and the patient developed a pneumothorax in the immediate perioperative period. A chest tube was inserted for resolution of the pneumothorax and the patients recovered without further complications.

The patient, in whom this medical event was classified as a observation, also had a PCD Transvene System implanted via a left subclavian approach. This patient also developed a pneumothorax in the immediate perioperative period. In this case, the pneumothorax resolved without intervention.

Pacemaker Syndrome

There were two reports of pacemaker syndrome which were classified as observations. The patients experienced symptoms of pacemaker syndrome with VVI bradycardia support pacing. The VVI standby rate was reprogrammed to a lower rate to allow for the patient's intrinsic heart rate to predominate which resolved the patient's symptoms.

Right Ventricle Perforation

This medical event was reported in five patients and was classified as a complication in all cases. In four cases, the right ventricular perforation was noted at the time of implant of the PCD Transvene System. In the final case, the right ventricular perforation occurring after a repositioning of the RV lead one month post implant.

One patient who experienced a right ventricular perforation ultimately expired in the perioperative period. This patient received a PCD Transvene System that consisted of a coronary sinus lead, right ventricular lead and subcutaneous patch. The right ventricular lead (Model 6884) was positioned easily with two attempts necessary to screw the helix into the myocardium. Only one lead configuration was tested and a total of six inductions

were performed. This patient's medical history was significant for chronic obstructive pulmonary disease that was being treated with steroid therapy.

The lead system was connected to the PCD Device and one final VF induction was performed. This episode was neither sensed or converted by the two 34 Joule shocks delivered manually from the PCD Device. Several external defibrillation and prolonged resuscitative measures were required to restore sinus rhythm. After this episode it was determined that the pacing thresholds had increased to greater than 10 Volts and there was no identifiable ventricular electrogram from the RV lead. The investigator felt at this time that this suggested either RV lead dislodgement or perforation, lead malfunction or device malfunction. However, due to the patient's poor pulmonary status the procedure was terminated without performing any further evaluations. The PCD Device VT/VF detection and therapies were deactivated for the immediate post-operative period. The investigator noted that the plan was to reevaluate the lead system post-operatively once the patient's status had stabilized.

The patient's recovery was uneventful over the next 48 hours with no significant chest pains or cardiac rubs on physical exam. ECG documentation indicated asynchronous pacing with non capture. The patient developed severe chest pain, dyspnea and profound hypotension. Despite intubation and administration of fluids and pressors he developed electromechanical dissociation followed by episodes of asystole and ventricular tachycardia/fibrillation. The diagnosis of cardiac tamponade was made but due to the patient's pulmonary disease pericardiectomy and repair of the myocardial perforation was not performed. The patient expired after prolonged resuscitative measures.

An autopsy identified a perforation of the right ventricle by the RV lead, accompanied by hemopericardium and presumed cardiac tamponade. No other potential causes of death could be identified.

The investigator classified this patient death as cardiac, non-sudden and related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and felt that the death was related to the specific implant procedure and not the PCD Transvene System.

In three of the remaining cases, the right ventricular perforation was diagnosised at the time of implant. Two of the patients ultimately required a thoracotomy for repair of the perforation and received PCD Epicardial Systems. In the third patient, the physician repositioned the RV lead with resolution of symptoms and the patient received a PCD Transvene System.

In all three of the cases, multiple repositioning of the RV lead was required (>5) in order obtain acceptable pacing thresholds due to poor lead/tissue interface.

In the final case, the right ventricular perforation occurred after a repositioning of the RV lead one month post implant. This patient was screened for a PCD Transvene System however did not meet the implant criteria and received a PCD Epicardial System. The RV lead was left in place for pace/sense function. Two weeks post implant, RV lead dislodgement was detected and reoperation was required for repositioning. Approximately one month post implant of the PCD Epicardial System, the patient presented with symptoms of shortness of breath and chest pain. Reoperation was required to repair the perforation and the pace/sense lead system was modified to an epicardial system.

Subclavian Vein Thrombosis

There have been four reports of subclavian vein thrombosis in the PCD Transvene System patient population.

In three cases this medical event was classified as an observation. Two patients were treated with thrombolytic therapy with resolution of the symptoms while the remaining patient required no therapy.

In one patient, initial thrombolytic therapy did not resolve the subclavian thrombosis and the physician elected to explant the PCD Transvene System. However, post explant of the system the subclavian vein thrombosis did not resolve. The patient ultimately received a PCD Epicardial System.

Lead Fractures

There have been four reports of right ventricular lead fractures, all of which were classified as complications. There were no reports of ineffective therapy for a spontaneous VT/VF episode due to the

right ventricular lead fracture. In this report, there have been a total of 757 right ventricular leads implanted. Thus the incidence of lead fracture in the right ventricular leads implanted is 0.5%.

In three patients, the right ventricular lead fracture was documented based on an increase in pacing thresholds. In the fourth patient, the diagnosis was based on the delivery of inappropriate VF therapy delivery. In all cases, the fracture was confirmed via chest x-ray. All of the systems were implanted via a subclavian approach and, for resolution, required reoperation, removal of the lead and implantation of new right ventricular lead. Analysis of the leads indicates that the conductor coil fracture was due to crushing of the lead body between the first rib and clavicle. These patients have experienced no further complications.

The Model 6966 technical manual recommends that the lead be inserted by venotomy through routes including the right or left cephalic vein or the external or internal jugular vein. The following "Caution" is provided if insertion is done via a subclavian approach:

If insertion is done via a subclavian approach, the lead should be positioned far laterally to avoid clamping the lead body between the clavicle and first rib. Clamping the lead may eventually cause the conductor to fracture, may cause damage to the insulation, or may cause other damage to the lead. This may result in complications such as loss of detection, loss of pacing therapies, or loss of cardioversion/defibrillation therapy. Certain anatomical abnormalities, such as thoracic outlet syndrome, may also precipitate pinching and subsequent fracture of the lead. If significant resistance is encountered during a subclavian stick implant procedure, do not force the lead by adjusting the patient's posture (i.e., raising the arm or putting a towel behind the person's back) to facilitate the passage of the lead. In such cases it is recommended that an alternate venous entry site be used.

The PCD Transvene System technical manuals discuss potential complications of use of the lead system one of which is potential conductor coil fracture. The possible effects of conductor fracture discussed in the technical manual include intermittent or continuous loss of defibrillation, cardioversion therapy, sensing or tachycardia therapy. It is recommended that if such a loss occurs, sensing thresholds and x-rays should be checked for lead dislodgement or conductor fracture.

Subcutaneous Patch (Model 6895/6999) Crinkling

This medical event was reported in twelve patients and was classified as a complication in 7 patients and as a observation in the remaining 5 patients. In the cases classified as a complication, the subcutaneous patch crinkling occurred in the perioperative period and required modification of the lead system.

In all of these cases, the physician felt that the defibrillation efficacy of the system had been compromised by the crinkling of the subcutaneous patch.

In 5 patients subcutaneous patch crinkling was demonstrated by routine chest x-ray post implant of the PCD Transvene System. Ventricular fibrillation was reinduced and successfully reverted. The investigators elected to make no modifications to the lead system.

Lead Dislodgement

There have been a total of 89 lead dislodgements reported in 87 patients. The **overall incidence** of lead dislodgement in this patient population is 11.7% (89 dislodgements/762 implants with a mean implant duration of 5.6 months). In 10.2% of the reported cases, (77/757), the dislodgement was classified as a **complication** and required reoperation. In 1.6% of the reported cases, (12/757), the dislodgement was classified as an **observation** and the reoperation was not required.

In none of the cases did the lead dislodgement result in ineffective therapy for a spontaneous VT or VF episode or patient death. It is important to note, that the majority (52.8%) of the lead dislodgements occurred in the first thirty days post implant of the PCD Transvene System. Table XII E-3 summarizes the overall incidence of lead dislodgement and those that occurred at implant duration greater than 30 days.

PCD Transvene System Dislodgement Experience		
All Lead Dislodgements		
	Complications	**Observations**
Overall Incidence	10.2% (77/757)	1.6% (12/757)
> 30 Days Incidence	4.4% (33/757)	1.2% (9/757)
Model 6884/6966 Right Ventricular Lead		
	Complications	**Observations**
Overall Incidence	2.8% (21/741)	0.1% (1/741)
> 30 Days	0.8% (6/741)	0.1% (1/741)
Model 6881/6963 Superior Vena Cava Lead		
	Complications	**Observations**
Overall Incidence	6.9% (37/535)	1.3% (7/535)
> 30 Days	4.1% (22/535)	1.1% (6/535)
Model 6881/6963 Coronary Sinus Lead		
	Complications	**Observations**
Overall Incidence	7.3% (19/261)	1.3% (7/261)
> 30 Days	1.9% (5/261)	0.8% (2/261)

Table XII E-3: PCD Transvene System Dislodgement Frequency Overview - 6/24/92

Lead dislodgements were documented by electrophysiologic evaluation (10 cases), chest x-ray obtained during routine follow-up (65 cases), pace/sense threshold evaluation during routine follow-up (13 cases) or due to inappropriate therapy delivery (2 cases). In 77 cases reoperation was required to reposition the lead and evaluate defibrillation system. In the remaining 12 cases, VF inductions were performed to evaluate the efficacy of the implanted lead system and based on the results the physician elected to make no surgical modifications to the system.

Lead dislodgements are not specific to the PCD Transvene System and have been reported with dual chamber pacemakers and the current market released implantable cardioverter defibrillator (ICD) system. The early history of dual chamber pacemakers

demonstrated a high lead dislodgement rate of at least 20%. (Smyth PND, et al. Permanent pervenous atrial sensing and pacing with a new J-shaped lead. J Thoracic Cardiovascular Surgery 1976;72:565-570.) Winkle, et al reported that the incidence of dislodgement of the superior vena cava spring leads used with the current market release ICD System to be 6.3% (Winkle, et al. Automatic Implantable Cardioverter-Defibrillator: Efficacy, Complications and Survival in Patients with Malignant Ventricular Arrhythmias. JACC Vol.11. No.6 June 1988: 1278-86).

The potential clinical impact of lead dislodgement was evaluated in the 87 patients who experienced a lead dislodgement. The evaluation included patient death, infection rate and spontaneous VT/VF episode efficacy. There were no patient deaths due to ineffective termination of spontaneous VT/VF episodes secondary to lead dislodgement reported. Eight patients (10.4%) did develop pocket infections after the reoperation required for repositioning of the dislodged lead.

In seven cases, eventual explant of the entire PCD Transvene System was required and the final patient was successfully treated with antibiotic therapy and the pocket infection resolved.

Spontaneous episode efficacy was also evaluated to determine whether prior to diagnosis of the lead dislodgement the patients were at risk of prolonged episodes of VT/VF. In 47 patients (53%) the lead dislodgement was identified prior to the patient's discharge from the hospital. Therefore more than half of the dislodgements were identified prior to the patient being in an outpatient setting where the risks of a lead dislodgement are greater. None experienced an episode of spontaneous VT/VF prior to the identification of the lead dislodgement.

In the remaining 40 patients, 21 patients experienced spontaneous VT episodes and 24 experienced spontaneous VF episodes prior to diagnosis of the lead dislodgement. The spontaneous VT episode efficacy was 97.9% and the spontaneous VF episode efficacy was 99.3% None of these episodes required Therapy #4 for successful termination. None of patients experienced prolonged episodes of VT/VF where the PCD Transvene System was ineffective in terminating the episode due to the lead dislodgement.

Table XII E-4 provides information on lead dislodgements with the PCD Transvene System and the number which were identified prior to hospital discharge and the number which were identified post hospital discharge.

PCD Transvene System Reported Lead Dislodgement			
Lead Model	**Frequency**	**Prior to Discharge**	**Post Discharge**
RV (6884/6966)	21	14	7
RV (SP2100)	1	1	-
CS (6881/6963)	23	17	6
SVC (6881/6963)	44	15	29
TOTAL	89	47	42

Table XII E-4: PCD Transvene System Lead Dislodgement Frequency - 6/24/92

The frequency of dislodgement of each lead model was determined based on the total number of leads of that type implanted. Table XII E-5 provides the frequency by lead model and position.

PCD Transvene System Frequency of Dislodgement By Lead Model			
Model Number	**# Dislodgements**	**# Implants**	**Overall Frequency**
RV - SP2100	1	16	6.3%
RV - 6884/6966	21	741	2.8%
CS - 6881/6963	23	261	8.8%
SVC - 6881/6963	44	535	8.2%

Table XII E-5: PCD Transvene System Frequency of Dislodgement By Lead Model - 6/24/92

The incidence of lead dislodgement by follow-up interval is provided in Table XII E-6. This data indicates that 52.8% of the lead dislodgements occurred in the first thirty days post implant of the PCD Transvene System while the remaining dislodgements (47.2%) occurred more than 30 days post implant of the PCD Transvene System.

PCD Transvene System Lead Dislodgement By Follow-Up Interval							
Model	≤ 1 Week	1-4 Weeks	1-3 M	3-6 M	6-9 M	9-12 M	12+ M
6884/6966-RV	5	9	7	-	-	-	-
SP2100-RV	-	1	-	-	-	-	-
6881/6963-CS	12	5	4	2	-	-	-
6881/6963-SVC	3	12	21	6	2	-	-
TOTAL	20	27	32	8	2	-	-

Table XII E-6: PCD Transvene System Lead Dislodgement by Follow-Up Interval - 6/24/92

The analysis in Table XII E-6 only reflects the incidence of dislodgement by follow-up interval and does not reflect the number of each lead model that had completed a particular follow-up interval. Table XII E-7 provides this particular analysis.

PCD Transvene System Dislodgement Experience By Completed Follow-Up	
Model 6884/6966 Right Ventricular Lead	
# Patients Completed Three Month Follow-Up	514
Dislodgement Rate in First 3 Months Post Implant	4.1% (21/514)
Model 6881/6963 Coronary Sinus Lead	
# Patients Completed Three Month Follow-Up	196
Dislodgement Rate in First 3 Months Post Implant	10.7% (21/196)
Model 6881/6963 Superior Vena Cava Lead	
# Patients Completed Three Month Follow-Up	349
Dislodgement Rate in First 3 Months Post Implant	10.3% (36/349)

Table XII E-7: PCD Transvene System Dislodgement Experience by Completed Follow-Up - 6/24/92

The dislodgement rate of the Model 6884/6966 right ventricular leads on a per-patient basis was expected to be no greater than 10% in the first three months post-implant. This is based on clinical experience with the Medtronic Model 4016 bradycardia pacing lead which is similar in design to the Model 6884/6966 right ventricular lead. The incidence of dislodgement of the Model 6884/6966 in the first three months post implant was 4.1%.

The dislodgement rate of the Model 6881/6963 lead in the coronary sinus position on a per-patient basis was not expected to be significantly greater than that reported for bradycardia coronary sinus leads - approximately 13%. The incidence of dislodgement of the Model 6881 lead in the coronary sinus lead position in the first three months post implant was 10.7%.

In the case of the Model 6881/6963 lead in the superior vena cava position, was compared to the AICD System experience with spring/patch defibrillation lead systems. As noted earlier. Winkle et al, reported a superior vena cava lead dislodgement rate of 6.3%. The incidence of dislodgement of the Model 6881/6963 lead in the superior vena cava position in the first three months post implant was 10.3%.

The PCD Transvene System technical manuals discuss potential complications of use of the lead system one of which is potential dislodgement of the leads. The possible effects of lead dislodgement discussed in the technical manual include intermittent or continuous loss of defibrillation, cardioversion therapy, sensing or tachycardia therapy. It is recommended that if such a loss occurs, sensing thresholds and x-rays should be checked for lead dislodgement.

In addition, the technical manual provides recommendations on positioning the PCD Transvene Lead System, securing the Model 6884/6966 electrode into the endocardium and use of the anchoring sleeve(s) provided with the lead system.

Early Device Explant

There were four patients in whom the PCD Device was explanted due to reasons other than death, infection or heart transplant. In all cases these medical events were classified as complications.

In the first patient the PCD Device was explanted for lower than expected battery voltage measurement for time in service. Analysis indicated the decreased battery voltage measurement was due to leakage at the input to one of the integrated circuits. This lead to a voltage drop across a resistor where the voltage measurement was taken. Analysis indicated the battery to be performing to specifications and the leakage to be a random event.

The second patient received inappropriate VF therapy during reformation of the device capacitors. Analysis of the explanted unit indicated that arcing occurred between the conductors in the high power hybrid. As a result, high voltage was momentarily applied to the low power circuitry, including the low power hybrid. This low power hybrid lost function including the capability to pace and transmit telemetry due to the excessive voltage applied.

Since this is the only device that exhibited this type of failure in the field and the hybrid manufacturing process has demonstrated that it will screen out infant mortality, this was determined to be a random component failure.

In the third patient, during the pre-hospital discharge electrophysiology study, VT was induced and cardioversion therapy failed to appropriately synchronize and deliver therapy for this induced episode. The PCD Device was explanted and the patient received a second device without difficulties. Analysis of the explanted PCD Device indicated a random device failure in the microprocessor and low power hybrid. The manufacturing process was modified to incorporate a screening process to identify any further devices which may exhibit this behavior.

In the final patient, the PCD Device exhibited a Power On Reset (POR) condition that could not be related to use of electrocautery or external defibrillation. The device was explanted and returned to Medtronic for analysis. Final results on the analysis are not available at the time of this submission but will be submitted to the FDA when they are available.

In all three cases, the patients received a second PCD Device without difficulties.

Resolution of Complications and Observations

The incorporation of programmable VT/VF detection and therapy algorithms allows the physician the flexibility to resolve clinical events via reprogramming and/or modification of drug therapy rather than invasive procedures. Certain complications, such as pocket infections, lead dislodgement or fractures, because of their potential negative impact on the patient's outcome will require invasive procedures for resolution. Table XII E-8 provides data on how the reported complications and observations were resolved. "**Reprogram**" indicates that only reprogramming was required, "**Drugs**" indicates that only modification of drug therapy was required and "**Reprogram/Drugs**" indicates that both a modification of programmed parameters and drug therapy was required to resolve the clinical event. "**Invasive**" indicates that a surgical procedure was required to resolved the clinical event and "**No Action**" indicates that the physician elected to not to treat the clinical event.

PCD Transvene System Resolution of Complications/Observations By Category	
Category	(b)(4)
Increased Defibrillation Requirements	
Inappropriate VF Therapy	
Inappropriate VT Therapy	
Loss of Capture	
Oversensing	
Undersensing	
Skin Erosion	
Pocket Infection	
Seroma	
Hematoma	
Pneumothorax	
Pacemaker Syndrome	
Right Ventricle Perforation	
Subclavian Vein Thrombosis	
Lead Fracture	
Subcutaneous Patch Crinkling	
RV Lead Dislodgement	
CS Lead Dislodgement	
SVC Lead Dislodgement	
Early Device Explant	
TOTAL	

(b)(4)

Table XII E-8: PCD Transvene System Resolution of Complications and Observations by Category - 6/24/92

Clinical Event Analysis Summary

The reported complications and observations in the PCD Transvene System clinical study are recognized clinical events that may occur with **any** of the current ICD devices. The incorporation of programmability in the PCD device has allowed the resolution of 33.1% of the reported observations without the need for invasive procedures. It is interesting to note that in 33.8% of the recognized clinical events, the physician elected to take no action to treat the clinical event.

Appropriate labelling has been incorporated in the PCD device technical manual to address the reported complications and observations.

F. Comparison with PCD Epicardial System Clinical Experience

A comparison of the reported complications and observations was made between the PCD Transvene System and the PCD Epicardial System. The PCD Epicardial System patient population used for comparison includes clinical experience as of May 15, 1992 with 742 patients and a mean implant duration of 9.7 months. These two patient groups are similar in the patient demographics and indication for implant of the PCD System. The reported incidence of complications, 18.2% for the PCD Transvene System and 12.8% for the PCD Epicardial System was similar for the two patient groups. In addition, the reported incidence of observations, 20.7% for the PCD Transvene System and 25.7% for the PCD Epicardial System was similar.

Table XII F-1 and F-2 provide a comparison of the reported complications/observations and their incidence in the two patient populations.

PCD Transvene System versus PCD Epicardial System Reported Complications		
Category	**PCD Transvene System (N=757)**	**PCD Epicardial System (N=742)**
Ineffective Therapies	0.8%	0.5%
Inappropriate Therapies	-	1.8%
Pacing or Pace/Sense Related	0.8%	3.5%
Infection Related - Explant	2.0%	1.9%
Infection Related - No Explant	1.5%	0.5%
Lead Related	6.6%	2.8%
Device Related	0.5%	0.9%

Table XII F-1: Reported Complications: PCD Transvene System versus PCD Epicardial System - 6/24/92

PCD Transvene System versus PCD Epicardial System Reported Observations		
Category	**PCD Transvene System (N=757)**	**PCD Epicardial System (N=742)**
Ineffective Therapies	0.5%	1.1%
Inappropriate Therapies	8.2%	10.6%
Pacing or Pace/Sense Related	4.1%	10.2%
Infection Related - Explant	-	-
Infection Related - No Explant	4.9%	2.2%
Lead Related	2.2%	1.2%
Device Related	-	-

Table XII F-2: Reported Observations: PCD Transvene System versus PCD Epicardial System - 6/24/92

The PCD Epicardial System requires a surgical thoracotomy for implantation because of the need to insert two or more epicardial patch leads. This exposes the patient to increased surgical risk and potentially limits the type of patient who may be considered for implant of the system. The requirement of surgical thoracotomy contributes significantly to perioperative complications, patient discomfort, and prolonged hospitalization.

Clinically significant medical events that may be associated with epicardial implants include atrial fibrillation with additional risk of inappropriate therapy, potential erosion of native coronary arteries or bypass grafts by the epicardial patches and requirement for repeated thoracotomy in seriously ill patients if an infection develops. The PCD Transvene System offers a less invasive, simpler and safer implantation technique and should decrease the incidence of complications and observations associated with epicardial system implants.

The overall reported incidence of complications and observations was similar in the two patient groups. Analysis was performed to evaluate if the incidence of specific complications and observations was different between the two patient populations.

The **incidence of inappropriate therapy delivery** in the two patient groups was evaluated. Inappropriate therapy delivery is defined as the delivery of either VT or VF therapy for reasons other than spontaneous VT or VF episode. This includes atrial fibrillation with a rapid ventricular response or sinus tachycardia that overlaps with the programmed detection criteria. In addition, inappropriate therapy may be delivered due to oversensing due to hardware issues such as a loose set screw. Specifically a comparison was made between the incidence of atrial fibrillation resulting in inappropriate therapy between the two patient groups and this data is presented in Table XII F-3.

Atrial fibrillation, with a risk of inappropriate shocks and the potential need for concomitant antiarrhythmic drug therapy, is a recognized medical event in patients receiving an ICD System utilizing an epicardial defibrillation lead system. The occurrence of atrial fibrillation in these patients may be related to the thoracotomy procedure required for implant, manipulation of the atrium during the implant procedure or the positioning of the epicardial patch leads near or on the atrium resulting in irritation and induction of atrial fibrillation. The incidence of inappropriate

therapy for atrial fibrillation in the PCD Epicardial System was 7.8% while that for that the PCD Transvene System was 4.7%. Though this difference was not statistically significant ($p = 0.089$) this difference was clinically important. An decreased incidence of inappropriate therapy results in a decreased potential risk for acceleration on non VT/VF rhythms as well as decreasing patient acceptance of ICD therapy. Though the introduction of a transvenous lead system has not totally removed the risk of inappropriate therapy for atrial fibrillation, from this clinical experience it appears that the there is a trend towards a decreased in the incidence of this observation.

PCD Transvene System versus PCD Epicardial System Incidence of Inappropriate Therapy for Atrial Fibrillation				
	PCD Transvene System		PCD Epicardial System	
	Number	Total %	Number	Total %
Inappropriate VF Therapy	5	1.6%	10	2.3%
Inappropriate VT Therapy	10	3.2%	24	5.5%
Overall Incidence	15	4.7%	34	7.8%

Table XII F-3: PCD Transvene System: Incidence of Inappropriate Therapy for Atrial Fibrillation - 6/24/92

The **incidence of pocket infection** in the two patient groups was also evaluated. In the patient receiving an ICD System with epicardial defibrillation lead systems, if an infection does develop patch explant is usually required resulting in repeated thoracotomy to remove the system. The incidence of pocket infection that required explant of the PCD System was similar in the between the PCD Transvene and Epicardial Systems (2.0% versus 1.9%).

This similarity in the incidence of pocket infection between the two patient groups indicates that even though the PCD Transvene System can require the evaluation of multiple lead orientations to obtain adequate defibrillation efficacy there is not a resultant increase in risk of pocket infection.

The reported incidence of infection in both patient groups is similar to that reported with current market released implantable cardioverter defibrillator system of 2.3% (Nisam et al, ICD Clinical Update: First Decade, Initial 10,000 Patients. PACE, Vol.14, February 1991, Part II, pg 255-262).

The final comparison was made between the incidence of **lead dislodgement** in the two patient groups. In both systems, the clinical impact of a lead dislodgement is the potential for inappropriate therapy delivery, nondetection of VT/VF or ineffective therapy for an episode of VT/VF. Also in both systems, reoperation is usually required to reestablish a lead system that provides adequate defibrillation efficacy. The overall incidence (complications and observations) of lead dislodgement in the PCD Epicardial System was 0.9% while the overall incidence (complications and observations) in the PCD Transvene System was 5.5%.

This difference was not unexpected since in the PCD Epicardial System the patch leads are usually physically sutured either to the epicardium or pericardium resulting in a marked decrease potential for dislodgement. In the case of the PCD Transvene System, there were typically two and perhaps three transvenous leads implanted. Though the leads are secured by suturing the anchoring sleeve at the venous entry site they are more susceptible to dislodgement due to patient activity, particularly movement of the upper extremities. Though the incidence was higher in the PCD Transvene System, the clinical outcome was identical in the two patient groups - there have been no reported patient deaths secondary to a lead dislodgement in either patient group.

This analysis indicates that the PCD Transvene System offers not only potential clinical advantages in removing the need for a thoracotomy for implantation and the associated mortality but has not increased morbidity as compared to patients receiving a PCD Epicardial System.

G. Comparison with AICD Epicardial System Clinical Experience

The Automatic Implantable Cardioverter/Defibrillator produced by Cardiac Pacemakers, Inc. is the only implantable cardioverter defibrillator device to have obtained approval from the U.S. FDA for market release. As such, this system represents the only market released device available for comparison to the PCD Transvene System. There are important differences in the capabilities and operation of these two systems, particularly in the area of antibradycardia and antitachycardia pacing. In addition, the current AICD System is implanted only with defibrillation lead systems requiring a thoracotomy. Nevertheless, a comparison of those aspects that are similar is provided in Table XII G-1.

PCD Transvene System
Comparison of Reported Complications
PCD versus AICD

Category	PCD%	AICD%
Fail to Cardiovert/ Defibrillate	0.8%	4.1%
Inappropriate/Problematic VT/VF Therapy Delivery*	8.2%	20%
Pocket Infection	2.0%	2.2%
Erosion	0.3%	0.7%

* Includes complications and observations

Table XII G-1: Comparison of Complication/Observation Rates: PCD Transvene System versus AICD System - 6/24/92

The AICD complications are based on a recent published article (Winkle, et al. Long-Term Outcome With the Automatic Implantable Cardioverter-Defibrillator; JACC, May, 1989; 13(6); 135-161.)

The incidence of failure to cardiovert and/or defibrillate was similar in the two groups. The instances of failure to cardiovert and/or defibrillate in the PCD Transvene System patient population were all associated with increased defibrillation requirements none of which resulted in patient death.

In three cases the implanted lead system was modified to provide adequate defibrillation efficacy, in two cases the patient's drug therapy was modified and in the final case reprogramming provided for adequate defibrillation efficacy.

The instances of failure to cardiovert or defibrillate in the Winkle, et al article were associated with patch dislodgement, patch crinkling, lead conductor fracture and elevated defibrillation thresholds.

The incidence of inappropriate/problematic VT/VF therapy delivery was lower in the PCD Transvene System patient population. This is to be anticipated since the device incorporates independently programmable detection algorithms for VT and VF. The reasons for inappropriate therapy included sinus tachycardia being detected as VT/VF and atrial fibrillation with rapid ventricular response being detected as VT/VF.

The circumstances reported in the Winkle, et al article were nonsustained VT, recurrent stable VT, sinus tachycardia, atrial fibrillation with rapid ventricular response and pacemaker interaction. The patients with VT complained of receiving multiple shocks with limited or no symptoms. The incorporation of antitachycardia pacing in the PCD Device decreases the need for delivery of cardioversion shocks for the termination of stable VT and increases patient acceptance of ICD therapy.

The incidence of pocket infection in the PCD Transvene System (2.0%) is similar to that reported with the AICD Epicardial System (2.2%).

Thus, the incidence of complications and observations was similar to that of the AICD in the categories of ineffective VT/VF therapy, infection and erosion. Clinically significant is that the incidence of inappropriate therapy delivery is lower in the PCD Transvene System than the AICD System.

This analysis indicates that the PCD Transvene System offers not only potential clinical advantages in removing the need for a thoracotomy for implantation and the associated morbidity but does not place the patient at additional risk as compared to patients receiving a AICD System.

H. Summary

1. The overall complication rate, defined as the ratio of the number of patients having at least one complication to the total number of patients, reported in this study was found to be 18.2%. The rate of observations was found to be 20.7%.

2. As compared to PCD Epicardial System clinical experience, the PCD Transvene System offers not only potential clinical advantages in removing the need for a thoracotomy for implantation and the associated morbidity and has not increased the incidence of comparable complications and observations.

3. The incidence of complications and observations was similar to that of the AICD System with no increase in patient morbidity.

4. The PCD Transvene System was safe with no patient deaths due to device malfunction in this patient population.

I. Conclusion

A total of 138 patients (18.2%) of the patients have experienced a relevant medical event which was classified as a complication while 157 patients (20.7%) have experienced a relevant medical event which was classified as an observation.

The incorporation of multiprogrammable features in the PCD device has decreased the incidence of certain reported complications and observations. Therefore, tiered therapy has been safely incorporated into the PCD device while maintaining an acceptable complication rate.

The PCD Transvene System offers not only potential clinical advantages in removing the need for a thoracotomy for implantation and the associated morbidity but maintains the safety of the PCD Epicardial System in terms of the number of patients experiencing a complication or observation.

The complications/observations reported in the PCD Transvene System experience are similar to those reported in the PCD Epicardial System. None of the clinical complications or observations reported to date have required a modification in the indication for implant for the PCD Transvene System or modification in the system labelling. This analysis indicates that the PCD device when implanted with a nonthoracotomy lead system is performing safely.

XIII. Patient Deaths

A. Section Overview

The positive impact of implantable cardioverter defibrillator (ICD) therapy on sudden cardiac death mortality has been well documented in the medical literature. The use of device therapy for the treatment of recurrent ventricular arrhythmias has become an accepted and important clinical tool.

The current market released implantable cardioverter defibrillator system requires a surgical thoracotomy for implantation because of the need to insert epicardial patch leads. This exposes the patient to increased surgical risk and potentially limits the type of patient who may be considered for implant of the system. The requirement of surgical thoracotomy contributes to the morbidity and mortality of these patients. The need for a simpler and safer implantation technique is widely recognized. The incorporation of a nonthoracotomy lead system, such as the PCD Transvene System, would decrease the potential perioperative and long term mortality and morbidity associated with current epicardial system implantation approaches.

In order to demonstrate the positive impact of the PCD Transvene System on patient survival, analysis of the sudden cardiac death survival in the PCD Transvene System patient population was performed and compared to the reported survival of similar patients treated with PCD Epicardial System, the market released Ventak-P Epicardial System and antiarrhythmic drug therapy.

As of June 24, 1992 there have been a total of **22 patient deaths** reported in this patient population who received a PCD Transvene System consisting of three leads (N=757). The PCD Transvene System sudden cardiac death survival rate in this patient group is 99.8%. This is marked improvement when compared with the reported survival of similar patient groups treated with drug therapy alone of between 34% and 73% at one year. **The PCD Transvene System Sudden Cardiac Death survival at one year of 99.8% which is very comparable to that of the PCD Epicardial System, 98.7% and commercially available implantable defibrillator, 98.6%.**

In summary, the incorporation of a nonthoracotomy defibrillation lead system has improved the type of therapy available for the treatment of recurrent VT/VF and decreased the potential mortality and morbidity associated with epicardial system implant approaches while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

B. Introduction

This section provides a summary of the patient deaths that have occurred worldwide in patients who have been implanted with a PCD device with an nonthoracotomy defibrillation lead system. Patient deaths which occurred prior to June 24, 1992 are included in calculations of patient survival and death rates for total, cardiac, and sudden mortality rates.

This section includes the following subsections:

• **Definitions**	Discussion of definitions used to classify each of the patient deaths
• **Physician Review**	Discussion of purpose of physician review board created to review all patient deaths
• **Death Analysis**	Analysis of patient deaths which includes patient characteristics, discussion of sudden cardiac deaths, perioperative deaths and survival data
• **Actuarial Survival**	One year actuarial survival analysis for patients who received a PCD Transvene System.
• **PCD Comparison**	Discussion of the PCD Transvene System experience in comparison to the PCD Epicardial System experience
• **AICD Comparison**	Discussion of the PCD Transvene System experience in comparison to the AICD Epicardial System experience
• **Death Summaries**	For each patient, a detailed summary of the circumstances of the patient death is provided. These are provided in Appendix D.

The section concludes with a summary and conclusions which can be drawn from the patient death clinical experience.

As of June 24, 1992 there have been a total of **22 patient deaths** reported in this patient population group of 757. Fifteen of the deaths occurred in the United States and the remaining seven deaths occurred in the International patient group.

The Table XIII B-1 summarizes how these patient deaths have been classified:

PCD Transvene System Summary of Death Classifications	
Death Classifications	
Classification	**All Patients (N=757)**
Sudden Cardiac	3
Non-Sudden Cardiac	16
Noncardiac	3
TOTAL	22

Table XIII B-1: Summary of PCD Transvene System Death Classifications - 6/24/92

There have been five perioperative deaths in the total group of 22 patient deaths with a resultant perioperative mortality of 0.7%.

None of the reported patient deaths have been related to the implanted PCD Transvene System.

There have been four patient deaths in the patients who did not meet the PCD Transvene System implant criteria. Two of these deaths have been classified as sudden cardiac however in both cases the investigator did not feel the patient death was related to the implanted PCD Transvene System. The remaining two deaths were classified as non-sudden cardiac and were related to end stage cardiac failure.

Finally, there have been no patient deaths reported secondary to ineffective treatment of a spontaneous VT/VF episode, lead dislodgement or lead fracture.

All of the patient deaths have been reviewed by a Clinical Event Review Committee (CERC) comprised of PCD Transvene System investigators and other physicians.

The primary objective of this committee was to determine whether the PCD Transvene System was related to the deaths and, if so, what changes may be required to prevent such events in the future and to review the classification of the deaths as specified by the primary investigator.

The data included in the following sections indicates that the PCD Transvene System has been safe and effective in reducing the Sudden Cardiac Death rate in the indicated patient population while maintaining a high efficacy rate in terminating spontaneous VT/VF episodes.

C. Definitions

Each patient death was classified by the primary investigator using the following definitions:

Non-Cardiac:	Deaths that occurred where the primary cause of death was not determined to be cardiac in nature, e.g. stroke, cancer, etc.
Cardiac:	Deaths that occurred where the primary cause of death was determined to be cardiac in nature.
Non-Sudden:	Deaths that occur greater than one hour after the onset of symptoms.
Sudden:	Deaths that occur within one hour of the onset of symptoms or where the death is unwitnessed. Sudden deaths were categorized as being **Witnessed** or **Unwitnessed**.
Perioperative:	Deaths that occur within thirty days of implant.
System Related:	A death which results from a malfunction (operation not according to design specification) of a PCD System component, or as a result of a device-induced arrhythmia, or an interaction between a PCD System component and the patient.
Procedure Related:	A death which occurs as a result of a procedure required to implant, follow, or test a PCD System.

This classification scheme was used to categorize patients for use in the actuarial analysis of survival. These definitions are identical to those in the medical literature discussing the Ventak-P Epicardial System clinical experience.

D. Physician Review of Deaths

All deaths and significant complications have been, and will continue to be, reviewed by a committee comprised of PCD device investigators and other physicians. Two committees have been formed, one to review North American deaths and complications, and the other for European clinical events.

The members of the **North American** committee are:

(b)(4), (b)(6)	
(b)(4), (b)(6)	Electrophysiologist; University of Washington;Seattle
	Electrophysiologist; University of Minnesota; Minneapolis
	Electrophysiologist; Foothills Hospital; Calgary, Alberta, Canada
	Cardiovascular Surgeon; Sacre Coeur Hospital; Montreal, Canada
	Cardiac Pathologist; University of Washington; Seattle

The members of the **European** committee are:

(b)(4), (b)(6)	
(b)(4), (b)(6)	Electrophysiologist, Heidelberg,Germany
	Electrophysiologist, Munster,Germany
	Electrophysiologist, Maastricht, Netherlands
	Electrophysiologist, Bonn,Germany
	Electrophysiologist, Stockholm, Sweden
	Electrophysiologist, Hamburg,Germany

These Clinical Event Review Committees (CERCs) have met to review the deaths that are reported in the following sections. All of the patient deaths have been reviewed by a committee (Clinical Event Review Committee) comprised of PCD investigators and other physicians.

The primary objective of this committee was to determine whether the PCD Transvene System was related to the deaths and, if so, what changes may be required to prevent such events in the future and to review the classification of the deaths as specified by the primary investigator.

Significant comments and modification to death classification by the CERC is provided, when present, in each of the detailed death summaries later in this section. It should be noted that the CERC agreed with the investigator's classification in all cases.

E. Circumstances of Patient Death Analysis

As of June 24, 1992 there have been 757 patients who have received a PCD Transvene System consisting of a three lead system. In this patient group, 22 patient deaths have been reported. Table XIII E-1 provides a summary of the patient characteristics of those patients who have expired.

PCD Transvene System Patient Death Clinical Characteristics	
Clinical Data	All Deaths
Number of Patients	(b)(4)
Mean Age	
Sex Male Female	
Primary Indication SCD VT SCD/VT	
Coronary Artery Disease	
NYHA Class Class I Class II Class III Class IV	
Mean Ejection Fraction Mean Range	
Death Classification Sudden Cardiac Non-Sudden Cardiac Noncardiac	
Perioperative Deaths	
PCD Related	
Spontaneous VT # Episodes # Patients	
Spontaneous VF # Episodes # Patients	

(b)(4)

Table XIIIE-1: PCD Transvene System Patient Death Clinical Characteristics - 6/24/92

In order to evaluate whether the patient death group differed clinically from the alive patient population group a comparison was made between the two groups. There was a statistical difference between the two patients groups in previous history of congestive heart failure, NYHA Classification and mean ejection fraction. The patient death group had a higher incidence of patient's with a previous history of congestive heart failure ($p = 0.030$), more patient's with a NYHA Classification of Class III/IV ($p = 0.001$) and a lower mean ejection fraction ($p = 0.001$).

Patient deaths were further analyzed based on the primary indication for implant of the PCD Transvene System. Table XIIIE-2 provides a further analysis of patient deaths by primary indication for PCD Transvene System implant.

PCD Transvene System Death Classification by Primary Indication			
Classification	**Indication for Implant**		
	SCD (N = 281)	**VT (N = 377)**	**SCD/VT (N = 99)**
Sudden Cardiac	-	3	-
Non-Sudden Cardiac	6	7	3
All Cardiac	6	10	3
Noncardiac	1	2	-
Total Deaths	**7**	**12**	**3**

Table XIIIE-2: PCD Transvene System Death Classification by Primary Indication for Implant - 6/24/92

Those patients whose indication for implant was **sudden cardiac death** accounted for 31.8% of the patient deaths. Those patients whose indication for implant was **recurrent ventricular tachycardia** accounted for 54.6% of the patient deaths. And those patients whose indication for implant was **ventricular tachycardia associated with sudden cardiac death** accounted for 13.6% of the patient deaths. This distribution of indications in the patient deaths reflects the distribution of indications in the patients receiving the PCD Transvene System.

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There was no difference in patient survival based on what PCD Transvene System lead configuration was implanted (i.e. RV/SVC/SQ, RV/CS/SQ or RV/CS/SVC) or the indication for implant of the PCD Transvene System.

Analysis was done on the distribution of patient deaths over time. As a reference, the mean follow-up for the entire patient data base is 5.6 months with the longest implant duration being 28.6 months.

Perioperative deaths were defined as deaths which occurred within 30 days of implant. Table XIII E-3 provides an analysis of patient deaths by follow-up interval.

PCD Transvene System Patient Deaths by Follow-Up Interval				
	Perioperative	1-3 M	3-6 M	> 6 M
Total by Interval	5	9	3	5

Table XIIIE-3: PCD Transvene System Patient Deaths by Follow-Up Interval - 6/24/92

There were five patient deaths in the perioperative period in patients who received a PCD Transvene System with a resultant perioperative mortality of 0.7%. The death classifications for these patients deaths was sudden cardiac death in two patients, non-sudden cardiac death in two patients and the remaining patient death was classified as noncardiac. This group of patients was predominately male and had a mean age of 67 years. The mean ejection fraction in this patient group was 20% and four of the patients had NYHA Classification of Class III/IV. As a group, these patients did not undergo prolonged implant procedures for the implantation of the PCD Transvene System. From this clinical data, it appears these patients had moderately depressed left ventricular function which would place them at higher risk post any type of surgical procedure.

As a final analysis, the non-sudden cardiac patient deaths were reviewed to determine if any were related to ventricular tachyarrhythmia episodes but the patient death occurred greater than one hour after onset of symptoms. Of the sixteen (16) non-sudden cardiac deaths, two were related to VT/VF episodes and the remaining were related to end stage congestive heart failure.

F. Actuarial Survival

The following represents a summary of the actuarial survival calculations for the PCD Transvene System. Actuarial survival analysis was completed from the perspective of **intention to treat** in those patients who were screened and those who received a PCD Transvene System (N = 757).

Those patients in whom the PCD Device was OFF at the time of death are included in the survival analysis. As a note, in the case of two patient deaths, the PCD Device was OFF at the time of death. One patient death was classified as non-sudden cardiac not related to an episode of VT/VF. The second patient death was classified as sudden cardiac and the patient had requested that the PCD Device be deactivated. The patient death which classified as non-sudden cardiac also occurred during the perioperative period.

Table XIII F-1, F-2 and Figure 1 provide the one year actuarial survival for all types of deaths in the patients who were screened and who received a PCD Transvene System. Note that the actuarial projections do not include perioperative deaths, except in the calculation of one-year survival from death due to all causes (shown in the row labelled **Overall**).

The positive impact of the PCD Transvene System on patient mortality is clearly obvious from this analysis. The sudden cardiac death survival rate in this patient group is 99.8%, both in the patient group that was screened and received a PCD Transvene System. This is marked improvement when compared with the reported survival of similar patient groups treated with drug therapy alone of between 34% and 73% at one year.

The PCD Transvene System Sudden Cardiac Death survival at one year is 99.8% which is very similar to that of the PCD Epicardial System, 98.7% and commercially available implantable defibrillator, 98.6%.

PCD Transvene System One Year Actuarial Survival	
	Screened Transvene System (N = 854)
Sudden Cardiac	99.8%
Non-Sudden Cardiac	97.1%
All Cardiac	97.0%
Noncardiac	99.4%
Overall	94.8%

Table XIII F-1: PCD Transvene System Actuarial Survival: Patients Screened - 6/24/92

PCD Transvene System One Year Actuarial Survival	
	Received Transvene System (N = 757)
Sudden Cardiac	99.8%
Non-Sudden Cardiac	96.8%
All Cardiac	96.6%
Noncardiac	99.4%
Overall	95.3%

Table XIII F-2: PCD Transvene System Actuarial Survival: Patients Received - 6/24/92

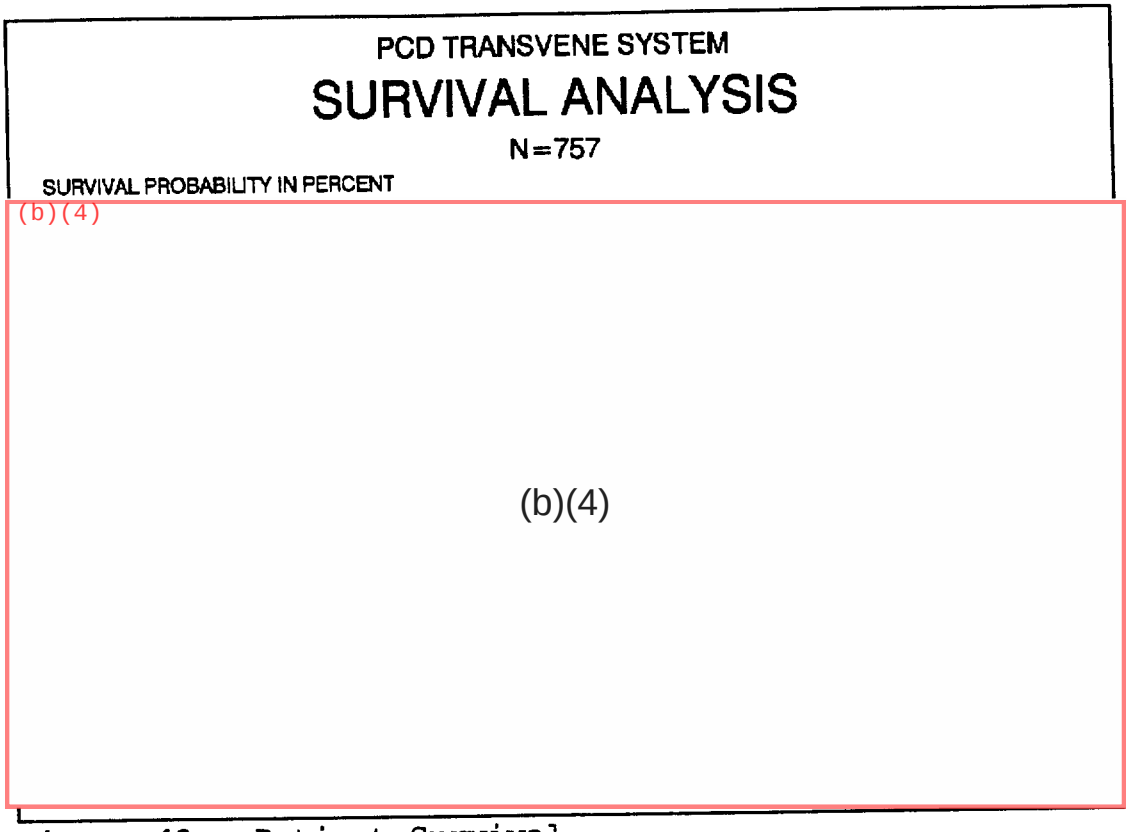

Figure 43: Patient Survival

G. Statistical Analysis For Predictors of Death

Statistical analysis on factors that may be predictive of death was conducted. Specific clinical characteristics of the patients who died were compared to those patients who received a PCD Transvene System and are still alive. Table XIII G-1 shows the factors that were analyzed and their respective P-Values. There was a statistical difference between the two patients groups in previous history of congestive heart failure, NYHA Classification and mean ejection fraction. This statistical difference was not unexpected since patients with more severe underlying cardiovascular disease are at risk for increased mortality. This data **does not** indicate that these patients should be contraindicated for a PCD Transvene System.

PCD Transvene System
Clinical Factors Predictive of Patient Death

VARIABLE	Transvene Deaths	Alive Transvene	Test	P-Value
Primary Indication			(b)(4)	
SCD	7 (31.8%)	274 (37.3%)		
VT	12 (54.6%)	365 (49.7%)		
SCD/VT	3 (13.6%)	96 (13.1%)		
Previous Cardiovascular History				
Coronary Artery Disease	18 (81.8%)	543 (73.9%)		
Myocardial Infarction	13 (59.1%)	503 (68.4%)		
Congestive Heart Failure*	12 (54.6%)	238 (32.4%)		
Cardiomyopathy	7 (31.8%)	231 (31.4%)		
NYHA classification*				
I/II	12 (54.6%)	597 (83.6%)		
III/IV	10 (45.4%)	117 (16.4%)		
Age	65.5 yrs	59.2 yrs		
Ejection Fraction*	24.5% (10-48%)	35.9% (7-88%)		

Table XIII G-1: PCD Transvene System: Analysis on Predictors of Death - 6/24/92

H. Comparison to PCD Epicardial System Clinical Experience

Despite their excellent clinical performance, epicardial defibrillation lead system have important limitations. The requirement for direct thoracic access contributes significantly to perioperative complications, patient discomfort and prolonged hospitalization. The availability of reliable nonthoracotomy lead systems should provide positive clinical impact on these issues while not negatively impacting patient survival. Therefore, a comparison of the one year actuarial survival rates for the PCD Transvene and Epicardial System was performed.

Table XIII H-1 provides a summary of the patient deaths reported in the two patient populations by classification. The PCD Epicardial System data (N = 742) includes patients who received the system as of May 14, 1992.

PCD Transvene System Death Classifications PCD Transvene System versus PCD Epicardial System		
Death Classification	**PCD Transvene System (N = 757)**	**PCD Epicardial System (N = 742)**
Sudden Cardiac	3	20
Non-Sudden Cardiac	16	41
All Cardiac	19	61
Noncardiac	3	27
TOTAL	22	88

Table XIII H-1: Death Classifications: PCD Transvene System versus PCD Epicardial System - 6/24/92

Table XIII H-2 provides a comparison of actuarial survival rates between the PCD Transvene and PCD Epicardial patient populations. The actuarial survival projections include perioperative deaths only in the calculation of survival from death due to all causes (shown in table row labelled **Overall**). Perioperative mortality includes those deaths which occur in the first thirty days post implant of the PCD System.

PCD Transvene System Comparison of Actuarial Survival PCD Transvene System versus PCD Epicardial System			(b)(4)
One Year Survival	PCD Transvene System	PCD Epicardial System	
Number of Patients	757	742	
Sudden Cardiac	99.8%	98.7%	
Non-Sudden Cardiac	96.8%	95.7%	(b)(4)
All Cardiac	96.6%	94.4%	
Noncardiac*	99.4%	97.3%	
Overall*	95.3%	87.2%	

* Statistically Significant

Table XIII H-2: Comparison of Actuarial Survival: PCD Transvene System versus PCD Epicardial System - 6/24/92

Also significant was the increase in overall survival in the patients receiving a PCD Transvene System. As previously noted, the Overall one year actuarial survival includes death from all causes. The overall one year survival for patients receiving the PCD Transvene System was 95.3%. This is significantly improved as compared to the overall one year actuarial survival for the PCD Epicardial System (87.2%) (b)(4) (b)(4)

This improvement in overall survival is primarily due to the marked improvement in perioperative mortality, the PCD Transvene System having a 0.7% perioperative mortality versus the a perioperative mortality of 4.7% in the PCD Epicardial System. This improvement in perioperative mortality is primarily due to the elimination of the need for surgical thoracotomy and its associated morbidity and mortality.

I. Comparison to AICD Epicardial System Clinical Experience

The Automatic Implantable Cardioverter Defibrillator (AICD) produced by Cardiac Pacemakers, Inc., is the only such device which has obtained market approval from the U.S. FDA to date. While there are important differences in the function of the AICD produced by CPI and the PCD System produced by Medtronic as well as the implanted defibrillation lead system, there is a natural desire for comparison of the clinical outcome, particularly the impact of these devices on death rate.

Table XIII I-1 provides a comparison of one year actuarial survival rates.

The patient population used for this comparison is the one which is described in Ventak-P Epicardial System Summary of Safety and Effectiveness, dated May 2, 1991, obtained through the freedom of information act.

For purposes of this comparison, only the **overall** actuarial survival rate includes perioperative deaths. All other calculations in both the PCD and Ventak-P group exclude perioperative deaths. Statistical analysis comparing the perioperative patient deaths is not possible since clinical data is not available on the AICD perioperative patient deaths.

For the Ventak-P Epicardial System, patient deaths were **censored** if the Ventak-P System had been either electively deactivated for various reasons prior to the patient's death, thus preventing the device from attempting to convert the arrhythmia or if the pulse generators were known to be nonfunctional and awaiting replacement. For purposes of this comparison, two patient deaths was **censored** in the PCD Transvene System patient population because the device was deactivated at the time of patient death.

PCD Transvene System Comparison of Actuarial Survival Rate PCD versus AICD		
One Year Survival	**PCD**	**Ventak-P**
Number of Patients	757	292
Sudden Cardiac	100.0%	98.6%
Overall	95.6%	90.8%

Table XIII I-1: Comparison of Actuarial Survival: PCD Transvene System versus AICD Epicardial System - 6/24/92

This comparison indicates that the projected survival from sudden cardiac death of patients receiving a PCD Transvene System is improved to that reported for the Ventak-P Epicardial System.

Thus the incorporation of programmable VT/VF detection and therapy algorithms has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

In addition, this comparison indicates that the projected survival from all causes of death **(Overall)** in patients receiving a PCD Transvene System is markedly improved as compared to the Overall one year survival reported for the AICD Epicardial System. This improvement is directly related to the decrease in the perioperative mortality in patients receiving a PCD Transvene System due to elimination of the requirement for a thoracotomy.

J. Summary

1. The projected one year survival for Sudden Cardiac Death, Non-Sudden Cardiac Death, All Cardiac Death and Overall were found to be 99.8%, 96.8%, 96.6%. and 95.3% respectively.

2. The perioperative mortality rate of 0.7% for the PCD Transvene System is significantly lower than that reported for implantable cardioverter defibrillator implants with an epicardial patch lead system.

K. Conclusion

The incorporation of a nonthoracotomy lead system, such as the PCD Transvene System, has decreased the potential perioperative and long term mortality and morbidity associated with current epicardial system implantation approaches.

The positive impact of the PCD Transvene System on patient mortality has been demonstrated by the analysis provided in this section. The sudden cardiac death survival rate for both patients who were screened for and received a PCD Transvene System is 99.8%.

This is marked improvement when compared with the reported survival of similar patient groups treated with drug therapy alone of between 34% and 73% at one year. **The PCD Transvene System Sudden Cardiac Death survival at one year of 99.8% which is very comparable to that of the PCD Epicardial System, 98.7% and commercially available implantable defibrillator, 98.6%.**

Also significant was the increase in overall survival in the patients receiving a PCD Transvene System. The overall one year survival for patients receiving the PCD Transvene System was 95.3%. This is significantly improved (b)(4) as compared to the overall one year actuarial survival for the PCD Epicardial System (87.2%) and the Ventak-P Epicardial System (90.8%).

This improvement in overall survival is primarily due to the marked improvement in perioperative mortality, the PCD Transvene System having a 0.7% perioperative mortality versus the a perioperative mortality of 4.7% in the PCD Epicardial System and 2.7% in the Ventak-P Epicardial System. This improvement in perioperative mortality is primarily due to the elimination of the need for surgical thoracotomy and its associated morbidity and mortality.

This improvement in both sudden cardiac death and overall one year survival indicates that the PCD Transvene System has performed safely and effectively in the indicated patient population.

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CLINICAL EXPERIENCE REPORT

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I
Clinical
Report

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A

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I. Clinical Experience Report

A. System and Study Description

The efficacy and safety of implantable cardioverter defibrillator (ICD) therapy for recurrent ventricular tachycardia (VT) and ventricular fibrillation (VF) has been well established. The current market released device provides defibrillation therapy for VF or hemodynamically unstable VT, however, this type of therapy may not be optimal for patients with stable, well tolerated VT that is amenable to antitachycardia pacing. It is necessary to perform a significantly more invasive procedure, a thoracotomy, in order to implant the epicardial leads. Thus, the need to incorporate programmability, multiple detection and therapeutic options, and a less invasive lead system has lead to the development of a tiered therapy device, the PCD™ Transvene™ System.

This report represents a full report of Medtronic's clinical experience with the Medtronic PCD Model 7217B Multiprogrammable Tachyarrhythmia Control System with Transvene Cardioversion and Defibrillation Electrodes (Reference IDE G870102). The data included in this analysis is all data that was received by Medtronic and entered onto the clinical database as of **February 1, 1993**.

The PCD Model 7217B Multiprogrammable Tachyarrhythmia Control System described in this submission is identical to the system which was recommended for approval by the FDA advisory panel on February 3, 1992, with the addition of Transvene leads and approved by the FDA February 11, 1993.

This summary provides an overview of the clinical experience which verifies that the PCD Transvene System is safe and effective in the indicated patient population.

1. Implanted Devices, Leads, and Pulse Generator

The Pacer-Cardioverter-Defibrillator (PCD) device is an implantable, multiprogrammable, automatic tachyarrhythmia control device. The PCD Device is used in conjunction with appropriate lead systems for the treatment of patients with ventricular tachycardia (VT) and/or ventricular fibrillation (VF). The PCD Device also provides backup pacing in the VVI mode and noninvasive electrophysiologic (EP) study capabilities.

The PCD Device is programmed with the market released Medtronic programmer and a Model 9788 or equivalent MemoryMod™ Cartridge. The PCD Device incorporates a two-way telemetry system which receives operational instructions from the programmer and transmits status, electrogram and event information back to the programmer for display and/or printout.

The External Tachyarrhythmia Control Device (ETCD) is an external, multiprogrammable, tachyarrhythmia control device. Its operation is similar to the PCD Device except that cardioversion and defibrillation therapies are delivered manually. In addition, it displays measurements of cardioversion and defibrillation therapy parameters. The ETCD is used for making defibrillation threshold measurements during the PCD Device implantation procedure.

Components

The Medtronic PCD Transvene System, which is represented in Figures 1A and 1B, for which market release approval is being requested, consists of the following components:

Implanted Device and Related Programming System
Pacer-Cardioverter-Defibrillator (PCD) Device
Model 7217B

Programmer
Model 9710 programmer and related accessories (currently market released), plus
Model 9788 MemoryMod™ Software Cartridge

Lead System
Electrode Leads:
Model 6966
Model 6963
Model 6999
Market Released Medtronic Epicardial Leads

Implant Measurements System
Model 5355 ETCD™ External Tachyarrhythmia Control Device
Model 5418 Patient Cable
Model 5414 Test Load
Model 5417 EGM Cable
Model 5419 Jumper Cable

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The physical characteristics of the Model 7217B are summarized in Table IA1-1:

PCD Model 7217B Physical Characteristics	
Feature	**Model 7217B**
Volume	(b)(4)
Weight	
Connector Module	
Power Source	(b)(4)
Sensing Configuration	
Pacing Configuration	

Table IA1-1: Features: Model 7217B - 2/1/93

The Model 7217B PCD Device uses the pace/sense leads for sensing, thus providing **standard bipolar** sensing. Pacing is delivered in the integrated bipolar configuration.

2. Study Design and Objectives

The clinical study was designed to evaluate the operation, safety and effectiveness of the PCD System components in detecting and treating episodes of ventricular tachycardia and ventricular fibrillation.

The analysis focuses on data supporting the safety and effectiveness of the PCD system, including the implantable pulse generator and associated transvenous lead system and its therapy in this patient population. The analysis includes the clinical experience with the PCD system, pace/sense, detection and therapy functions in both the acute and chronic implant settings. In addition, data is provided on clinical observations, clinical complications and deaths in this patient population.

The objectives of the clinical study were:

* to evaluate the sensitivity and specificity of the PCD Device with Transvene lead systems to detect episodes of VT and VF, and to evaluate the ability of the system to appropriately discriminate between VT/VF and other potentially nonmalignant rhythms;

* to monitor the efficacy of the PCD Device with Transvene lead systems in treating VT and VF episodes. VT/VF therapy efficacy is determined as the ratio of successful termination of episodes detected to the total number of episodes detected in which one or more therapies were delivered (Successful Termination/Number of Detected Episodes with Therapy Delivered). Investigators were free to choose from any of the available leads and VT/VF therapies that the efficacy was first evaluated acutely;

* to evaluate the performance of the Model 6966, 6963 and 6999 Transvene leads;

* to monitor the patient selection criteria and patient management methods required by the PCD Device and Transvene leads.

Clinical data was collected at the following study points to support the safety and efficacy of the PCD System:

(b)(4)

(b)(4)

Specific data was collected at each of these points to meet the objectives of the clinical study. This included:

Pre-implant Patient Assessment (b)(4) (b)(4)

(b)(4)

(b)(4)

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Lead System Testing - implant evaluation was performed to verify that one of the specified lead systems was capable of properly detecting and treating episodes of ventricular fibrillation and, when appropriate, ventricular tachycardia. The Market Released Model 5355 ETCD™ or the 2394 External Cardioverter Defibrillator (ECVD) was used for testing.

This testing included (b)(4) The PCD Device implant criteria were:

1) (b)(4)

2)

Implanted Pulse Generator Testing - this implant evaluation was performed to demonstrate proper detection and termination of ventricular fibrillation by the implanted PCD System with VF Therapy #1 programmed to (b)(4) in addition to pacing and sensing thresholds.

Pre-hospital Discharge Testing - testing performed at the pre-hospital discharge included proper detection and termination of induced ventricular tachycardia. Final sensing and therapy parameters are programmed at the PHD.

Follow-up Evaluation - regular testing was performed to evaluate the chronic stability of detection and therapy parameters of the PCD System. This testing included (b)(4)

(b)(4)

Patients were evaluated prior to hospital discharge and/or one (1) month post implant, three months post-implant and then at intervals of every three months. In some cases additional testing was performed at physician discretion to evaluate spontaneous events and/or potential clinical complications.

Medtronic collected all clinical data on the PCD System and its components under the clinical protocol outlined in the Investigational Plan. A common protocol was used on all study patients on a worldwide basis.

B

Clinical data presented in this summary includes experience with the Model 7216A and 7217B PCD Devices with the Model 6966, 6884, 6963, 6881, 6999, and 6895 Transvene Leads (the only difference between the Models 6884/6881/6895 and Models 6966/6963/6999 are the size of the connector pins). This report presents the clinical evaluation of the safety and efficacy of the PCD Device with Transvene Leads implanted in 757 patients of which 657 have implant durations equal to or greater than six months.

International centers were subject to the appropriate requirements (e.g., the Declaration of Helsinki) in order that the data met the statutory requirements of the FDA. All clinical data, U.S. and International, obtained with the PCD System with Transvene Leads is included in this report.

Patient data from U.S. and International patients, Model 7216A and 7217B, and the three implanted lead configurations (RV/CS/SQ, RV/SVC/SQ, and RV/CS/SVC) analyzed in this report were compared with the appropriate statistical tests to justify data pooling. Data analyzed included: age, sex, ejection fraction, primary indication, NYHA classification, and underlying heart disease. No clinically significant differences were found among the patient groups.

Indicated Patient Population

The PCD System is intended to treat patients at risk of sudden cardiac death due to ventricular tachyarrhythmias which have been shown to be reliably terminated, and in the case of VF, terminated at an energy level below the maximum output of the PCD Device.

Results provided in this application will support Medtronic's request for market release of the PCD Transvene System for use in the following patient population:

* Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or

* Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise,

or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

These are the same indications that were approved for the PCD Epicardial System.

For this patient population the primary benefits from the use of the PCD System center on the detection and termination of life-threatening ventricular arrhythmias. The use of pacing therapies for the treatment of ventricular tachycardia reduces patient trauma associated with higher energy cardioversion pulses and extends the longevity of the PCD pulse generator.

The PCD System allows the titration of therapies for patients with ventricular tachycardia while providing the critical defibrillation backup. Defibrillation backup is important in the event that an episode of VT accelerates to VF whether spontaneously or as a result of a delivered therapy. The capacity to provide programmable extrastimuli pacing allows noninvasive electrophysiologic studies to be performed. The potential benefits from permanent cardiac pacing provide support for chronic and transient episodes of bradycardia. Finally, the benefits of programmability of tachyarrhythmia detection and therapy parameters, VVI parameters and stored telemetry data on the delivery of therapy may avert the need for reoperation in the event of changing patient conditions or complications.

Study Controls

The clinical experience obtained in the PCD Epicardial System clinical study provides a concurrent control for comparing the clinical performance of the PCD Transvene System. Using the PCD Epicardial System clinical data as a control is appropriate because the patients were being enrolled in the two studies concurrently by the same investigators, and the patient indications, implant criteria, and clinical data requirements were identical for the two patient groups.

The Ventak-P Epicardial System is used as a historical control, since it was the most similar implantable

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defibrillation system that was market released and had published performance data.

The PCD investigators believe that there is a class of patients who cannot tolerate the thoracotomy required for the utilization of the epicardial patch lead defibrillation lead system and who are at high risk of sudden cardiac death. For these patients, the PCD Transvene System is the only therapy available. Therefore, randomization between the Epicardial and the Transvene lead systems would not be feasible or clinically or ethically appropriate in these patient groups. There was no market released transvenous system available which would make a randomized study design possible.

3. Justification for Data Pooling

This section will describe the results of the analysis to demonstrate that the data from the U.S. and International investigative centers and the two device model numbers may be pooled. This section will also compare the three lead systems which will be presented throughout the report.

a. Comparison of U.S. and International Patients

Statistical comparisons were made between the two populations age, sex, ejection fraction, primary indication, NYHA, and previous cardiovascular history. Table E1 in Appendix E summarizes the results of statistical analysis.

All study investigators used the same:

a. patient selection criteria,
b. investigational protocol procedures, and
c. indications for implant of PCD™ Transvene™ System.

Of the variables analyzed patient age, ejection fraction, primary indication, NYHA classification, coronary artery disease and cardiomyopathy showed a statistically significant difference between the U.S. and the International patient populations at a 0.05

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significance level. The difference in NYHA classification becomes insignificant when adjusting for multiple inference using the Hochberg procedure (Dunnett and Tamhane, "A Step-Up Multiple Test Procedure," Journal of the American Statistical Association, March 1992, 87:162-170). See Appendix E for multiple inference adjustments. Coronary artery disease, ejection fraction, cardiomyopathy, primary indication and age remain statistically significant after adjusting for multiple inference. The U.S. patient population has a higher percentage of patients with coronary artery disease and cardiomyopathy, lower mean ejection fraction, more patients with VT as their primary indication and a higher mean age. The difference in age may explain the differences in underlying disease and cardiac ejection fraction. These factors that are statistically significant but are not considered to be clinically significant enough to require stratification of the U.S. and International patient populations. The differences may have to do with regional attitudes toward access to health care for the aged.

b. Comparison of Model 7216A and Model 7217B

Table E2 in Appendix E summarizes the results of statistical analysis comparing the Model 7216A to Model 7217B. No parameters were found to be statistically significant between the two PCD models at a 0.05 significance level.

c. Lead Configurations

Table E3 in Appendix E shows comparisons of patient variables for the three lead systems. This was done to document that there were no significant differences in patient characteristics between the implanted lead configurations.

Of the variables analyzed in Table E3 sex and cardiomyopathy showed a statistically significant difference between the three lead configurations at a 0.05 significance level. The difference in sex and percentage of patients with cardiomyopathy

becomes insignificant when adjusting for multiple inference using the Hochberg procedure (Dunnett and Tamhane, "A Step-Up Multiple Test Procedure," Journal of the American Statistical Association, March 1992, 87:162-170). See Appendix E for multiple inference adjustments.

d. Statistical Analysis Conclusions

The statistical comparisons between the U.S. and International populations indicated no clinically significant differences therefore the data may be pooled. Analysis of the patients receiving the two PCD models indicates no statistically significant differences therefore the data from the two devices may be pooled.

The results from the comparison of lead systems indicated no statistically significant differences in patient demographics, primary indication, or heart disease.Data Pooling/U.S. Demographics

B. Overview of Clinical Experience

This report covers a total of 762 implants of the PCD Device with the Transvene Defibrillation Lead System in 757 patients who received a 3 lead system. There was a total of 97 patients that were screened for Transvene system that did not meet the implant criteria and received a Medtronic Epicardial system and a total of 43 patients that received a non-standard lead system. These patients are described in Section C2, Patients not Meeting Implant Criteria and Section D4, Non-standard Lead Configurations, respectively.

A total of 78 investigative centers participated in the clinical trial with 35 centers in the U.S. and 43 Internationally. The first implant occurred internationally on October 20, 1989, and the first implant in the U.S. occurred on October 16, 1990. Table IB-1 shows the distribution of Model 7216A and Model 7217B patients between U.S. and International investigators.

PCD Transvene System Implant Distribution			
	Total	U.S.	Int'l
7216A	18 (2.4%)	3 (0.7%)	15 (4.8%)
7217B	744 (97.6%)	444 (99.3%)	300 (95.2%)

Table IB-1: PCD Transvene System - Implant Distributions - 2/1/93

The mean documented implant duration for this patient population is 11.7 months and ranged from implant to 37.4 months. The cumulative implant duration is 8894.8 months. There are 657 patients with implant durations equal to or greater than 6 months and 393 patients with implant durations equal to or greater than 1 year.

The patient population enrolled in the clinical trial was predominately male (80.6%) with a mean age of 59.4 years. In half of the patients (49.8%), the primary indication for implant was recurrent, sustained ventricular tachycardia without an episode of sudden cardiac death. Sudden Cardiac Death was the primary indication for 37.1% of the patients and SCD in combination with recurrent, sustained VT was the primary indication in 13.1%. Coronary artery disease was the primary heart disease in 74.1% of the patient population with a mean reported ejection fraction of 35.6% Table IB-2 provides a data summary on these patients. Also included is the data summary of the patients with 6 months and 12 months of follow-up.

PCD Transvene System Data Summary			
	All Patients (3 Electrode Systems)	Patients with 6 months of Follow-up	Patients with 12 months of Follow-up
Number of Patients	757	657	393
Device Months Follow-up	8894.8	8602.6	6454.6
Mean Follow-up Time	11.7 mo	13.0 mo	16.3 mo
Maximum Follow-up Time	37.4 mo	37.4 mo	37.4 mo
Number, % Male Number, % Female	610 80.6% 147 19.4%	527 80.2% 130 19.8%	310 78.9% 83 21.1%
Mean Age	59.4 yrs	59.1 yrs	58.8 yrs
Primary Indication: SCD VT SCD/VT	 281 37.1% 377 49.8% 99 13.1%	 249 37.9% 326 49.6% 82 12.5%	 150 38.2% 191 48.6% 52 13.2%
Coronary Artery Disease	561 74.1%	483 73.5%	272 69.2%
Mean Ejection Fraction	688 35.6%	595 36.6%	357 38.0%
Defibrillation Pathway: Sequential Simultaneous Single	 574 75.3% 178 23.4% 10 1.3%	 496 74.9% 156 23.6% 10 1.5%	 296 74.9% 93 23.6% 6 1.5%
Mean LED	16.0J (N=702)	16.0J (N=609)	15.6J (N=365)
Mean DFT	14.8J (N=316)	14.8J (N=277)	14.3J (N=184)
Spontaneous VT: Number of Patients Number of Episodes % Success	 316 10027 98.4%	 288 8820 98.3%	 186 6338 99.0%
Spontaneous VF: Number of Patients Number of Episodes % Success	 317 1982 98.4%	 292 1742 98.3%	 176 1105 98.6%
One Year SCD Survival	99.5%	99.7%	100.0%

Table IB-2: PCD System Data Summary - All Transvene Patients versus Transvene Patients with 6 mo Follow-up - 2/1/93

1. Implant Information

Implants of the PCD Device may use two or three Transvene leads. The physician has the flexibility to use whichever lead system best meets the patient's needs.

The venous entry site used for placement of the Transvene leads is determined by the implanting physician. Table IB1-1 shows that the Left Subclavian vein is the most popular venous entry site regardless of type of lead or intended lead location. The total number of RV lead entry sites is greater than the total number of patients included in this report because of patients with multiple lead evaluation sessions (e.g. patients that received a second PCD Transvene system if the initial system was removed due to infection).

PCD Transvene System Venous Entry Site			
	RV Lead Models 6884/6966/SP2100	CS/SVC Lead Models 6881/6963	All Transvene Leads
Left Subclavian	483	583	1066
Right Subclavian	40	47	87
Left Cephalic	213	180	393
Right Cephalic	8	7	15
Left Internal Jugular	7	9	16
Right Internal Jugular	11	9	20
Other	5	4	9
Total	767	839	2097

Table IB1-1: Venous Entry Site - 2/1/93

The location of the subcutaneous patch is presented in Table IB1-2. Location is defined by both anatomical line and intercostal space. The study protocol does not restrict investigators in subcutaneous patch placement. Investigators are free to place it in the most appropriate location for each individual patient.

The most common subcutaneous patch location laterally is the mid axillary line (55.7%). the next most common location is the anterior axillary line (34.3%). The majority of subcutaneous patches are placed between the third and sixth intercostal (53.4%).

The majority of the investigators (92.8%) placed the patch electrode subcutaneously. Fifty-two (52) or 7.2% if investigators placed the patch electrode in a submuscular location.

PCD Transvene System
Location of the Subcutaneous Patch Electrode

Intercostal Space	Mid Clavicular Line	Anterior Axillary Line	Mid Axillary Line	Posterior Axillary Line	Subscapular	Total
1-2	(b)(4)					
3-6						
7-11						
Not Specified						
Total						

(b)(4)

Table IB1-2: Location of the Subcutaneous Patch Electrode - 2/1/93

Table IB1-3 illustrates the lowest energy of defibrillation (LED) and defibrillation threshold (DFT) for the implanted lead systems. The implant criteria for the PCD Device was 3 of 4 episodes of VF successfully terminated at 18 Joules or less with a given lead configuration. Some patients did not have a LED at implant. The LED is only identified if the investigator reported the induced rhythm as VF. Conversion of VT or V Flutter (as defined by the physician) to sinus rhythm was not included in the determination of the LED. In addition, it is not a protocol requirement to obtain a DFT at implant. However, recommendations have been provided to those institutions that prefer to obtain DFT's during the implant procedure.

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PCD Transvene System Mean LED and DFT Values				
Lead System	Implant Frequency	Mean LED	Implant Frequency	Mean DFT
Total Systems	702	16.0J	316	14.8J
RV-SVC-SQ	455	16.7J	187	15.8J
RV-CS-SQ	210	14.6J	110	12.8J
RV-CS-SVC	37	15.2J	19	16.0J

Table IB1-3: PCD Transvene System - LED and DFT Values - 2/1/93

The mean implant Lowest Energy of Defibrillation (LED) for all lead systems was 16.0J and mean implant Defibrillation threshold (DFT) for all lead systems was 14.8J. As the mean DFT's and LED's indicate, VF was reliably terminated at an energy value below the maximum output (34 Joules) of the PCD Device.

There was a statistically significant difference between the mean DFT obtained with the RV-CS-SQ lead configuration and the mean DFT obtained with the other lead configurations. Since there were no differences in the patient populations implanted with any of the 3 lead configurations, this may be a configuration that results in lower DFTs than the other configurations. In theory, this may be due to better defibrillation current distribution throughout the myocardium. There is no intent to show that a lower DFT results in a better patient outcome. The premise of the PCD Epicardial and Transvene studies was to demonstrate that if a patient was evaluated at implant and shown to meet the implant criteria, that they would be reliably defibrillated over time, and therefore, have a high probability of survival from SCD regardless of which lead system or defibrillation pathway was chosen or the absolute value of the DFT.

Follow-up Data - Quantity

The combined experience from the Model 7216A and the Model 7217B with Transvene lead systems discussed in this analysis is 762 implants in 757 patients followed for a

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mean of 11.7 months. Maximum follow-up is 37.4 months with 8894.8 total device months of experience. Six-hundred-fifty-seven (657) patients have been followed for at least 6 months and 393 patients have a minimum of one year of follow-up.

Table IB1-4 shows the follow-up time in months for the PCD Transvene System patient population.

PCD Transvene System Follow-up Quantity	
Mean Follow-up	11.7 Months
Std. Dev.	6.5 Months
Maximum	37.4 Months
Minimum	0 Months

Table IB1-4: Follow-up Time - Months (n = 757) - 2/1/93

Compliance

Follow-ups designated as the corresponding scheduled visit and performed between 21 and 59 days post-implant are considered to be 1-month follow-ups; those between 60 and 135 days are considered to be 3-month follow-ups; and those between 136 and 225 days are considered to be 6-month follow-ups; and those between 227 and 317 days are considered to be 9-month follow-ups; and those between 318 and 408 days are considered to be 12-month follow-ups. Follow-ups not designated as a scheduled visit or outside these intervals are counted as interim visits and do not contribute to compliance.

No devices were known to have been implanted by non-investigators, by investigators without IRB approval or equivalent, without patient Informed Consent, or without submission of Implant Data Forms to Medtronic. Implantation of the PCD Epicardial system outside the U.S. was performed in accordance with the "Declaration of Helsinki" or within the laws or regulations of the respective country, whichever accorded greater protection to the patient. Requirements for testing identified in the

Investigational Plan for test procedures were all fulfilled during the investigation. Table IB1-5 contains the follow-up compliance report.

PCD Transvene System Patient Compliance									
Follow-up Visit Status	1 Mth	3 Mth	6 Mth	9 Mth	12 Mth	15 Mth	18 Mth	21 Mth	24 Mth
Follow-up in on time	(b)(4)								
Follow-up not yet due									
Patient discontinued before F.U. date									
Follow-up not in but subsequent one in									
SUBTOTAL - IN COMPLIANCE									
Lost to Follow-up									
Follow-up in early									
Follow-up in late									
Follow-up missing									
SUBTOTAL - OUT OF COMPLIANCE									
TOTAL									
COMPLIANCE RATE(%)									

(b)(4)

Table IB1-5: Follow-up Compliance Report - PCD Transvene System Worldwide Experience - 2/1/93

2. Spontaneous VT and VF Episode Experience

Of the 757 patients who received a PCD Transvene System, 597 patients (78.9% - 597/757) have either experienced a spontaneous VT/VF episode or had VT/VF induced during a post implant electrophysiology study. A total of 458 patients (60.5%) have experienced a spontaneous episode of either VT and/or VF that has been detected and treated by the PCD Device. A total of 141 (18.6%) experienced VT only, 142 patients (18.8%) experienced VF only and 175 patients (23.1%) experienced both an episode of VT and VF.

There have been a total of 12,009 episodes of spontaneous VT or VF as detected by the PCD. The overall PCD Device success rate in terminating spontaneous VT/VF episodes as detected by the PCD is presented in Table IB2-1.

For those episodes where all four programmed VT/VF therapies failed to terminate the episode, the clinical follow-up data form was reviewed for investigator's comments on the episode. The investigator reviewed the patient's symptoms at the time of the episode as well as the stored episode information provided by the PCD Device and indicates on the clinical dataform whether the ineffective therapy was due to a nonventricular tachyarrhythmia such as sinus tachycardia or atrial fibrillation. If there is no such indication on the clinical dataform, it is assumed that the ineffective therapy was for a spontaneous VT or VF episode. It should be noted that for all current ICD Systems, the delivery of inappropriate therapy for atrial fibrillation or sinus tachycardia is a known risk of the therapy.

PCD Transvene System Success Rate for Spontaneous VT/VF Episodes		
	Spontaneous VT Episodes	Spontaneous VF Episodes
Mean Follow-Up	11.7 months	11.7 months
Number of Episodes	10,027	1982
Number of Patients with Episodes	316	317
% Overall Efficacy	9,864/10,027 98.4%	1951/1982 98.4%
% Unsuccessful Termination (VT or VF)	68/10,027 0.7%	5/1982 0.3%
% Unsuccessful Termination (AF,ST, other)	95/10,027 0.9%	26/1982 1.3%

Table IB2-1: PCD Transvene System: Success Rate for Termination of Spontaneous VT/VF Episodes (n = 757) - 2/1/93

a. **Spontaneous VT**

For the purposes of this clinical trial, spontaneous VT was defined as those episodes that satisfied the programmed VT detection criteria. Specifically, all programmed VT detection criteria must be fulfilled to detect a VT episode. Successful termination of the episode was defined as satisfying the VT episode termination criteria.

To date, 10,027 spontaneous episodes of VT have been detected by the PCD Device in 316 patients. The mean number of episodes per patient with VT was 31.7 (316/10,027) and ranged from 1 - 531 episodes.

Most spontaneous VT episodes (90.7%) were successfully treated with VT Therapy #1 and 98.4% were successfully treated with one of the four programmable VT therapies.

Of the 9864 successfully terminated spontaneous VT episodes, 91.4% were treated with one of the programmed antitachycardia pacing therapies incorporated in the PCD Transvene System. The clinical benefit of tiered therapy is the reduction of delivery of high energy shocks for the treatment of stable recurrent ventricular tachycardia. This greatly enhances the patient acceptance of ICD therapy since antitachycardia pacing is usually not perceived by the patient.

Sixty patients experienced 163 (1.6%) episodes in which the PCD Device was ineffective in terminating a spontaneous episode of VT despite delivery of all four programmed VT therapies. Thirty-nine patients experienced 95 ineffective episodes that were due to sinus tachycardia or atrial fibrillation/flutter (SVT) with a rapid ventricular response that had been detected as VT. These episodes were resolved with either modification of programmed parameters or of antiarrhythmic drug therapy. It should be noted that the PCD Device responded appropriately based on the programmed detection parameters.

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The remaining 68 episodes occurred in 21 patients in which the programmed VT therapies were ineffective in terminating a spontaneous VT episode. **No patient deaths occurred as a result of ineffective VT therapy**. Reprogramming and pharmacologic intervention resolved these events.

b. Spontaneous VF

For purposes of this clinical trial, VF is defined as those episodes that satisfy the programmed VF detection criteria. Specifically, all programmed VF detection criteria must be fulfilled to detect a VF episode. Successful termination of the episode is defined as satisfying the VF detection criterion for episode termination.

To date, 1982 spontaneous episodes of VF have been detected by the PCD Device in 317 patients. The mean number of episodes per patient was 6.3 and ranged from 1 - 77 episodes. A review of the chart by the investigator for this patient that experienced the 77 episodes of VF revealed that 75 were most likely due to atrial fibrillation. VF detection parameters were modified in this patient.

Most (89.1%) spontaneous VF episodes were successfully treated with VF Therapy #1 and 98.4% were successfully treated with one of the four programmable VF therapies.

Sixteen patients experienced 31 episodes (1.3%) in which the PCD Device was ineffective in terminating a spontaneous episode of VF despite delivery of all four programmed VF therapies. Nine patients had 22 reported ineffective VF spontaneous episodes that were due to sinus tachycardia or atrial fibrillation with rapid ventricular response rather than VF. Reprogramming and pharmacologic intervention resolved these problems.

Four patients experienced 5 ineffective episodes that were detected as VF by the PCD® System. One of these patients (b)(6) required external defibrillation

to convert the VF episode. This patient's antiarrhythmic drug regimen was modified to improve defibrillation efficacy. Another patient (b)(6) had an episode recorded as ineffective on the event counters but presented in sinus rhythm. Subsequent evaluation demonstrated appropriate PCD function. Another of these patients (b)(6) had two spontaneous episodes of VT that were detected as VF by the PCD while in the hospital for progressive CHF. These episodes required external cardioversion. The patient requested the PCD be turned OFF. The patient was alive at the last known follow-up. The last of these four patients (b)(6) experienced cardiac arrest at home and was found by the paramedics to be in sinus rhythm. While on a monitor the patient developed VF. The PCD delivered the programmed therapy which terminated the episode but the patient developed EMD, arrived at the ER comatose and died.

Four patients (one patient (b)(6) experienced 2 episodes due to AF but is described below again) experienced 4 episodes in which the PCD detected the episodes as VF but were actually episodes due to extraordinary circumstances. One patient (b)(6) experienced an episode where all four therapies failed secondary to RV lead fracture. The patient had Twiddlers Syndrome. Reoperation was required. It appears that the inappropriate therapy was not due to VT/VF but due to noise. Another patient (b)(6) had a surgical procedure (CABG) where the CS lead dislodged post surgery. The episode that was detected was due to the lead dislodgement. The third patient (b)(6) had incessant episodes of fast VT (cycle length 280 ms) that were eventually resolved by drugs. The fourth patient (b)(6) was in the hospital and there was an episode of VF detected by the PCD and therapy was delivered. However, the device was interrogated before termination of the episode was detected by the PCD. There was external intervention (transthoracic defibrillation) associated with the terminal event. However, the patient ultimately expired. The device was not interrogated again.

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The evaluation of spontaneous episode experience indicates that the PCD Transvene System's VT and VF detection and therapy functions have performed safely and effectively in the indicated patient population.

3. Summary of Complications and Observations

The use of a multiprogrammable implantable cardioverter defibrillator (ICD) device allows the physician to resolve most relevant medical events by noninvasively changing programmed parameters thus, avoiding invasive procedures. However, there will continue to be certain relevant medical events which will require invasive procedures for resolution.

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following definitions:

COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

As of February 1, 1993, there have been a total of 176 complications identified in 147 patients and 212 observations identified in 178 patients in the PCD Transvene System patient population. Thus, 19.4% (147/757) of the patients have experienced a clinical event which was defined as a complication and 23.5% (178/757) of the patients have experienced a clinical event which was defined as an observation.

Table IB3-1 summarizes the reported PCD Transvene System complications and observations by category. The reported complications and observations are recognized clinical events that may occur with **any** of the current ICD devices. These complications and observations are discussed in the PCD device and Transvene manual. **None of the reported complications or observations have resulted in a patient death.**

PCD Transvene System Reported Complications/Observations By Category		
Category	**Complications**	**Observations**
	Num (% of Pts)	**Num (% of Pts)**
Increased Defibrillation Requirements	9 (1.2%)	8 (1.1%)
Inappropriate VF Therapy Delivery	-	14 (1.9%)
Inappropriate VT Therapy Delivery	-	57 (2)* (7.5%)
Loss of Capture	6 (0.8%)	11 (1)* (1.7%)
Oversensing	-	52 (2)* (6.9%)
Undersensing	-	-
Skin Erosion	5 (0.7%)	1 (0.1%)
Pocket Infection	24 (3.2%)	10 (1.3%)
Seroma	6 (0.8%)	14 (1.8%)
Hematoma	6 (0.8%)	17 (2.2%)
Pneumothorax	2 (0.3%)	1 (0.1%)
Pacemaker Syndrome	-	2 (0.3%)
Perforation	6 (0.8%)	-
Subclavian Vein Thrombosis	1 (0.1%)	3 (0.4%)
Lead Fracture	9 (1.2%)	-
Subcutaneous Patch Crinkling	7 (0.9%)	5 (0.7%)
Early Device Explant	4 (0.5%)	-
Total Lead Dislodgement	86 (5)* (11.4%)	12 (1.6%)
Total	171 (176)	**207 (212)***

Table IB3-1: PCD Transvene System: Reported Complications and Observations - 2/1/93

* This number indicates the number of patients with 2 events

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Table IB3-2 and Table IB3-3 presents the complications and observation as they occurred overtime (months).

PCD Transvene System Reported Complications Over Time (Months)							
	≤ 1	1-3	3-6	6-9	9-12	12+	Total
Increased Defibrillation Requirements	4	3	-	-	1	1	9
Inappropriate VF Therapy Delivery	-	-	-	-	-	-	-
Inappropriate VT Therapy Delivery	-	-	-	-	-	-	-
Loss of Capture	6	-	-	-	-	-	6
Oversensing	-	-	-	-	-	-	-
Undersensing	-	-	-	-	-	-	-
Skin Erosion	-	1	1	-	-	3	5
Pocket Infection	2	11	5	4	-	2	24
Seroma	2	3	-	-	1	-	6
Hematoma	3	2	1	-	-	-	6
Pneumothorax	2	-	-	-	-	-	2
Pacemaker Syndrome	-	-	-	-	-	-	-
Perforation	5	-	-	1	-	-	6
Subclavian Vein Thrombosis	-	1	-	-	-	-	1
Lead Fracture	-	-	3	4	-	2	9
Subcutaneous Patch Crinkling	2	3	2	-	-	-	7
Early Device Explant	1	2	1	-	-	-	4
RV Lead Dislodgement	14	8	1	1	-	-	24
CS Lead Dislodgement	13	4	2	1	2	-	22
SVC Lead Dislodgement	14	18	8	1	1	3	45
All Complications	68	56	24	12	5	11	176

Table IB3-2: PCD Transvene System: Reported Complications Over Time - 2/1/93

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PCD Transvene System Reported Observations Over Time (Months)							
	≤ 1	1-3	3-6	6-9	9-12	12+	Total
Increased Defibrillation Requirements	2	1	2	-	3	-	8
Inappropriate VF Therapy Delivery	7	4	2	1	-	-	14
Inappropriate VT Therapy Delivery	12	13	12	11	6	5	59
Loss of Capture	3	3	-	-	2	4	12
Oversensing	13	11	10	9	4	7	54
Undersensing	-	-	-	-	-	-	-
Skin Erosion	-	1	-	-	-	-	1
Pocket Infection	2	5	2	-	-	-	10
Seroma	11	-	1	2	-	-	14
Hematoma	11	6	-	-	-	-	17
Pneumothorax	1	-	-	-	-	-	1
Pacemaker Syndrome	-	1	1	-	-	-	2
Perforation	-	-	-	-	-	-	-
Subclavian Vein Thrombosis	1	-	2	-	-	-	3
Lead Fracture	-	-	-	-	-	-	-
Subcutaneous Patch Crinkling	1	1	1	2	-	-	5
Early Device Explant	-	-	-	-	-	-	-
RV Lead Dislodgement	-	1	-	-	-	-	1
CS Lead Dislodgement	3	1	-	-	-	-	4
SVC Lead Dislodgement	-	4	1	2	-	-	7
All Complications	67	52	34	26	15	18	212

Table IB3-3: PCD Transvene System: Reported Observations Over Time - 2/1/93

Table IB3-4 contains a description of the lead dislodgements that have occurred in less than 30 days and in greater than 30 days. The ≤30 day period is defined as the acute period. This definition is consistent when compared to endocardial bradycardia lead terminology.

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PCD Transvene System Reported Complications/Observations Lead Dislodgements <30 days and >30 days				
Category	Complications		Observations	
	Num (% of Pts)		Num (% of Pts)	
	<30 days	>30 days	<30 days	>30 days
RV Lead Dislodgement n=741	14 (1.9%)	10 (1.3%)	0 (0)	1 (0.1%)
CS Lead Dislodgement n= 261	12 (4.6%)	10 (3.8%)	2 (0.8%)	2 (0.8%)
SVC Lead Dislodgement n=535	16 (3.0%)	29 (5.4%)	1 (0.2%)	6 (1.1%)
Total Lead Dislodgement n=757	42 (5.6%)	49 (6.5%)	3 (0.4%)	9 (1.2%)

Table IB3-4: PCD Transvene System: Lead Dislodgements <30/>30 days - 2/1/93

There have been a total of 58 lead dislodgements reported in patients at greater than 30 days. None of the lead dislodgements resulted in an ineffective therapy for a spontaneous VT of VF episode or patient death. Lead dislodgements were documented by fluoroscopic examination during electrophysiologic evaluation, chest x-ray obtained during routine follow-up, or during pacing/sensing threshold evaluation during routine follow-up. In 49 cases, reoperation was required to reposition the lead and reestablish an effective defibrillation lead system and in 9 cases repositioning of the lead was not required..

Lead dislodgements are not specific to the PCD Transvene System and have been reported with dual chamber pacemakers and the current market released implantable cardioverter defibrillator (ICD) system. The early history of dual chamber pacemakers witnessed a high lead dislodgement rate of at least 20% (Smyth, PND, et al. Permanent perivenous atrial sensing and pacing with a new J-shaped lead. J Thoracic Cardiovascular Surgery. 1976;72:565-570). Winkle, et al reported that the incidence of dislodgement of the superior vena cava spring leads with the current market release ICD system to be 6.3%. (Winkle, et al. Automatic Implantable Cardioverter-Defibrillator: Efficacy, Complications, and Survival in Patients with Malignant Ventricular Arrhythmias. JACC. June 1988; Vol.11, No.6:1278-86).

In an attempt to reduce the rate of lead dislodgement, modifications were made to the lead anchoring sleeve and a second sleeve was added to the lead. The sleeve was modified to increase the grip pressure on the lead body and two sleeves were provided on each lead at the time of manufacture. Analysis has been completed on 439 patients implanted with the Transvene system using leads that are packaged with two anchoring sleeves. **(NOTE: These 439 patients were enrolled in the Clinical Trial after 6-24-92 and are <u>not</u> included in the 757 patient population).** Table IB3-5 contains a data summary for the 439 patients. This group of patients has similar characteristics to the 757 patient population in most areas with a slightly higher percentage of patients with VT reported as the primary indication for implant than the 757 group of patients (61.1% vs 49.8%).

PCD Transvene System Data Summary of Patients with Two Anchoring Sleeves	
Number of Patients	439
Number, % Male Number, % Female	354 80.6% 85 19.4%
Mean Age	61.2 yrs
Primary Indication: SCD VT SCD/VT	 137 31.2% 268 61.1% 34 7.7%
Coronary Artery Disease	324 73.8%
Mean Ejection Fraction	32.5% (N=390)

Table IB3-5: PCD System Data Summary for Patients with Two Anchoring Sleeves - 2/1/93

Of these 439 patients, 292 have completed their 1 month follow-up and 195 have completed their 3 month follow-up and 17 have completed a 6 month follow-up. Since the introduction of the dual anchoring sleeve the incidence of lead dislodgement has been dramatically reduced. There has been 13 dislodgements in 10 patients for a per patient incidence of dislodgement of 2.3% (10/439).

U.S. versus International

Table IB3-6 contains a summary of the complications and observations for the U.S. patients versus the Internal patients.

PCD Transvene System
Reported Complications/Observations
By Category - U.S. and International

Category	Complications		Observations	
	Num (% of Pts)		Num (% of Pts)	
	U.S.	Int'l	U.S.	Int'l
Increased Defibrillation Requirements	6 (1.4%)	3 (1.0%)	4 (0.9%)	4 (1.3%)
Inappropriate VF Therapy Delivery	-	-	3 (0.7%)	11 (3.5%)
Inappropriate VT Therapy Delivery	-	-	19 (4.3%)	38 (12.1%)
Loss of Capture	4 (0.9%)	2 (0.6%)	4 (0.9%)	9 (2.9%)
Oversensing	-	-	31 (7.0%)	21 (6.7%)
Undersensing	-	-	-	-
Skin Erosion	1 (0.2%)	4 (1.3%)	1 (0.2%)	-
Pocket Infection	12 (2.7%)	12 (3.8%)	7 (1.6%)	3 (1.0%)
Seroma	4 (0.9%)	2 (0.6%)	1 (0.2%)	13 (4.1%)
Hematoma	4 (0.9%)	2 (0.6%)	6 (1.4%0	11 (3.5%)
Pneumothorax	1 (0.2%)	1 (0.3%)	1 (0.2%)	-
Pacemaker Syndrome	-	-	2 (0.5%)	-
Perforation	4 (0.9%)	2 (0.6%)	-	-
Subclavian Vein Thrombosis	1 (0.2%)	-	2 (0.5%)	1 (0.3%)
Lead Fracture	5 (1.1%)	4 (1.3%)	-	-
Subcutaneous Patch Crinkling	-	7 (2.2%)	3 (0.7%)	2 (0.6%)
Early Device Explant	4 (0.9%)	-	-	-
Total Lead Dislodgement	53 (12.0%)	33 (10.5%)	6 (1.4%)	6 (1.9%)
Total	99	72	90	119

Table IB3-6: PCD Transvene System: Reported Complications and Observations - 2/1/93

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4. Summary of Patient Deaths

The positive impact of implantable cardioverter defibrillator (ICD) therapy on sudden cardiac death mortality has been well documented in the medical literature. The use of device therapy for the treatment of recurrent ventricular arrhythmias has become an accepted and important clinical tool. An analysis of the sudden cardiac death and overall survival in the PCD Transvene System patient population was performed based on the categorization by the investigators and subsequently reviewed by the Clinical Event Review Committee (CERC).

For purposes of the clinical study, each of the patient deaths was categorized using the following definitions:

Non-Cardiac:	Deaths that occurred where the primary cause of death was determined to be non cardiac in nature, e.g. stroke, cancer, etc.
Cardiac:	Deaths that occurred where the primary cause of death was determined to be cardiac in nature.
Non-Sudden:	Deaths that occur greater than one hour after the onset of symptoms.
Sudden:	Deaths that occur within one hour of the onset of symptoms or where the death is unwitnessed. Sudden cardiac deaths were also categorized as being **Witnessed** or **Unwitnessed.**
Perioperative:	Deaths that occur within thirty days of implant.
System Related:	A death which results from a malfunction (operation not according to design specification) of a PCD System component, or as a result of a device induced arrhythmia, or an interaction between a PCD System component and the patient.
Procedure Related:	A death which occurs as a result of a procedure required to implant, follow or test a PCD System.

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All deaths and significant complications have been and will continue to be reviewed by a committee comprised of PCD Transvene System investigators and other physicians. Two committees (Clinical Event Review Committees) have been formed, one to review North American deaths and complications, and the other to review European clinical events. The primary purpose of these reviews was to determine whether the PCD System was related to the deaths or significant complications that have occurred and, if so, what changes may be required to prevent such events in the future.

There have been a total of 51 patient deaths reported in the PCD Transvene System patient population. Table IB4-1 summarizes how these patient deaths have been classified.

PCD Transvene System
Summary of Death Classifications
(n = 757)

Classifications	Number of Deaths
Sudden Cardiac	5
Non-Sudden Cardiac	31
Noncardiac	15
TOTAL	51

Table IB4-1: PCD Transvene System - Summary of Death Classifications - 2/1/93

None of the patient deaths were attributed to a malfunction of the PCD Transvene System.

Actuarial survival analysis on the PCD Transvene System was done on all patients who were either evaluated for implantation or in whom the device was implanted. Thus, the analysis is done from the perspective of **intention to treat.** Those patients in whom the PCD Device was OFF at the time of death or in whom no device was implanted **are** included in the survival analysis. Those patients that were screened for a PCD Transvene System but failed to receive a Transvene system and received a Medtronic Epicardial system are also included in this analysis.

Projected one year survival calculations for the various death classifications are provided in Table IB4-2. **The actuarial projections include perioperative deaths only in the calculation of one year survival from death due to all causes (shown in the row labelled Overall).** The perioperative death rate defined as deaths which occurred within thirty days of implant was 0.7% (5/757) which is considerably less than the perioperative mortality for the PCD System with Epicardial leads (5.3% - 39/742). Included in this table are the projected one year survival calculations for patients who ultimately received a PCD Transvene System (n = 757) and all patients that were screened for a PCD Transvene System (n = 854) regardless of implant outcome. The outcome of the 854 patients screened for a PCD Transvene System are described more fully in section IC2.

PCD Transvene System One Year Actuarial Survival		
	Received a Transvene System (N=757)	**Screened for a Transvene System (n=854)**
Sudden Cardiac Death	99.5%	99.4%
Non-Sudden Cardiac	96.2%	96.6%
All Cardiac	95.8%	96.1%
Noncardiac	98.1%	98.3%
Perioperative	0.7%	1.6%
Overall	93.3%	92.9%

Table IB4-2: PCD Transvene System - One Year Actuarial Survival - 2/1/93

The positive impact of the PCD Transvene System on patient mortality is clearly obvious from this analysis. The sudden cardiac death survival rate in this patient group is 99.5% for those in the patient group that received a Transvene System and 99.4% for those who were screened for a Transvene System. This is marked improvement when compared with the reported survival of similar patient groups treated with drug therapy alone of between 34% and 73% at one year.

Figure 1 contains the survival curve for sudden cardiac and total deaths for the 757 patients that received a PCD Transvene System.

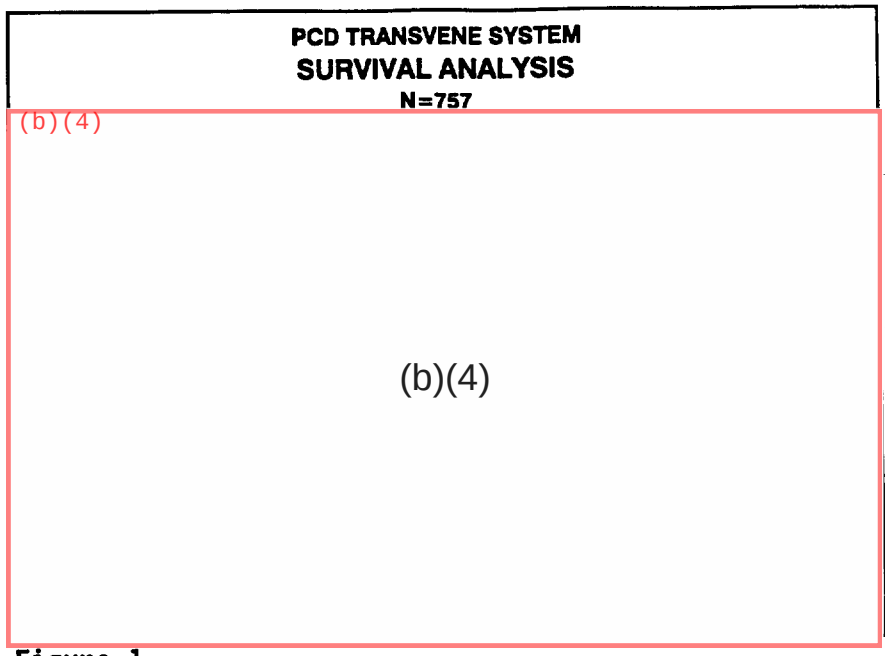

Figure 1

C. Specific Patient Populations

1. Clinical Experience By Primary Indication

Medtronic is requesting approval for use of the PCD Transvene System in the following patient population:

* Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or

* Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

Note: These patient indications are identical to those approved for the Medtronic PCD Epicardial System.

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Sudden cardiac death without recurrent VT (**SCD**) was the indication for implant in 37.1% of the patients, recurrent ventricular tachycardia without an episode of sudden cardiac death (**VT**) was the indication for implant in 49.8% of the patients, and sudden cardiac death and recurrent VT (**SCD/VT**) was the indication for implant in 13.1% of the patients.

The performance of the PCD Transvene System in these three groups are summarized in Table IC1-1.

In all three patient groups, coronary artery disease was the predominant heart disease and the patients exhibited moderate left ventricular dysfunction as demonstrated by mean ejection fractions of less than 40%. The mean LED at the time of implant was similar among the patient groups as was the mean DFT.

The overall efficacy in terminating spontaneous VT/VF episodes in the SCD patient group was 98.4%, in the VT patient group 98.3%, and in the SCD/VT group 99.1%. Thus, independent of the indication for implant, the PCD Transvene System was highly effective in terminating spontaneous episodes of VT/VF.

The one year sudden cardiac death survival rates for all groups was greater than 98.6%

This analysis indicates that the PCD Transvene System has performed safely and effectively in the indicated patient groups and should be approved for use in the indicated patient population.

PCD Transvene System Data Summary by Primary Indication				
	SCD	VT	SCD/VT	All Patients
# of Patients	281 (37.1%)	377 (49.8%)	99 (13.1%)	757
Number, % Male Number, % Female	212 75.4% 69 24.6%	309 82.0% 68 18.0%	89 89.9% 10 10.1%	610 80.6% 147 19.4%
Mean Age	56.8 yrs	61.2 yrs	60.0 yrs	59.4 yrs
Coronary Artery Disease	191 68.0%	292 77.5%	78 78.8%	229 72.2%
Mean Ejection Fraction	39.1% (N=259)	33.7% (N=339)	32.5% (N=90)	35.6% (N=688)
Defibrillation Pathway: Sequential Simultaneous Single	 201 71.5% 74 26.3% 6 2.2%	 295 77.6% 82 21.6% 3 0.8%	 76 76.8% 22 22.2% 1 1.0%	 574 75.3% 178 23.4% 10 1.3%
Mean LED	15.3J (N=264)	16.2J (N=351)	17.3J (N=87)	16.0J (N=702)
Mean DFT	14.0J (N=117)	15.5J (N=155)	13.9J (N=44)	14.8J (N=316)
Spontaneous VT: # of Patients # of Episodes % Success	 58 1157 99.2%	 206 7591 98.1%	 52 1279 99.0%	 316 10027 98.4%
Spontaneous VF: # of Patients # of Episodes % Success	 107 686 96.9%	 162 916 99.1%	 48 380 99.5%	 317 1982 98.4%
1 Year SCD Survival	100.0%	99.4%	98.6%	99.5%

Table IC1-1: PCD Transvene System Data Summary by Primary Indication - 2/1/93

2. Patients Not Meeting Implant Criteria

a. Overview

For purposes of the PCD Transvene System, the implant criteria was defined as successful VF termination at least 3 times in 4 attempts with the final lead configuration with an output energy of 18 Joules or less.

A total of 897 patients had an evaluation of a PCD Transvene System and are divided into the following groups: (1) patients who received a PCD Transvene System, (2) patients screened for a PCD Transvene System and received a PCD Epicardial System, and (3) patients who received a non-standard lead system. Figure 1 provides an overview of the outcome of these patients.

As can be seen, 88.6% (757/854) of the patients who were screened for a PCD Transvene System ultimately received a 3 lead system. Of these 757 patients, 71.7% (543 patients) met the recommended defibrillation implant criteria, which compares favorably with the predicted success rates published in the literature (Wilber et al). However, 28.3% (214/757) of the patients did not meet the recommended defibrillation efficacy implant criteria and still received the PCD Transvene System.

Ninety-seven (97) patients (10.8%) were screened for a Transvene lead system but received an epicardial system. Forty-three (43) patients (4.8%) were screened for a Transvene lead system but received an non-standard system.

PCD TRANSVENE SYSTEM IMPLANT EVALUATION

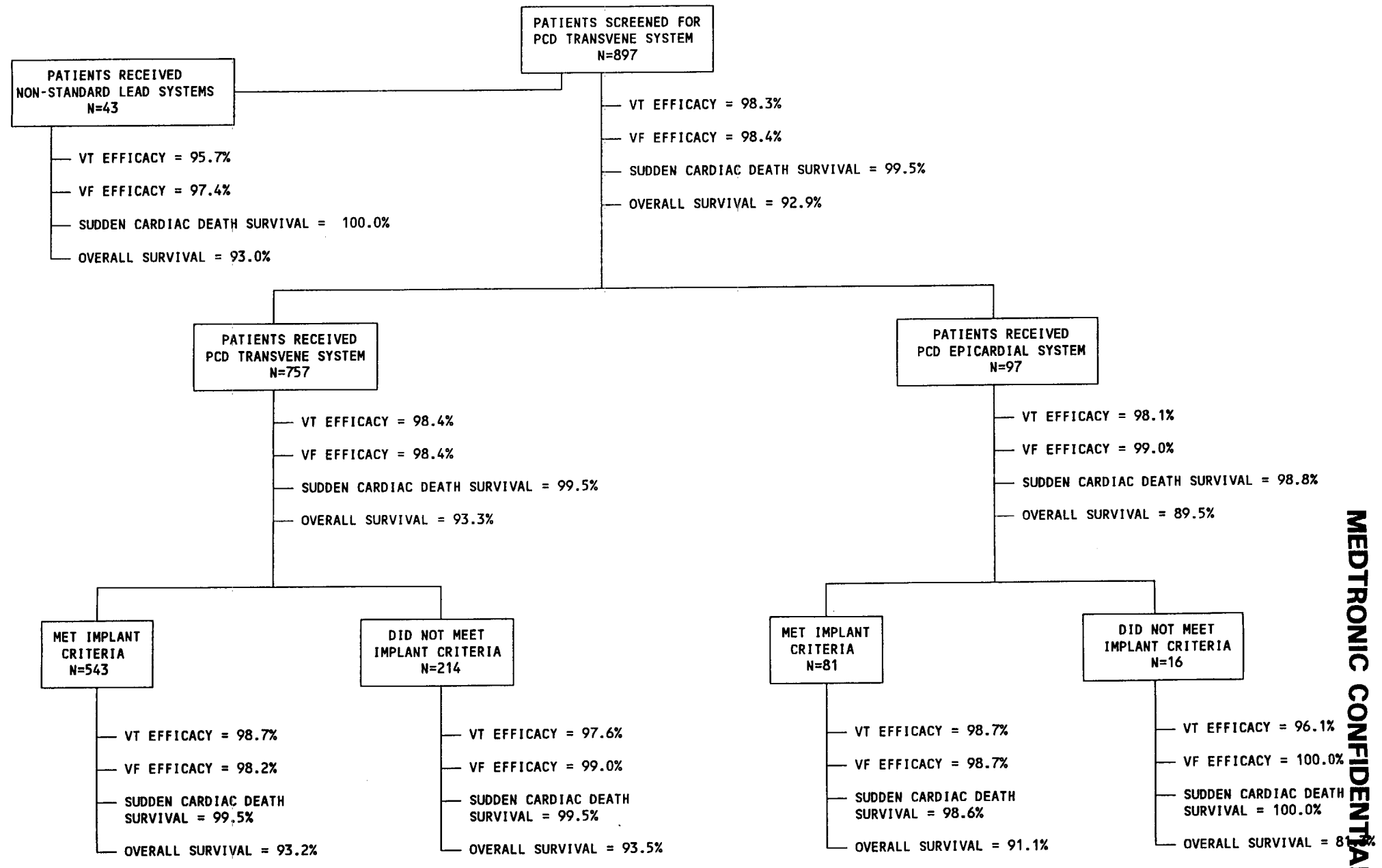

Figure 1: Patients Screened for a Transvene System

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b. Reasons for Not Meeting Implant Criteria

The physician's justification for implanting the PCD Transvene System despite not meeting the recommended defibrillation implant criteria are presented in Table IC2-1. As noted previously, the patients not meeting implant criteria (N=214) were divided into three groups (1) Successful defibrillation at an energy level of equal to or less than 24 Joules (79.4% of the patients); (2) Difficult to induce VF (11.2% of the patients); and (3) Implant procedure terminated due to poor patient condition (9.4% of the patients).

PCD Transvene System Reasons for Not Meeting Implant Criteria Physician Justification	
Reason	**Number of Patients (% of Total)**
Success at $\leq$ 24 Joules	170 (79.4%)
Difficult/Unable to Induce VF	24 (11.2%)
Patient Condition	20 (9.4%)
Total	214

Table IC2-1: PCD Transvene System: Physician Justification for Not Meeting Implant Criteria - 2/1/93

Table IC2-2 contains the patient characteristics of the patients not meeting implant criteria presented by physician justification.

PCD Transvene System Patients Not Meeting Implant Criteria by Justification			
	Success at ≤ 24 Joules	Difficult/Unable to Induce VF	Patient Condition
Number of Patients	170	24	20
Mean Follow-Up	9.6 months	9.8 months	14.4 months
Male Female	151 (88.8%) 19 (11.2%)	19 (79.2%) 5 (20.8%)	18 (90.0%) 2 (10.0%)
Mean Age	59.8 yrs	57.5 yrs	60.0 yrs
Indication SCD VT SCD/VT	 63 (37.1%) 77 (45.3%) 30 (17.6%)	 6 (25.0%) 13 (54.2%) 5 (20.8%)	 3 (15.0%) 9 (45.0%) 8 (40.0%)
Cardiovascular History CAD Cardiomyopathy	 132 (77.7%) 58 (34.1%)	 19 (79.2%) 2 (8.3%)	 14 (70.0%) 5 (25.0%)
Mean EF	32.7%	37.7%	36.8%
NYHA Class I II III IV	 45 (27.6%) 90 (55.2%) 24 (14.7%) 4 (2.5%)	 5 (22.7%) 14 (45.5%) 7 (31.8%) 0	 2 (10.0%) 10 (70.0%) 4 (20.0%) 0

Table IC2-2: PCD Transvene System: Patient Characteristics by Justification - 2/1/93

Table IC2-3 contains the clinical outcomes the patients not meeting implant presented by physician justification.

PCD Transvene System Patients Not Meeting Implant Criteria 170 Patients with Successful Defibrillation at 24J			
	Success at ≤ 24 Joules	Difficult/Unable to Induce VF	Patient Condition
Number of Patients	170	24	20
Spontaneous VT Episode Efficacy	2206/2240 98.5%	129/159 81.1%	372/376 98.9%
Spontaneous VF Episode Efficacy	522/525 99.4%	100/102 98.0%	48/50 96.0%
Number of Patient Deaths	10/170 5.9%	1/24 4.2%	2/10 10%
Perioperative Mortality	1/170 0.6%	0	0
One Year Survival			
Sudden Cardiac	99.4%	100.0%	100.0%
Non-Sudden Cardiac	98.7%	100.0%	85.5%
All Cardiac	98.1%	100.0%	85.5%
Noncardiac	96.3%	100.0%	100.0%
Overall	94.0%	100.0%	85.5%

Table IC2-3: PCD Transvene System: Patients Not Meeting Implant by Justification - Clinical Outcome - 2/1/93

In summary, the physician made an appropriate judgement to implant the PCD Transvene system based on the clinical outcome of the patient especially those patients with a 10 Joule safety margin. Their outcome is clinically equivalent to that of the entire 757 patient population.

1) **Success at $\leq$ 24 Joules**

There were 170 patients in whom the PCD Transvene System was implanted with a defibrillation safety margin of at least 10 Joules. Table IC2-4 provides an overview of these patients clinical experience.

These data indicate that the final implanted PCD Transvene System was evaluated and significant attempts were made to meet the recommended implant criteria. In most of these patients (79.4%), a safety margin of 10 Joules was obtained between the successful defibrillation energy (24 J or less) for ventricular fibrillation and the maximum output of the PCD Device (34 J). The investigators decided in certain circumstances that this was appropriate demonstration of device effectiveness and that the PCD Transvene System could be implanted.

Of these patients, 159 (93.5%) have had VT or VF induced at a chronic follow-up visit and in each case, VT or VF was successfully terminated by the PCD Transvene System. In addition, 65 patients (38.2%) have experienced a spontaneous VF episode with an overall efficacy of 99.4%.

Thus, the clinical outcome in these patients was not adversely affected by not meeting implant criteria since their spontaneous VF episode efficacy was 99.4% and the one year sudden cardiac death actuarial survival was also 99.4%. The duration of follow up, an average of 9.7 months, is similar to that of the entire patient group (11.7 months).

PCD Transvene System Patients Not Meeting Implant Criteria 10J Safety Margin Provided	
Number of Patients	170
Lowest Energy of Defibrillation	
1 Success with 10J Safety Margin	87
2 Success with 10J Safety Margin	58
3 Success with 10J Safety Margin	18
> 3 Success with 10J Safety Margin	7

Table IC2-4: PCD Transvene System: Patients Not Meeting Implant Criteria with 3/4 Successes at ≤ 24 Joules Clinical Experience - 2/1/93

2) Difficult or Unable to Induce VF

There were 24 patients who did not meet the recommended PCD Transvene System implant criteria because at least three episodes of VF were not induced at the time of implant. Of these, 15 patients had ventricular tachycardia induced and successfully reverted. The remaining 9 patients had ventricular flutter induced and successfully reverted. In all 24 patients, the lowest successful energy was equal to or less than 18 Joules.

The indication for implant was sudden cardiac death (SCD) in 6 patients (25%), recurrent ventricular tachycardia (VT) in 13 patients (54.2%) and sudden cardiac death associated with recurrent ventricular tachycardia (SCD/VT) in 5 (20.8%) patients. Thus the majority of the patients, 75%, had documented recurrent ventricular tachycardia as part of their ventricular tachyarrhythmia history. Eight of these patients (33.0%) were on Amiodarone therapy which may have contributed to the inability to induce VF.

Of the 24 patients who did not meet the recommended PCD Transvene System implant criteria because at least three episodes of VF were not induced at the time of implant, 13 patients (54.2%) have experienced a spontaneous VF episode and 21 patients (87.5%) have had VT or VF induced

during a chronic follow-up. In all cases, VF was successfully reverted by the PCD Transvene System.

There has been one reported patient death (b)(6) in this patient group (at xx months) with a resultant one year sudden cardiac death and overall actuarial survival of 100%.

3) **Patient Condition**

There were 20 patients in whom the implant procedure was terminated due to poor patient condition. These patients received a PCD Transvene System without at least a 10 Joule defibrillation safety margin. The implant circumstances of these patients are summarized as follows:

- At least one successful defibrillation was obtained at an energy level greater than 24 Joules but less than 34 Joules (**N = 11 patients**);
- Multiple inductions of VT were performed and successfully reverted with an energy level of 18 Joules or less. However, induced VF was not successfully reverted by an energy level of less than or equal to 34 Joules (**N = 6 patients**); and
- Physician elected to terminate the procedure due to the patient's condition before inductions with the final implanted lead configuration were performed (**N = 3 patients**).

The mean ejection fraction of this group was 26.9%, indicating more severe underlying cardiovascular disease, and may have contributed to the physicians decision to terminate the implant procedure prior to meeting implant criteria. This group had a mean of 6.8 VF inductions, 2.2 lead configurations evaluated and a mean duration of VT/VF for the implant procedure of 220 total seconds. The circumstances of the implant procedures, mainly the duration of induced ventricular tachyarrhythmia and associated hemodynamic compromise, limited the number of inductions that could be performed and whether the recommended implant criteria could be met.

Of these 20 patients, VT or VF has been induced at a chronic follow-up visit in 16 patients (80%) and in all cases successful defibrillation with the implanted PCD Transvene System was documented.

The overall spontaneous VF episode efficacy for this patient group was 96.0%. However, examination of events indicated that one patient experienced multiple episodes of atrial fibrillation that was detected as VF and in whom all four programmed VF therapies were ineffective. This patient's antiarrhythmic drug therapy was modified and there were no further reports of ineffective therapies.

Thus there have been no patients who have experienced an actual spontaneous VF episode where all four programmed VF therapies failed to terminate the episode.

There have been two reported patient deaths, Patient ID (b)(6) which was classified as non-sudden cardiac secondary to end stage heart failure and Patient ID (b)(6) which was also classified as non-sudden cardiac. The one year sudden cardiac death survival in this patient population is 100% while the overall one year survival was 85.5%. This lower overall one year survival may be due to the lower mean ejection fraction of this patient group.

The VF Therapy efficacy and SCD survival in these twenty patients was not adversely affected by not meeting implant criteria since there was no reports of failure to terminate a spontaneous VF episode and the overall one year sudden cardiac death survival was 100%.

c. **Complications and Observations: Patients Not Meeting Implant Criteria**

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following previously described definitions:

COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

Of the 170 patients with successful defibrillation at 24 Joules, as of February 1, 1993, there have been a total of 41 complications reported in 33 patients and 34 observations reported in 31 patients in the PCD Transvene System patient population. Thus, 19.4% (33/170) of the patients had a clinical event reported which was categorized as a complication and 18.2% (31/170) of the patients had a clinical event reported which was categorized as an observation. The percent of patients with complications reported in the overall population of 757 patients was 19.4% (147/757), the same percentage as in this subgroup of 170. There were 23.8% (180/757) of the patients in the overall population with reported observations, a slightly higher percentage than in this subgroup of 170 patients.

Of the 24 patients that did not meet the implant criteria due to difficulty or inability to induce sustained VF, as of February 1, 1993, there have been a total of 4 complications reported in 4 patients and 10 observations reported in 8 patients in the PCD Transvene System patient population. Thus, 16.7% (4/24) of the patients had a clinical event reported which was categorized as a complication and 30.0% (8/24) of the patients had a clinical event reported which was categorized as an observation.

Of the 20 patients that did not meet the implant criteria due to patient condition, as of February 1, 1993, there have been a total of 6 complications reported in 4 patients and 7 observations reported in 5 patients in the PCD Transvene System patient population. Thus, 20.0% (4/20) of the patients had a clinical event reported which was categorized as a complication and 25.0% (5/20) of the patients had a clinical event reported which was categorized as an observation.

Table IC2-5 and IC2-6 summarizes the reported PCD Transvene System complications and observations by category in these 3 patient groups, respectively. The reported complications and observations are recognized clinical events that may occur with **any** of the current ICD devices. These complications and observations are discussed in the PCD device and Transvene manual. **None of the reported complications or observations have resulted in a patient death.**

PCD Transvene System Reported Complications Patients Not Meeting Implant Criteria by Justification			
Justification	**Success at ≤ 24 Joules n=170**	**Difficult/Unable to Induce VF n=24**	**Patient Condition n=20**
	Num (% of Pts)	Num (% of Pts)	Num (% of Pts)
Increased Defibrillation Requirements	5 (2.9%)	-	-
Inappropriate VF Therapy Delivery	-	-	-
Inappropriate VT Therapy Delivery	-	-	-
Loss of Capture	-	-	-
Oversensing	-	-	-
Undersensing	-	-	-
Skin Erosion	-	1 (4.2%)	1 (5.0%)
Pocket Infection	3 (1.8%)	-	3 (15.0%)
Seroma	2 (1.2%)	-	-
Hematoma	1 (0.6%)	-	-
Pneumothorax	-	-	-
Pacemaker Syndrome	-	-	-
Perforation	1 (0.6%)	-	-
Subclavian Vein Thrombosis	1 (0.6%)	-	-
Lead Fracture	2 (1.2%)	-	1 (5.0%)
Subcutaneous Patch Crinkling	2 (1.2%)	-	-
Early Device Explant	1 (0.6%)	-	-
Total Lead Dislodgement	23 (13.5%)	3 (12.5%)	1 (5.0%)
Total	**41**	**4**	**6**

Table IC2-5: PCD Transvene System: Reported Complications - By Justification - 2/1/93

PCD Transvene System Reported Observations Patients Not Meeting Implant Criteria by Justification			
Justification	Success at ≤ 24 Joules n=170	Difficult/Unable to Induce VF n=24	Patient Condition n=20
	Num (% of Pts)	Num (% of Pts)	Num (% of Pts)
Increased Defibrillation Requirements	-	1 (4.2%)	-
Inappropriate VF Therapy Delivery	-	-	1 (5.0%)
Inappropriate VT Therapy Delivery	10 (5.9%)	3 (12.5%)	2 (10.0%)
Loss of Capture	5 (2.9%)	1 (4.2%)	-
Oversensing	7 (4.1%)	4 (16.7%)	-
Undersensing	-	-	2 (10.0%)
Skin Erosion	-	-	-
Pocket Infection	2 (1.2%)	-	-
Seroma	3 (1.8%)	-	-
Hematoma	2 (1.2%)	1 (4.2%)	1 (5.0%)
Pneumothorax	-	-	-
Pacemaker Syndrome	-	-	-
Perforation	-	-	-
Subclavian Vein Thrombosis	1 (0.6%)	-	1 (5.0%)
Lead Fracture	-	-	-
Subcutaneous Patch Crinkling	1 (0.6%)	-	-
Early Device Explant	-	-	-
Total Lead Dislodgement	3 (1.8%)	-	-
Total	34	10	7

Table IC2-6: PCD Transvene System: Reported Observations - By Justification - 2/1/93

d) Comparison of Patients Not Meeting Implant Criteria Versus those Patients who Met the Implant Criteria

Table IC2-7 provides a comparison of patient characteristics between patients who met the PCD Transvene System implant criteria and those patients who did not meet the implant criteria but still received the PCD Transvene System. The characteristics of the 97 patients that were screened for a PCD Transvene system and received an Epicardial system if also provided.

PCD Transvene System
Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria

Patient Characteristics

Data	Met Criteria	Did Not Meet Criteria	Received EPI
Number of Patients	543	214	97
Mean Follow-Up	12.3 months	10.1 months	12.3 months
Male*	422 (77.7%)	188 (87.9%)	88 (90.7%)
Female	121 (22.35)	26 (12.1%)	9 (9.3%)
Mean Age	59.4 yrs	59.6 yrs	58.0 yrs
Indication			
SCD	209 (38.5%)	72 (33.6%)	33 (34.0%)
VT	278 (51.2%)	99 (46.3%)	52 (53.6%)
SCD/VT	56 (10.3%)	43 (20.1%)	12 (12.4%)
Cardiovascular History			
CAD	396 (72.9%)	165 (77.1%)	74 (76.3%)
Cardiomyopathy	173 (31.9%)	65 (30.4%)	28 (28.9%)
Mean EF	36.3%	33.7%	32.6%
NYHA Class			
I	164 (30.9%)	53 (25.8%)	28 (29.5%)
II	278 (52.4%)	114 (56.6%)	52 (54.7%)
III	82 (15.4%)	34 (16.6%)	13 (13.7%)
IV	7 (1.3%)	4 (2.0%)	2 (2.1%)
Number ON Drugs at Implant	223 (41.1%)	97 (45.3%)	40 (41.2%)
Number ON Amiodarone	78 (14.4%)	38 (17.8%)	19 (19.6)

Table IC2-7: PCD Transvene System: Patients Meeting Implant Criteria vs Not Meeting Implant Criteria - Comparison of Pt Characteristics - 2/1/93

Statistical analysis was completed on the 543 patients that net implant criteria versus the 214 patients that did not meet criteria. Statistical analysis indicated three significant differences between these two patient groups - patient sex, indication for implant and mean ejection fraction.

Patients not meeting implant criteria had a statistically higher percentage of patients who were male ($p = 0.002$). This difference reflects that the majority of patients with coronary disease with concomitant life threatening ventricular arrhythmias are males.

Analysis indicated the patients not meeting the implant criteria had a statistically higher percentage of patients whose primary indication for implant was sudden cardiac death associated with recurrent ventricular tachycardia ($p = 0.002$). This difference reflects the physicians use of the PCD Transvene System.

Finally, patients who did meet the implant criteria had a statistically lower mean ejection fraction ($p = 0.0342$) which reflects a higher degree of underlying cardiovascular disease in these patients.

It should be noted, that none of these differences should be used as predictors for patients who should be screened for a PCD Transvene System.

Implant data obtained in these two patient groups is presented in Table IC2-8. As would be expected the patients not meeting the implant criteria had higher mean DFT and LED values when compared to the patients who did meet the implant criteria. However, the mean DFT (18.8J) and LED (19.5J) values obtained in patients not meeting implant criteria provided at least a 10 Joule defibrillation safety margin between the successful energy and the maximum output of the PCD Device (34J) in nearly all (97.4%) of the patients.

PCD Transvene System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Implant Data		
Data	**Meeting Criteria**	**Not Meeting Criteria**
Number of Patients	543	214
Mean Number of Inductions	7.0	8.2
Number of Configurations	2.0	2.7
Mean DFT	13.4J	18.8J
Mean LED	14.8J	19.5J
Implanted Lead System		
RV-SVC-SQ	351 (64.6%)	145 (67.8%)
RV-CS-SQ	159 (29.3%)	63 (29.4%)
RV-CS-SVC	33 (6.1%)	6 (2.8%)
Defibrillation Pathway		
Sequential	414 (75.7%)	160 (74.4%)
Simultaneous	127 (23.2%)	51 (23.7%)
Single	6 (1.1%)	4 (1.9%)

Table IC2-8: PCD Transvene System: Patients Not Meeting Implant Criteria versus Patients Meeting Implant Criteria - Comparison of Implant Data - 2/1/93

When the mean number of inductions and the mean number of configurations tested of 8.2 and 2.7, respectively, for those patients that did not meet the implant criteria is compared to those that did meet the implant criteria, 7.0 and 2.0, it is apparent the implanting physicians did induce more VF and were more likely to try more than 1 lead configuration in an attempt to meet the implant criteria.

In order to determine if the patient's not meeting implant criteria had higher risk for morbidity and mortality, a comparison of their clinical outcome was made with those patients who did meet the implant criteria. This comparison is provided in Table IC2-9.

PCD Transvene System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Implant Data		
Data	**Meeting Criteria**	**Not Meeting Criteria**
Number of Patients	543	214
Spontaneous VT Episode Efficacy	98.7%	97.6%
Spontaneous VF Episode Efficacy	98.2%	99.0%
Number of Patient Deaths	37	14
Perioperative Mortality	0.7%	0.5%
One Year Survival		
Sudden Cardiac	99.5%	99.5%
Non-Sudden Cardiac	95.8%	97.2%
All Cardiac	95.4%	96.7%
Noncardiac	98.5%	97.1%
Overall	93.2%	93.5%

Table IC2-9: PCD Transvene System: Patients Not Meeting Implant Criteria versus Patients Meeting Implant Criteria - Comparison of Clinical Outcome - 2/1/93

The two patient groups had similar efficacy in the treatment of spontaneous VT/VF episodes. Importantly, in the patient population who did not meet the implant criteria there were no patients who experienced actual spontaneous VF episodes where all programmed PCD Device therapies failed to terminate the episode.

Five patients experienced 7 episodes in which the PCD® Device was ineffective in terminating a spontaneous episode of VF despite delivery of all four programmed VF therapies. Three patients had 5 reported ineffective VF spontaneous episodes that were due to sinus tachycardia or atrial fibrillation with rapid ventricular response rather than VF. Reprogramming and pharmacologic intervention resolved these problems.

Two patients experienced 2 episodes in which the PCD detected the episodes as VF but were actually episodes due

to extraordinary circumstances. The first patient (b)(6) had incessant episodes of fast VT (cycle length 280 ms) that were eventually resolved by drugs. The second patient (b)(6) was in the hospital and there was an episode of VF detected by the PCD and therapy was delivered. However, the device was interrogated before termination of the episode was detected by the PCD. There was external intervention (transthoracic defibrillation) associated with the terminal event. However, the patient ultimately expired. The device was not interrogated again.

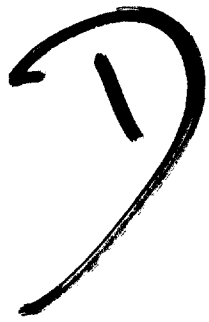
Eighteen patients experienced 68 episodes in which the PCD Device was ineffective in terminating a spontaneous episode of VT despite delivery of all four programmed VT therapies. Nine patients experienced 44 ineffective episodes that were due to sinus tachycardia or atrial fibrillation/flutter (SVT) with a rapid ventricular response that had been detected as VT. These episodes were resolved with either modification of programmed parameters or of antiarrhythmic drug therapy. It should be noted that the PCD Device responded appropriately based on the programmed detection parameters.

The remaining 24 episodes occurred in 8 patients in which the programmed VT therapies were ineffective in terminating a spontaneous VT episode. **No patient deaths occurred as a result of ineffective VT therapy.** Reprogramming and pharmacologic intervention resolved these events.

There was no difference in the one year sudden cardiac survival or the overall survival in the two groups although follow-up was shorter for patients not meeting implant criteria (10.1 vs 12.3 months). This indicates, that despite not meeting the implant criteria these patients were not at higher risk of sudden cardiac death.

Conclusion

In conclusion, 214 patients received the PCD Transvene System despite not meeting the recommended implant criteria. These 214 patients are divided into the following groups:



- successful defibrillation of VF at 24 Joules or less (170/214),
- difficult to induce at least three episodes of VF at implant (24/214), and
- worsening patient condition which prevented further inductions (20/214).

It should be noted that 91% (194/214) of the patients not meeting the recommended implant criteria had at least one successful termination of induced ventricular tachyarrhythmia (VT, VFlutter or VF) at 24 Joules or less. Additionally, their clinical outcome, especially in the 170 patients with successful defibrillation of VF at $\leq$24 Joules is similar and is part of the support to request changing the implant criteria to the following:

* Two consecutive successful defibrillations with the final lead configuration with a stored output of 24 Joules or less; or

* Three successful defibrillations in four attempts with the final lead configuration at a stored output energy of 24 J or less.

D. System Comparison

The efficacy and safety of implantable cardioverter defibrillator (ICD) therapy for recurrent ventricular tachycardia (VT) and ventricular fibrillation (VF) has been well established. The Ventak-P Epicardial System provides cardioversion and defibrillation therapy for VT and hemodynamically unstable VT. However, this type of therapy may not be optimal for patients with stable, well tolerated VT that is amenable to antitachycardia pacing due to the pain associated with cardioversion shock therapy. The need to incorporate programmability, multiple detection and therapeutic options has lead to the development of the PCD Device.

However, the Ventak-P Epicardial System and PCD Epicardial System are implanted only with a defibrillation lead system requiring a thoracotomy. The PCD Transvene System allows the implantation of an ICD System without the potential increased perioperative morbidity and mortality associated with a thoracotomy. This allows the application of ICD therapy in patients who may not otherwise be candidates for this type of therapy.

In the PCD Transvene System PMA Application a comparison of the PCD Transvene System clinical experience was made to both the Ventak-P Epicardial System and the PCD Epicardial System. (Reference: Clinical Experience Report Section X, Comparison to AICD Clinical Results and Section XI, Comparison to PCD Epicardial System Clinical Results). A comparison to the Ventak-P Epicardial System was done because this was the most similar FDA approved ICD System available at the time of the original submission. A comparison to the PCD Epicardial System was done since this system incorporated the same tiered therapy ICD Device as well as being a concurrent clinical study using the same protocol and clinical investigators.

The comparison between the Ventak-P Epicardial System and the PCD Transvene System was limited in scope due to the limited availability of clinical data from the Ventak-P Epicardial System Summary of Safety and Effectiveness, but included patient characteristics, implant defibrillation thresholds, incidence of spontaneous VT/VF episodes, incidence of complications and one year actuarial survival.

The comparison between the PCD Transvene System and the PCD Epicardial System included patient characteristics, implant data, implant defibrillation thresholds, programmed parameter status, spontaneous VT/VF episode efficacy, incidence of complications and observations and one year actuarial survival.

1. **Comparison to AICD (Ventak-P) Epicardial System**

   The current AICD (Ventak-P) Epicardial System is implanted only with a defibrillation lead system requiring a thoracotomy. The PCD Transvene System allows the implantation of an implantable cardioverter defibrillator (ICD) system without the potential increased perioperative morbidity and mortality associated with a thoracotomy. This allows the application of ICD therapy in patients who may not otherwise be candidates for this type of therapy. Though the PCD Transvene System will have complications and observations that are specific to the lead system, the overall performance should be at least equivalent to that reported with the current AICD Epicardial System.

This section provides a comparison of the PCD Transvene System clinical experience to that of the reported AICD Epicardial System clinical experience. The following areas will be discussed:

- Patient characteristics
- Clinical performance
- Survival analysis

For purposes of comparison, the Ventak-P Epicardial System patient population described in the Summary of Safety and Effectiveness Data (PMA Application Number P890061) dated May 2, 1991 will be used. A copy of this summary was obtained through the Freedom of Information Act.

a. Patient Characteristics

In comparing the clinical experience with the PCD Transvene System to the reported Ventak-P Epicardial System clinical experience, it is important to determine that the patients who received the device are comparable.

The characteristics of the patients receiving the PCD Transvene System were compared to the characteristics of patients discussed in the Ventak-P Summary of Safety and Effectiveness Data and are presented in Table ID1-1.

PCD Transvene System Comparison of Patient Characteristics PCD versus AICD		
	PCD	**Ventak-P**
Number of Patients	757	292
Mean Follow-Up Time	11.7 months	6.8 months
% Males **% Females**	610 (81%) 147 (19%)	231 (79%) 61 (21%)
Mean Age	59.4 years	61.5 years
Primary Indication: **SCD** **VT** **SCD/VT**	 281 (37%) 377 (50%) 99 (13%)	 49 (16%) 169 (59%) 73 (25%)
Coronary Artery Disease	561 (74%)	228 (78%)
Mean Ejection Fraction	35.6%	34%
Drug Therapy at Implant	42%	45.0%
Concomitant Surgery	0%	18.0%

Table ID1-1: Comparison of Patient Characteristics, PCD versus Ventak-P 2/1/93

The two patient groups are comparable in mean age and mean ejection fraction. Both groups had moderately depressed left ventricular function demonstrated by the mean ejection of 35.6% for the PCD Transvene System patient group and 34% for the Ventak-P Epicardial System patient group.

Analysis indicated that no statistical differences between the PCD Transvene System and Ventak-P Epicardial System patient populations except in the category of patient indication. There are more patients that had Sudden Cardiac Death as the primary indication in the PCD Transvene population than in the AICD population ($p = 0.001$).

b. Clinical Characteristics

Areas of clinical performance that were compared were implant defibrillation thresholds, incidence of spontaneous VT/VF events, incidence of

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complications and patient survival. These specific areas were selected in order to evaluate the system performance in the two patient populations.

1) Implant Defibrillation Thresholds

For the purposes of the PCD Transvene System clinical study, determination of defibrillation threshold was not mandatory. However, the preferred method of evaluating defibrillation efficacy was to determine the defibrillation threshold using a testing sequence of 18J, 15J, 10J, 5J with a failure at any level causing a return to 18 J for the remaining attempts. For the purposes of this report a defibrillation threshold was defined as the energy at the lowest successful defibrillation attempt, provided a patient had a failure below their lowest defibrillation success or a success at $\leq$ 5J. The rhythm treated must have been VF to be included in the analysis.

It should be noted, that it was expected that the PCD Transvene System would have a higher mean defibrillation threshold as compared to a traditional epicardial defibrillation lead system. In a epicardial system, the increased electrode surface area would theoretically decrease defibrillation requirements.

A total of 316 patients had a defibrillation threshold determined at the time of PCD device implant. The mean defibrillation threshold (DFT) for all lead systems was 14.8J. The recommendation for VF Therapy #1 is to program the stored energy to twice the implant DFT or 18 Joules, whichever is greater. Thus an adequate defibrillation safety margin was provided when following the VF therapy programming recommendations.

In the Ventak-P Epicardial System, the mean defibrillation threshold at implant was 13.4J. Thus the two systems had similar defibrillation thresholds at implant despite the fact that one system utilized an epicardial defibrillation lead system while the other utilized a transvenous defibrillation lead system.

These data indicate that the PCD Transvene System had comparable implant defibrillation threshold performance when compared to the reported Ventak-P Epicardial System clinical experience.

2) Incidence of Spontaneous VT/VF Episodes

The incidence of spontaneous VT/VF episodes in the Ventak-P Epicardial System and PCD Transvene System patient population was evaluated by utilizing the stored episode information provided by both devices.

In the Ventak-P device, the total number of shocks delivered to the patient is provided via interrogation of the device. The PCD device provides information on the total number of VT and VF episodes detected by the PCD device and the total number of VT and VF episodes successfully treated by the PCD device as well as the number of VT/VF episodes where the PCD device was ineffective. In addition, the last 20 intervals of the last episode satisfying detection criteria along with the first 10 intervals after the last therapy delivered are recorded by the device. These data assist the physician in evaluating the frequency of VT/VF episodes, the efficacy of the PCD device programmed parameters and the need for reprogramming.

In the Ventak-P Epicardial System experience of 292 patients with a mean follow-up of 6.8 months, 137 (46.9%) received a device countershock in response to a spontaneous

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ventricular tachyarrhythmia episode as defined by the Ventak-P Device detection criteria.

In the PCD Transvene System experience of 757 patients with a mean follow-up of 11.7 months, 458 patients (60.5%) have received device therapy in response to a spontaneous ventricular tachyarrhythmia episode as defined by the PCD Transvene System detection criteria.

A total of 10,027 spontaneous VT and 1982 spontaneous VF episodes have been recorded by the PCD device episode counters. Of the 9864 successfully treated spontaneous VT episodes, 91.4% were treated with one of the programmed antitachycardia pacing therapies incorporated in the PCD device. The clinical benefit of tiered therapy is the reduction of delivery of high energy shocks for the treatment of stable recurrent ventricular tachycardia that may be responsive to antitachycardia pacing.

3) Incidence of Complications

Table ID1-2 provides a comparison of reported complications and observations. The AICD clinical experience data is from the Winkle, et al Long Term Outcome with Automatic Implantable Cardioverter-Defibrillator; JACC, May 1989; 13(6); 135-161. This article was selected because it provides a detailed clinical complication experience on a large patient population, 270 patients. Note that the percentage reported in the PCD Transvene System includes **both complications and observations**. In the following table, the complications are reported for the categories of Failure to Cardiovert/Defibrillate, Pocket Infection, and Erosion. Observations are reported in the Inappropriate/Problematic VT/VF Therapy Delivery category.

PCD Transvene System Comparison of Complication/Observation Rates PCD versus AICD		
Category	**PCD%**	**AICD%**
Fail to Cardiovert/Defibrillate	2.3%	4.1%
Inappropriate/Problematic VT/VF Therapy Delivery	9.6%*	20%
Pocket Infection (explant)	2.9%	2.2%
Erosion	0.8%	0.7%

* Includes Observations only; there were no Complications in this category.

Table ID1-2: Comparison of Complication/Observation Rates: PCD Transvene System vs AICD Epicardial System - 2/1/93

The incidence of failure to cardiovert and/or defibrillate was lower in the PCD Transvene System patient population. The instances of failure to cardiovert and/or defibrillate in the PCD Transvene System patient population were associated with increased defibrillation requirements during induced episodes, none of which resulted in patient death.

The failures to cardiovert/defibrillate reported in the Winkle, et al article were associated with patch dislodgement, patch crinkling, lead conductor fracture and elevated defibrillation thresholds.

The incidence of inappropriate/problematic VT/VF therapy delivery was lower in the PCD Transvene System patient population. This is to be anticipated since the device incorporates independently programmable detection algorithms for VT and VF. The reasons for inappropriate VT/VF therapy delivery included sinus tachycardia being detected as VT or VF and atrial fibrillation with rapid ventricular response being detected as VT or VF.

The overdetection circumstances reported in Winkle, et al were nonsustained VT, VT, sinus

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tachycardia, atrial fibrillation with rapid ventricular response, sensing lead fracture and pacemaker interaction. The patients with VT complained of receiving multiple shocks with limited or no symptoms. The incorporation of antitachycardia pacing in the PCD device decreases the need for delivery of cardioversion shocks for the termination of stable VT and increases patient acceptance of ICD therapy.

In the Winkle, et al experience all patients with pocket infection had the devices explanted. In the PCD Transvene System experience, the incidence of device explant secondary to pocket infection was 2.9% which was comparable to Winkle's article.

Thus, the incidence of complications and observations in the categories of ineffective VT/VF therapies, infection requiring explant and erosion was similar to that of the AICD Epicardial System. The incidence of inappropriate delivery of therapy is lower in the PCD Transvene System experience than in the AICD Epicardial System experience, which is clinically significant.

This analysis indicates that the PCD Transvene System offers clinical advantages in reducing the need for a thoracotomy for implantation and reducing the number of shocks due to successful antitachyarrhythmia pacing and inappropriate therapy incidence.

c. Survival Analysis

The Ventak-P Epicardial System produced by Cardiac Pacemaker, Inc, has obtained market approval from the U.S. FDA to date. While there are important differences in the function of the Ventak-P Epicardial System and the PCD Transvene System, the Ventak-P Epicardial system is the most comparable Market Released system. Table ID1-3 summarizes how the

patient deaths have been classified for the PCD Transvene System and the Ventak-P epicardial System.

PCD Transvene System Comparison of Death Classification PCD Transvene System versus Ventak-P Epicardial System		
	PCD Transvene System	Ventak-P Epicardial System
Sudden Cardiac	5	4
Non-Sudden Cardiac	31	8
All Cardiac	15	6
Unknown	0	1
Total	51	19
Perioperative	5 (0.7%)	8 (2.7%)

Table ID1-3: PCD Transvene System - Death Classification- PCD Transvene VS Ventak=P - 2/1/93

A total of 51 deaths (6.7%) were reported in the PCD Transvene System patient population. Of the 35 cardiac deaths, 30 were non-sudden cardiac and 5 were sudden cardiac. Sixteen deaths were classified as noncardiac. Five of the 51 total deaths occurred within the perioperative period (death less than 30 days post implant) with a resultant perioperative mortality of 0.7%.

In the Ventak-P Epicardial System patient population a total of 19 deaths (6.5%) were reported. Of the 12 cardiac deaths, 4 were classified as sudden cardiac and 8 were classified as non-sudden cardiac. Six of the deaths were classified as noncardiac and the cause of one was unknown. Eight of the deaths occurred within the perioperative period with a resultant perioperative mortality of 2.7%. The PCD Transvene System population had a lower perioperative mortality, 0.7% vs 2.7% (p=0.006).

For purposes of this comparison, only the overall actuarial survival rate includes perioperative deaths. All other calculations in both the PCD Transvene System and Ventak-P Epicardial System group exclude perioperative deaths.

For the Ventak-P Epicardial System, patient deaths were **censored** if the Ventak-P device had been either electively deactivated for various reasons prior to the patient's death, thus preventing the device from attempting to convert the arrhythmia or if the pulse generators were known to be nonfunctional and awaiting replacement. For purposes of this comparison, seven patient deaths were **censored** in the PCD Transvene System patient population because the devices were deactivated at the time of patient death.

Table ID1-4 contains the survival comparison of the PCD Transvene System versus the Ventak-P Epicardial System.

PCD Transvene System Survival Comparison PCD versus Ventak-P		
	PCD Transvene System	Ventak-P Epicardial System
Sudden Cardiac	99.7%	98.6%
Overall	94.2%	90.8%

Table ID1-3: PCD Transvene System - Survival Comparison - PCD vs Ventak-P - 2/1/93

The PCD Transvene System sudden cardiac death survival of 99.7% at one year is comparable to that of the Ventak-P Epicardial System sudden cardiac death survival rate of 98.6%. More importantly, the overall one year actuarial survival for the PCD Transvene System was 94.2% as compared to 90.8% for the Ventak-P Epicardial System. This difference was primarily due to the improvement in the reported perioperative mortality in the PCD Transvene System patient population. [Note:

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Confidence interval analysis was performed indicating that there was a statistical difference in the reported **Overall** mortality. The survival probability at one year for the Transvene population was 95.3%. From the analysis run, using commercially available statistical software package (SAS), the survival standard error was also calculated. The confidence interval was calculated by taking the survival probability (b)(4) (b)(4) (survival standard error). The survival standard error was 1.1, therefore, the confidence interval for (b)(4) (b)(4)

This comparison of actuarial survival rates indicates that the projected sudden cardiac death survival of patients receiving a PCD System patient population is comparable to that reported for the Ventak-P Epicardial System. Thus, the incorporation of programmable VT/VF detection and therapy algorithms has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

In addition, the elimination of a surgical thoracotomy for implant in the PCD Transvene System has improved the perioperative mortality and overall one year survival when compared to the Ventak-P Epicardial System.

2. Comparison to PCD Epicardial Study

The PCD Epicardial System uses the same tiered therapy device that combines features of bradycardia support pacing, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. This system has incorporated programmability and multiple detection and therapeutic options that allows the titration of device therapy to a patient's specific clinical arrhythmia history.

The PCD Epicardial System requires a thoracotomy for implantation because of the need to insert epicardial patch leads. This exposes the patient to surgical risk and

potentially limits the type of patient who may be considered for implant of the system. The need for a simpler and safer implantation technique is widely recognized. The incorporation of a nonthoracotomy lead system, such as the PCD Transvene System, should decrease the potential perioperative and long term mortality and morbidity associated with current epicardial system implantation approaches.

The PCD Epicardial System and PCD Transvene System are identical except for the implanted defibrillation lead system. Thus, the performance of the PCD device, associated support equipment, is similar in the two systems and therefore a comparison of clinical experience should focus on those areas where the implanted lead system may impact clinical outcome.

This section provides a comparison of the PCD Transvene System clinical experience to the reported PCD Epicardial System clinical experience. The following areas will be discussed:

- Patient characteristics
- Implant Data
- Spontaneous VT/VF Episode Efficacy
- Complications and Observations
- Survival analysis

This analysis will show that the incorporation of a nonthoracotomy defibrillation lead system has maintained the type of therapy available for the treatment of recurrent VT/VF and decreased the potential mortality and morbidity associated with epicardial implant approaches while maintaining the positive impact of ICD therapy on VT/VF episode efficacy and patient survival.

The PCD Epicardial System clinical data was chosen as a control because the patients were being enrolled in the two studies concurrently by the same investigators, and the patient indications, implant criteria, and clinical data requirements were identical for the two patient groups.

a. **Patient Characteristics**

In comparing the clinical experience with the PCD Transvene System to the PCD Epicardial System clinical experience, it is important to determine that the patients who received the device are comparable.

Table ID2-1 contains the characteristics of the 757 patients receiving the PCD Transvene System versus the characteristics of the 742 patients who received the PCD Epicardial System as of 1/5/93.

PCD Transvene System
Comparison of Patient Characteristics

	PCD Transvene System	PCD Epicardial System
Number of Patients	(b)(4) (b)(4)	
Mean Follow-Up Time	11.7 months	16.3 months
% Males* % Females	(b)(4) (b)(4) 80.6% 19.4%	(b)(4) (b)(4) 85.8% 14.2%
Mean Age	59.4 years	59.6 years
Primary Indication* SCD VT SCD/VT	(b)(4) (b)(4) 37.1% 49.8% 13.2%	(b)(4) (b)(4) 28.8% 54.6% 16.6%
Cardiovascular History Coronary Artery Disease Cardiomyopathy	(b)(4) (b)(4) 74.1% 13.1%	(b)(4) (b)(4) 76.7% 29.9%
Mean Ejection Fraction	35.6%	34.0%
Number of Drugs Failed*	2.3	3.0

* Statistically Significant

Table ID2-1: Comparison of Patient Characteristics, PCD Transvene System versus PCD Epicardial System - 2/1/93

Both groups had moderately depressed left ventricular function demonstrated by the mean ejection of 35.6% for the PCD Transvene System patient group and 34.0% for the PCD Epicardial patient group.

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Analysis indicated that the PCD Transvene System patient population had a higher percentage of patients whose indication for implant was sudden cardiac death ($p = 0.002$) and higher percentage of females ($p = 0.007$). It is not expected that these differences will result in a different clinical outcome in the PCD Transvene System patient population as compared to the PCD Epicardial System. This difference in patient indication is a reflection of the physicians use of the PCD Transvene System.

It is interesting to note, that there was a statistical difference in the number of antiarrhythmic drugs tested between the two patient groups ($p = 0.001$). The PCD Transvene System patient group failed a mean of 2.3 antiarrhythmic drugs prior to implant while the PCD Epicardial System patient group failed a mean of 3.0 antiarrhythmic drugs. This difference is a reflection of the differences in the indications for implant between the two patient groups. The PCD Transvene System patient group had a higher incidence of patients whose primary indication for implant was sudden cardiac death. These patients are not required to have drug therapy screening, therefore, fewer drugs were tested in this group.

b. Implant Data

In both systems, lead system testing was performed to verify that one of the specified lead systems was capable of properly detecting and treating episodes of ventricular fibrillation and, when appropriate ventricular tachycardia. This testing included pacing and sensing thresholds during sinus rhythm, evaluation of VF electrogram amplitudes and defibrillation efficacy evaluation. The implant criteria for both systems was identical and was:

1. Successful VF termination at least 3 times in 4 attempts with an output energy of 18 Joules or less and

2. At least a 2:1 VF sensing safety margin

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Pace/Sense Performance

In both the PCD Transvene and PCD Epicardial Systems, sensing is performed in a standard bipolar configuration and pacing is performed in the integrated bipolar configuration. The pace/sense implant criteria for both systems was:

Pacing Threshold:
R-Wave Amplitude:
Slew Rate:
Resistance:

(b)(4)

(b)(4)

Table ID2-2 provides a comparison of the mean pace/sense values obtained at the time of implant for the PCD Transvene and Epicardial Systems. It should be noted that the pace/sense values presented for the PCD Epicardial System are for the Model 7217B PCD Device.

PCD Transvene System
Performance Comparison
Implant Pace/Sense Parameters

Parameter	PCD Transvene System	PCD Epicardial System
Pacing Threshold*	(b)(4)	
R Wave Amplitude*		
Slew Rate*		
Resistance*		

* Statistically Significant

Table ID2-2: PCD Transvene System: Comparison of Implant Pace/Sense Parameters - 2/1/93

The implant pace/sense parameters obtained for the PCD Transvene System indicates that the lead system provided adequate pacing and safety margins. There was a statistically significant difference in all of the implant pace/sense parameters ($p = 0.001$). This is anticipated because

endocardial pace/sense parameters are better than epicardial values for bradycardia pacing electrode systems.

Electrogram amplitudes were evaluated at follow-up evaluations of both systems to evaluate the performance of the pace/sense lead system and assure adequate safety margin for detection of both baseline rhythms and ventricular tachyarrhythmias. In addition, pacing thresholds were also evaluated at follow-up evaluations to assure an adequate safety margin for capture during both bradycardia and antitachycardia pacing therapies. A comparison of the chronic pace/sense performance for the two systems is presented in Table ID2-3. It should be noted that there was no statistical difference in the chronic pace/sense performance of the two systems.

PCD Transvene System Performance Comparison Chronic Pace/Sense Parameters		
Parameter	**PCD Transvene System**	**PCD Epicardial System**
Electrogram Amplitude	(b)(4) (b)(4)	
Pulse Width Threshold		

Table ID2-3: PCD Transvene System: Comparison of Chronic Pace/Sense Parameters - 2/1/93

The incidence of loss of capture requiring lead system modification in the PCD Transvene System was 0.8% while the incidence in the PCD Epicardial System was 2.0%. There were no reports of undersensing requiring lead modification in the PCD Transvene System while the incidence in the PCD Epicardial System was 0.8%.

This comparison of implant and chronic pace/sense data performance indicates that the performance of the PCD Transvene System is similar to that reported with the PCD Epicardial System and potentially may be improved over the PCD Epicardial system. The

PCD Transvene System provides appropriate acute and chronic safety margins for sensing of sinus rhythm and ventricular tachyarrhythmia as well as appropriate safety margins for pacing therapy.

Implant Defibrillation Thresholds

For the purposes of both systems, determination of defibrillation threshold was not mandatory. However, the preferred method of evaluating defibrillation efficacy was to determine the defibrillation threshold using a testing sequence of 18J, 15J, 10J, 5J with a failure at any level causing a return to 18 J for the remaining attempts.

A defibrillation threshold was defined as the energy at the lowest successful defibrillation attempt, provided a patient had a failure below their lowest defibrillation success or a success at $\leq$ 5J. The rhythm treated must have been VF to be included in the analysis.

Table ID2-4 provides a comparison of defibrillation thresholds determined at implant for the PCD Transvene and PCD Epicardial Systems.

PCD Transvene System
Performance Comparison
Implant Defibrillation Thresholds

System	Mean DFT
PCD Transvene System*	14.8J
PCD Epicardial System	9.8J

* Statistically Significant ($p \leq 0.05$)

Table ID2-4: PCD Transvene System: Comparison of Implant DFT - 2/1/93

The PCD Transvene System did have a significantly higher mean implant defibrillation threshold ($p = 0.0001$). It should be noted, that it was expected that the PCD Transvene System would have a higher mean defibrillation threshold as compared to a traditional epicardial defibrillation lead

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system. In a traditional epicardial system, the increased electrode surface area would theoretically decrease defibrillation requirements.

The programmed defibrillation pathways for the two patient populations is presented in Table ID2-5. The implanted PCD Transvene Systems are almost exclusively three lead systems and this explains the decreased use of SINGLE pathway. The use of SIMULTANEOUS pathway is higher in the PCD Transvene System and indicates that in a group of patients the incorporation of multiple defibrillation pathways allowed an increase in the ability to meet the PCD Transvene System implant criteria. Most of the PCD Epicardial System implants used a two patch system resulting in the increased use of the SINGLE pathway.

PCD Transvene System Performance Comparison Programmed Defibrillation Pathway		
Defibrillation Pathway	**PCD Transvene System**	**PCD Epicardial System**
Sequential	(b)(4)	
Simultaneous		
Single		

Table ID2-5: PCD Transvene System: Comparison of Programmed Defibrillation Pathway - 2/1/93

The differences in the programmed status of the PCD device in the PCD Transvene System are a reflection of the type of patients who received the device and the defibrillation energy requirements for each lead system. It is important to note that the PCD device performed safely and effectively in both patient populations.

c. Spontaneous VT/VF Efficacy

The primary benefits from the use of the PCD System center on the detection and termination of life-threatening ventricular tachyarrhythmias. An

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additional benefit of the PCD Transvene System is the elimination of the need for a thoracotomy for implantation of the defibrillation lead system and the resultant decrease in potential patient morbidity and mortality associated with a thoracotomy. This clinical benefit should not be gained at the expense of providing effective termination of spontaneous VT and VF episodes. Table ID2-6 provides a comparison of the efficacy of the PCD Transvene and PCD Epicardial System in treating spontaneous episodes of VT and VF.

PCD Transvene System Performance Comparison		
Spontaneous VT Episodes		
	PCD Transvene System	**PCD Epicardial System**
Mean Follow-Up	11.7 months	16.3 months
Number of Patients with VT Episodes	316	386
Number of Episodes	10,027	20,061
% Overall Efficacy	9,864/10,027 98.4%	19,726/20,061 98.3%
% Unsuccessful Termination (VT)	68/10,027 0.7%	150/20,061 0.8%
% Unsuccessful Termination (AF,ST)	95/10,027 0.9%	185/20,061 0.9%
Spontaneous VF Episodes		
	PCD Transvene System	**PCD Epicardial System**
Mean Follow-Up	11.7 months	16.3 months
Number of Patients with VF Episodes	317	342
Number of Episodes	1982	2,636
% Overall Efficacy	1951/1982 98.4%	2601/2636 98.7%
% Unsuccessful Termination (VF)	5/1982 0.3%	15/2636 0.5%
% Unsuccessful Termination (AF,ST, Other)	26/1982 1.3%	24/2636 0.8%

Table ID2-6: PCD Transvene System: Comparison of Spontaneous VT/VF Episode Efficacy - 2/1/93

The overall success rate of the PCD Transvene System in terminating spontaneous episodes of VT or VF is 98.5%. This success rate compares very favorably with the overall success rate of the PCD Epicardial System which was 98.4%. Therefore, the PCD Transvene System offers the potential of decreased patient morbidity and mortality without decreasing the treatment efficacy of spontaneous VT/VF episodes.

d. Complications and Observations

A comparison of the reported complications and observations was made between the PCD Transvene System and the PCD Epicardial System. The PCD Epicardial System patient population used for comparison included clinical experience as of January 5, 1992 with 742 patients and a mean implant duration of 16.3 months. These two patient groups are similar in the patient demographics and indication for implant of the PCD System. In the PCD Transvene System patient population, 19.4% of the patients experienced a clinical complication and 23.8% of the patients experienced a clinical observation. In the PCD Epicardial System, 14.2% of the patients experienced a clinical complication and 32.9% of the patients experienced a clinical observation.

Table ID2-7 and ID2-8 provide a comparison of the reported complications/observations and their incidence in the two patient populations.

PCD Transvene System PCD Transvene System versus PCD Epicardial System Reported Complications		
Reported Complications	**PCD Transvene System (N = 757)**	**PCD Epicardial System (N = 742)**
Increased Defibrillation Requirements	1.2%	0.5%
Inappropriate Therapy	-	2.2%
Pace/Sense Related	0.8%	3.5%
Infection Related - Explant	2.9%	2.3%
Lead Related	15.1%	3.0%
Device Related	0.5%	0.9%

Table ID2-7: Reported Complications: PCD Transvene System versus PCD Epicardial System - 2/1/93

PCD Transvene System PCD Transvene System versus PCD Epicardial System Reported Observations		
Reported Observations	**PCD Transvene System (N = 757)**	**PCD Epicardial System (N = 742)**
Ineffective Therapy	1.1%	1.1%
Inappropriate Therapy	9.6%	13.6%
Pace/Sense Related	9.0%	14.0%
Infection Related	5.3%	2.6%
Lead Related	2.3%	1.2%
Device Related	-	-

Table ID2-8: Reported Observations: PCD Transvene System versus PCD Epicardial System - 2/1/93

e. Survival Analysis

Despite their excellent clinical performance, epicardial defibrillation lead system have important limitations. The requirement for direct thoracic access contributes significantly to patient morbidity and mortality, patient discomfort and prolonged hospitalization. The availability of reliable nonthoracotomy lead systems should provide

positive clinical impact on these issues while not negatively impacting patient survival. Therefore, a comparison of the one year actuarial survival rates for the PCD Transvene and Epicardial System was performed.

Table ID2-9 provides a summary of the patient deaths reported in the two patient populations by classification. As a reference, the mean follow-up time for the PCD Transvene System patient population was 11.7 months while for the PCD Epicardial System it was 16.3 months. Patients with the device programmed OFF and perioperative deaths are not mutually exclusive.

PCD Transvene System Death Classifications PCD Transvene System versus PCD Epicardial System		
Death Classification	**PCD Transvene System (N=757)**	**PCD Epicardial System (N=742)**
Sudden Cardiac	5 0.7%	24 3.2%
# Off	1 0.1%	3 0.4%
# Perioperative	2 0.3%	9 1.2%
Non-Sudden Cardiac	31 4.1%	54 7.3%
# Off	4 0.5%	12 1.6%
# Perioperative	2 0.3%	18 2.4%
All Cardiac	36 4.8%	78 10.5%
# Off	5 0.7%	15 2.0%
# Perioperative	4 0.5%	27 3.6%
Noncardiac	15 2.0%	34 4.6%
# Off	2 0.3%	7 0.9%
# Perioperative	1 0.1%	12 1.6%
Total	51 6.7%	113 15.2%
# Off	7 0.9%	23 3.1%
# Perioperative	5 0.7%	39 5.3%

Table ID2-9: Death Classifications: PCD Transvene System versus PCD Epicardial System - 2/1/93

Table ID2-10 provides a comparison of actuarial survival rates between the PCD Transvene and PCD Epicardial patient populations. The actuarial survival projections include perioperative deaths only in the calculation of

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survival from death due to all causes (shown in table row labelled **Overall**). Perioperative mortality includes those deaths which occur in the first thirty days post implant of the PCD System.

PCD Transvene System Comparison of Actuarial Survival PCD Transvene System versus PCD Epicardial System			(b)(4)
One Year Survival	**PCD Transvene System**	**PCD Epicardial System**	
Number of Patients	757	742	
Sudden Cardiac	99.5%	98.9%	
Non-Sudden Cardiac	96.2%	96.7%	(b)(4)
All Cardiac	95.8%	95.7%	
Noncardiac	98.1%	98.0%	
Overall*	93.3%	88.6%	

* (b)(4) (b)(4)

Table ID2-10: Comparison of Actuarial Survival: PCD Transvene System versus PCD Epicardial System - 2/1/93

There was a significant increase in overall survival in the patients receiving a PCD Transvene System. As previously noted, the Overall one year actuarial survival includes death from all causes. The overall one year survival for patients receiving the PCD Transvene System was 93.3%. This is significantly improved as compared to the overall one year actuarial survival for the PCD Epicardial System (88.6%) (b)(4) (b)(4) This improvement in overall survival is primarily due to the marked improvement in perioperative mortality, the PCD Transvene System having a 0.7% (5/757) perioperative mortality versus the a perioperative mortality of 5.3% (39/742) in the PCD Epicardial System. This improvement in perioperative mortality is primarily due to the elimination of the need for a thoracotomy and its associated morbidity and mortality.

3. Patients Followed For ≥ One Year

a. Patient Characteristics

Table ID3-1 provides a data summary on the patients followed for a year or more. This table includes patient characteristics, defibrillation pathway configuration, mean LED and DFT, spontaneous VT and VF experience and efficacy. The characteristics of this subset of patients are similar to the original 757 patient population. Patients followed for a year or more had a similar percentage of patients having a history of coronary artery disease (69.2% vs 74.1%) and a similar mean ejection fraction (38% vs 35.6%). The differences are small and are not suspected to have an impact on implant duration or survival. Note that since by definition all patients have been followed for at least one year, the overall survival probability and the sudden cardiac survival probability is 100% at one year.

PCD Transvene System Data Summary	
	Patients with **12** months of Follow-up
Number of Patients	393
Device Months Follow-up	6454.6
Mean Follow-up Time	16.3 mo
Maximum Follow-up Time	37.4 mo
Number, % Male **Number, % Female**	310 78.9% 83 21.1%
Mean Age	58.8 yrs
Primary Indication: **SCD** **VT** **SCD/VT**	 150 38.2% 191 48.6% 52 13.2%
Coronary Artery Disease	272 69.2%
Mean Ejection Fraction	357 38.0%
Defibrillation Pathway: **Sequential** **Simultaneous** **Single**	 296 74.9% 93 23.6% 6 1.5%
Mean LED	15.6J (N=365)
Mean DFT	14.3J (N=184)
Spontaneous VT: **Number of Patients** **Number of Episodes** **% Success**	 186 6338 99.0% (6273/6338)
Spontaneous VF: **Number of Patients** **Number of Episodes** **% Success**	 176 1105 98.6% (1090/1105)

Table ID3-1: PCD System Data Summary - Transvene Patients with 12 month Follow-up - 2/1/93

b. Spontaneous VT/VF Efficacy

The primary benefits from the use of the PCD System center on the detection and termination of life-threatening ventricular tachyarrhythmias. Table

life-threatening ventricular tachyarrhythmias. Table ID3-2 provides a comparison of the efficacy of the PCD Transvene System in patients with at least 12 months of follow-up in treating spontaneous episodes of VT and VF.

PCD Transvene System Patients with 12 Mths Follow-up	
Spontaneous VT Episodes	
Number of Episodes	6338
% Overall Efficacy	99.0% 6273/6338
Spontaneous VF Episodes	
Number of Episodes	1105
% Overall Efficacy	98.6% 1090/1105

Table ID3-2: PCD Transvene System: Comparison of Spontaneous VT/VF Episode Efficacy -

c. Complications and Observations

The use of a multiprogrammable implantable cardioverter defibrillator (ICD) device allows the physician to resolve most relevant medical events by noninvasively changing programmed parameters thus, avoiding invasive procedures. However, there will continue to be certain relevant medical events which will require invasive procedures for resolution.

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following previously described definitions:

COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse

effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

As of February 1, 1993, of the 393 patients with implant durations of greater than or equal to one year, there have been a total of 89 complications reported in 76 patients and 122 observations reported in 99 patients in the PCD Transvene System patient population. Thus, 19.3% (76/393) of the patients had a clinical event reported which was categorized as a complication vs 19.4% (147/757) in the overall population and 25.2% (99/393) of the patients had a clinical event reported which was categorized as an observation vs 23.8% (180/757) in the overall population.

Table ID3-3 Summarizes the reported PCD Transvene System complications and observations by category. The reported complications and observations are recognized clinical events that may occur with any of the current ICD devices. These complications and observations are discussed in the PCD device and Transvene manual. **None of the reported complications or observations have resulted in a patient death.**

PCD Transvene System Reported Complications/Observations in Patients followed for 1 Year or more: By Category		
Category	**Complications**	**Observations**
	Num (% of Pts)	Num (% of Pts)
Increased Defibrillation Requirements	3 (0.8%)	2 (0.5%)
Inappropriate VF Therapy Delivery	-	10 (2.5%)
Inappropriate VT Therapy Delivery	-	40 (10.2%)
Loss of Capture	2 (0.5%)	6 (1.5%)
Oversensing	-	29 (7.4%)
Undersensing	-	-
Skin Erosion	2 (0.5%)	1 (0.3%)
Pocket Infection	5 (1.3%)	7 (1.8%)
Seroma	1 (0.3%)	9 (2.3%)
Hematoma	1 (0.3%)	7 (1.8%)
Pneumothorax	2 (0.5%)	1 (0.3%)
Pacemaker Syndrome	-	1 (0.3%)
Perforation	1 (0.3%)	-
Subclavian Vein Thrombosis	-	1 (0.3%)
Lead Fracture	6 (1.5%)	-
Subcutaneous Patch Crinkling	5 (1.3%)	3 (0.8%)
Early Device Explant	3 (0.8%)	-
Total Lead Dislodgement	56 (14.2%)	6 (1.5%)
Total	**89**	**122**

Table ID3-3: PCD Transvene System: Reported Complications and Observations - 2/1/93

Table ID3-4 contains a description of the lead dislodgements that have occurred in less than 30 days and in greater than 30 days.

PCD Transvene System Reported Complications/Observations in Patients followed ≥1 Year Lead Dislodgements <30 days and >30 days N=393			
Complications		Observations	
<30 days	>30 days	<30 days	>30 days
27 (6.9%)	29 (7.4%)	0 (0)	6 (1.5%)

Table ID3-4: PCD Transvene System: Lead Dislodgements occurring <30/>30 days in patients followed for greater than or equal to one year as of 2/1/93

There have been a total of 35 lead dislodgements reported in patients at greater than 30 days. None of the lead dislodgements resulted in an ineffective therapy for a spontaneous VT or VF episode or patient death. Lead dislodgements were documented by fluoroscopic examination during electrophysiologic evaluation, chest x-ray obtained during routine follow-up, or during pacing/sensing threshold evaluation during routine follow-up. In 29 cases, reoperation was required to reposition the lead and reestablish an effective defibrillation lead system. In 6 cases, lead repositioning was not required.

Lead dislodgements are not specific to the PCD Transvene System and have been reported with dual chamber pacemakers and the current market released implantable cardioverter defibrillator (ICD) system. The early history of dual chamber pacemakers witnessed a high lead dislodgement rate of at least 20% (Smyth, PND, et al. Permanent perivenous atrial sensing and pacing with a new J-shaped lead. J Thoracic Cardiovascular Surgery. 1976;72:565-570). Winkle, et al reported that the incidence of dislodgement of the superior vena cava spring leads with the current market release ICD system to be 6.3%. (Winkle, et al. Automatic

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Implantable Cardioverter-Defibrillator: Efficacy, Complications, and Survival in Patients with Malignant Ventricular Arrhythmias. JACC. June 1988; Vol.11, No.6:1278-86).

In summary, this group represents the majority of the overall population and the characteristics of the 393 patients with implant durations of greater than or equal to one year were similar to the overall population of 757 patients.

d. Survival Analysis

There have been a total of 7 patient deaths reported in this subset of patients. The deaths occurred greater than 12 months from the date of implant. Table ID3-5 summarizes how these patient deaths have been classified.

PCD Transvene System
Summary of Death Classifications
in Patients followed for a Year or more

Classifications	Number of Deaths
Sudden Cardiac	0
Non-Sudden Cardiac	5
Noncardiac	2
TOTAL	7

Table ID3-5: PCD Transvene System - Summary of Death Classifications - 2/1/93

Table ID3-6 summarizes the 18 month and 2 year actuarial survival of the patinets followed for at least 1 year.

PCD Transvene System 18 month and 2 Year Actuarial Survival		
	18 months	2 year
Sudden Cardiac Death	100%	100%
Non-Sudden Cardiac	98.3%	96.7%
All Cardiac	98.3%	96.7%
Noncardiac	99.5%	98.6%
Overall	97.8%	95.4%

Table IB3-6: PCD Transvene System - One Year Actuarial Survival - 2/1/93

4. Non-Standard Lead Configurations

In addition to the 757 patients presented in this report there were 43 patients who received defibrillation lead systems that were different from the three "Standard" systems. Even though these lead systems were different from the majority of systems evaluated they were evaluated by the investigator at time of implant and found to be efficacious.

Seven (7) of the 43 non-standard systems were in patients that had previously received a market released epicardial defibrillation system and one or more Transvene was added to the system to improve defibrillation efficacy. Twenty-four (24) patients had hybrid systems of Medtronic epicardial patches used with one or more Transvene leads. Six patients had two lead Transvene systems implanted. Four patients had Transvene leads placed in "nonstandard" locations (Pulmonary Artery, Right Atrium, and Great Cardiac Vein). Two patients have two Transvene leads connected together with a high voltage Y-adaptor and are programmed to single pathway defibrillation. One of these is a four lead system (SVC/SQ&CS/RV), the other is a three lead system (SVC&SQ/RV).

Table ID4-1 contains the distribution of the non-standard lead systems.

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PCD Transvene System "Nonstandard" Defibrillation Lead Systems	
Market Released Epicardial-Transvene Hybrid	(b)(4)
Medtronic Epicardial-Transvene Hybrid	
Two Lead Transvene	
"Nonstandard" Anatomic Locations	
"Nonstandard" Electrical Configuration	

Table ID4-1: Non-standard Defibrillation Lead Systems - 2/1/93

These non-standard lead systems have a mean defibrillation threshold similar to the overall patient population and have performed safely and effectively during the follow-up period. The efficacy of termination of spontaneous episodes of ventricular fibrillation is 100%.

(b)(4), (b)(6)

a. Patient Characteristics

Table ID4-2 contains the data summary of the patients that received the standard lead systems and the 757 patients that received a 3 lead Transvene lead system.

PCD Transvene System Data Summary: Non-Standard Lead Systems		
	Non-Standard Lead Systems	**All Patients**
# of Patients	43	757
Number, % Male **Number, % Female**	32 74.4% 11 25.6%	610 80.6% 147 19.4%
Mean Age	54.4 yrs	59.4 yrs
Primary Indication: **SCD** **VT** **SCD/VT** **Other**	 16 37.2% 20 46.5% 6 14.0% 1 2.3%	 281 37.1% 377 49.8% 99 13.1% -- --
Coronary Artery Disease	31 72.1%	561 74.1%
Mean Ejection Fraction	36.0% (N=40)	35.6% (N=688)
Defibrillation Pathway: **Sequential** **Simultaneous** **Single**	 27 62.8% 5 11.6 11 25.6%	 574 75.3% 178 23.4% 10 1.3%
Mean LED	15.3J (N=32)	16.0J (N=703)
Mean DFT	12.6J (N=13)	14.8J (N=316)
Spontaneous VT: **# of Patients** **# of Episodes** **% Success**	 16 278 95.7%	 316 10,027 98.4%
Spontaneous VF: **# of Patients** **# of Episodes** **% Success**	 20 113 97.4%	 317 1,982 98.4%
1 Year SCD Survival	100.0%	99.5%

Table ID4-2: Data Summary - Non-Standard Lead Systems - 2-1-93

b. Spontaneous VT/VF Efficacy

The primary benefits from the use of the PCD System center on the detection and termination of life-threatening ventricular tachyarrhythmias. Table

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ID4-3 provides the efficacy of the non-standard lead configurations in treating spontaneous episodes of VT and VF.

PCD Transvene System Non-Standard Lead Configurations	
Spontaneous VT Episodes	
Number of Episodes	278
% Overall Efficacy	266/278 95.7%
% Unsuccessful Termination (VT)	0/278 0.0%
% Unsuccessful Termination (AF,ST)	12/278 4.3%
Spontaneous VF Episodes	
Number of Episodes	113
% Overall Efficacy	110/113 97.3%
% Unsuccessful Termination (VF)	0/113 0.0%
% Unsuccessful Termination (AF,ST)	3/113 2.7%

Table ID4-2: PCD Transvene System: Comparison of Spontaneous VT/VF Episode Efficacy - 2/1/93

c. Complications and Observations

The use of a multiprogrammable implantable cardioverter defibrillator (ICD) device allows the physician to resolve most relevant medical events by noninvasively changing programmed parameters thus, avoiding invasive procedures. However, there will continue to be certain relevant medical events which will require invasive procedures for resolution.

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following previously described definitions:

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COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

Table ID4-3 Summarizes the reported PCD Transvene System complications and observations by category for the patients that received a non-standard lead configuration. The reported complications and observations are recognized clinical events that may occur with **any** of the current ICD devices. These complications and observations are discussed in the PCD device and Transvene manual. **None of the reported complications or observations have resulted in a patient death.**

PCD Transvene System Reported Complications/Observations in Patients with Non-Standard Lead Configurations: By Category		
Category	**Complications**	**Observations**
	Num (% of Pts)	Num (% of Pts)
Increased Defibrillation Requirements	-	-
Inappropriate VF Therapy Delivery	-	-
Inappropriate VT Therapy Delivery	-	2 (4.7%)
Loss of Capture	-	-
Oversensing	-	4 (9.3%)
Undersensing	-	-
Skin Erosion	-	-
Pocket Infection	1 (2.3%)	2 (4.7%)
Seroma	-	-
Hematoma	-	-
Pneumothorax	-	-
Pacemaker Syndrome	-	-
Perforation	-	-
Subclavian Vein Thrombosis	-	-
Lead Fracture	1 (2.3%)	-
Subcutaneous Patch Crinkling	-	-
Early Device Explant	-	-
Total Lead Dislodgement	2 (4.7%)	1 (2.3%)
Total	**4**	**9**

Table ID4-3: PCD Transvene System: Reported Complications and Observations - 2/1/93

d. Survival Analysis

There were 2 patient deaths in the 42 patients that received a non-standard lead system. One was classified as non-sudden cardiac and one was classified as non cardiac. Table ID4-4 containes the one year actuarial survival for the patients with non-standard lead systems.

PCD Transvene System 1 year Actuarial Survival	
Sudden Cardiac Death	100%
Non-Sudden Cardiac	95.2%
All Cardiac	95.2%
Noncardiac	100.0%
Overall	93.0%

Table ID4-4: PCD Transvene System - One Year Actuarial Survival - 2/1/93

E. PCD System Performance

1. Explants; Leads and PCD Devices

Transvene Lead Performance

The Transvene Lead System consists of a Right Ventricular Lead, a Coronary Sinus/Superior Vena Cava lead, and a Subcutaneous Patch lead. There have been a total of 757 Right Ventricular leads (15 with the SP2100 and 742 with the Model 6884/6966), 796 Coronary Sinus/Superior Vena Cava leads (Model 6881/6963), and 718 Subcutaneous Patch leads (Models 6895/10317/6999) implanted with a cumulative implant duration of 8894.8 months. The reported incidence of fracture for the RV lead is 0.9% (7/757) and 0.3% (2/757) for the SQ lead.

A Model 6884, screw-in, right ventricular, pace/sense, cardioversion/ defibrillation lead was returned to Medtronic 27 months post implant. The lead was returned to Medtronic following explant from a patient that was undergoing a heart/lung transplant. Note that the lead had been fully functional while implanted and was found to be fully functional upon explant.

Upon undergoing further analysis at Medtronic, some MIO (metal ion oxidation) was observed on the lumen of the middle insulation approximately 20 cm proximal of the pacing tip electrode, and on the outside of the inner insulation. The MIO was further characterized to be

"cosmetic" in that it had not functionally affected the lead in any way. Cosmetic MIO is defined as any crack that has not breached the insulation.

Initial analysis indicated that the presence of the MIO was in the clavicular region of the body; i.e., the location, 20 cm proximal of the tip, would be in the first rib clavicle region of a small adult. There was no evidence, however, of conductor coil fracture and the lead was fully functional. Given the Model 6884 lead is generally implanted via subclavian vein insertion, this type of observation may occasionally be expected. However, subsequent analysis of the patient X-rays showed that the area of MIO was actually in the right ventricle. The patient's right ventricle was extremely dilated, secondary to pulmonary hypertension. Therefore, 20 cm from the proximal tip electrode located the area of MIO at the point of maximum curvature of the lead, in the right ventricle, rather than in the clavicular region.

Detailed Analysis Results

Visual/Microscopic

Shallow (cosmetic) environmental stress cracking (ESC) was visible. No coil deformation was visible in the first rib/clavicle region. Possible MIO was visible 20 cm proximal of the electrode tip extending approximately 0.5 cm on the middle insulation. Possible MIO was also visible on the innermost insulation starting at 19.3 cm proximal of the electrode tip and extending 5.4 cm proximally.

Scanning Electron Microscopy

MIO was observed on the lumen of the middle insulation and on the outside of the innermost insulation. The MIO penetration was less than five percent of the insulation wall thickness. In addition to the insulation, both the middle and inner coils were evaluated up to 2500 times magnification. There were no anomalies apparent on the inside or outside of the middle coil in the region of the MIO. The innermost coil showed no signs of crush or fatigue in the region of the MIO.

FTIR-ATR

FTIR spectra were obtained for a control area (no MIO) of the inner tubing and the cracked area of the tubing. Relative ratios of key bonds were calculated using the absorption intensities. These ratios indicated that the ether segments were oxidized in the polyurethane, which is characteristic of MIO. In addition, peaks appeared, indicative of carboxylic acids or esters (oxidation byproducts).

Discussion

Contrary to the initial dimensional analysis of this lead that indicated the area of MIO was located to the clavicular region of implant, review of the patient's X-rays revealed that the heart was significantly enlarged due to the advanced disease state. Subsequently, a significant portion of the insulated lead body was located in the heart, including the portion with cosmetic MIO. Typically, 20 cm proximal of the tip electrode approximates the clavicular region.

Consistent with our previous analysis of MIO relative to the 6884/6966 lead, the observed MIO did not, in any way, affect the clinical performance of this lead. Patient data analysis shows that the implanted lead system, inclusive of the 6884 lead, performed appropriately. Of six spontaneous VT/VF episodes reported (4VT/2VF), all were appropriately detected and treated via the implanted PCD Transvene system.

In addition, the presence of MIO on the middle insulation is not entirely unexpected (reference February 18, 1993, Medtronic/FDA meeting). If the middle insulation had been degraded to the point of electrically shorting the sensing ring (middle conductor coil) to the common defibrillation electrode (middle coil), an integrated bipolar sensing system would, in essence, be created. In this type of system, sensing occurs between the unipolar pacing tip and the common defibrillation electrode, versus standard, or true, bipolar sensing between the pace/sense tip and the ring electrodes. This type of sensing system is identical to the CPI Endotak configuration, as well as Medtronic's earlier

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design of a Transvene RV lead, i.e., the Model SP2100. These types of integrated systems have been shown to be clinically acceptable. Note that canine testing of a shorted, RV cardioversion/defibrillation lead, indicated that this type of failure does not result in the lack of therapy delivery.

If the innermost insulation had degraded such that the pacing tip electrode shorted, this could manifest as intermittent sensing of the brady pace/sense function of the lead. This type of anomalous system performance is expected to be observed at follow-up sessions, given the frequent monitoring of patients (every three months) or as necessary when the patient experiences VT/VF episodes or anything unusual. Similar to brady pacing patients, problems related to pace/sense performance are typically observed at the time of follow-up (pace/sense threshold measurements are standard follow-up procedure for both brady and tachy lead systems) and/or when the patient reports to his/her physician for any unusual events, e.g., intermittent pacing/sensing.

The extensive dilatation of the right ventricle in which this lead was implanted resulted in a large portion of insulated lead body being in the right ventricle, as opposed to primarily just the cardioversion/defibrillation electrode coil. Subsequently, this lead may have been subject to more flexing in the heart than what is typical for the RV lead. Note: this was demonstrated in the videotape that was presented to FDA at the February 18, 1993, Medtronic/FDA meeting.

Clinical data from brady pacing leads indicates that the portion of the lead subject to the flexing motion in the heart may be related to the occurrence of MIO in brady lead bodies. Brady pacing leads, proximal to the tip/ring electrodes are subject to more flexing motion, relative to a cardioversion/defibrillation RV lead, while contained in the heart. On the other hand, cardioversion/defibrillation leads, like the 6884/6966, are comprised of a comparatively stiff portion proximal to the tip/ring electrode. This length of defibrillation electrode, 5 cm, appears to flex less than a typical brady pacing lead while in the heart, as a result of

greater stiffness. However, in the extremely hypertrophic heart, as was the case with this particular RV lead, the lead may be subject to more flexing, similar to that of a brady pacing lead.

Conclusions

As noted, Medtronic cannot assure that MIO, or other lead failure mechanisms will not occur in the 6884/6966 lead. However, one should consider the actual benefits of the lead versus the **potential** for MIO occurrence. Specifically, clinical data to date for the Transvene system show that one year actuarial survival from SCD is 99.5 percent and the average hospital stay for Transvene implant is only seven days (versus ten for an epicardial system)*. Regarding the potential for MIO occurrence, analysis shows this would result in a bipolar integrated sensing system, or in an intermittent pace/sense system. Integrated sensing has been shown to be clinically acceptable, and intermittent pacing/sensing is assessed as part of standard follow-up procedures. Additionally, with postmarket surveillance mechanisms in place, such as returned product analysis and chronic lead monitoring, Medtronic is well positioned to appropriately evaluate and manage potential failure mechanisms of implantable cardiac leads. We are committed to these surveillance mechanisms in the interest of delivering optimal implantable technology products to the health care market.

Based on the clinical data collected, the Transvene leads have performed safely and reliably.

PCD Devices

In the 762 implants, a total of 63 units (8.3%) were explanted secondary to patient deaths, infection, heart transplant, low battery voltage measurement and PCD Device performance issues. Table IE1-1 provides an overview of the units explanted, and returned to Medtronic for analysis and reason for explant.

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PCD Transvene System Reasons for PCD Device Explant n = 762		
Reason	**All Models**	
	Explanted	Received for analysis
Patient Death	22	17
Infection	22	10
Cardiac Transplant	9	5
Low Battery Voltage Measurement	1	1
PCD Device Performance Issues	4	4
L23	1	1
Lead Issues	4	4
Total	63	42

Table IE1-1 Reasons for PCD Device Explant - 2/1/93

The investigational plan requests that if the patient expires during the course of the clinical study that the PCD device be explanted and returned to Medtronic for analysis. There were 51 reported patient deaths and 22 devices were explanted. Seventeen have been received at Medtronic for analysis. In the 29 deaths where the device was not explanted, the patients expired and were buried before the devices could be explanted.

Results of analysis performed on the 42 explanted devices is presented in Table IE1-2.

PCD Transvene System Final Analysis on Explanted PCD Devices (N = 762)	
Within Normal Specifications	36
Hermetic Leakage at IC	1
Random Component Failure	2
Shorted on Pulse 2 Output	2
L23	1
Analysis Pending	0
Total	42

Table IE1-2: Final Analysis on Explanted PCD Devices - 2/1/93

Of the 42 devices explanted, final analysis on 36 units indicated that the devices were functioning within normal specifications.

Six PCD Devices were explanted for the following device performance issues:

- explanted due to a Power On Reset (POR) condition that was not related to the delivery of external defibrillation or cautery (N=1);
- explanted for lower than expected battery voltage for time in service, includes L23 (N=2);
- explanted secondary to failure to appropriately synchronize and deliver cardioversion therapy for an induced VT episode (N=1); and
- explanted post inappropriate delivery of VF therapy during a manual capacitor charge time (N=2).

These devices are discussed in detail in the discussion that follows.

In the case of the device explanted for PCD Device performance issue (b)(4) (b)(4) the device experienced a Power On Reset (POR) condition that was not related to

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the delivery of external defibrillation or electrocautery. Under certain conditions, the use of direct defibrillation or electrosurgical cautery in the icinity of a Model 7217B PCD System (i.e., device and electrodes) may cause the device to be set to its reset parameter values (VT/VF detection and therapies disabled and nominal VVI pacing parameters). In the case of this patient, the POR condition occurred during the pre-hospital discharge evaluation and the patient was under no increased risk.

Since external defibrillation or electrocautery had not been used near the device, it was recommended that the device be explanted. The patient received a second PCD Device without difficulties. The explanted PCD Device underwent initial evaluation and was found to be performing within specifications.

Analysis of the device which had the documented short on the Pulse 2 output was found in a device which was explanted secondary to patient death. The death was classified as nonsudden and not related to the implanted PCD Transvene System. It appears that this diode failed post explant of the system probably due to electrocautery being used at the time of explant and was not related to the patient's death.

There was one device (b)(4) that was explanted due to lower than expected battery voltage for time in service. Analysis indicated that hermetic leakage at the input to one of the integrated circuits lead to a voltage drop across a resistor where the voltage measurement is taken. Thus the actual battery voltage was appropriate but the telemetry reading was incorrectly low.

There have been no reports of lower than expected battery voltage for time in service due to failure in an integrated circuit which increases current drain or leakage of tantalum capacitors on the printed circuit board as reported in the PCD Epicardial System experience.

None of these issues are related to the PCD device battery performance. The battery has performed according to

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specifications and there is no clinical data indicating otherwise.

In the case of the PCD Device (b)(4) which did not appropriately synchronize cardioversion therapy, during the pre-hospital discharge electrophysiology study, VT was induced and cardioversion therapy failed to appropriately synchronize and deliver therapy for the induced episode. The PCD Device was explanted and the patient received a second device without difficulties. Analysis of the explanted PCD Device indicated a random device failure. The manufacturing process was modified to incorporate a screening process to identify any further devices which may exhibit this behavior.

In the PCD Device (b)(4) in which VF therapy was delivered during a capacitor charge time, appropriate function of the Model 7217B PCD Device was documented at the time of implant. At the time of the one month follow-up, the device was interrogated and there were no spontaneous episodes between hospital discharge and the one month follow-up. During the monitor, the capacitors were being charged according to protocol and the patient indicated she felt a sensation in her abdomen. Subsequently, the PCD device did not respond to telemetry.

The patient was monitored again in an effort to assess telemetry. Another programmer was used and various radiofrequency sensitivities were used in attempts to gain telemetry. Still there was no response. The implanted system was assessed via x-ray and device (leads) dislodgement was not seen. Alternative implant, e.g., another commercially available defibrillator, was not considered an option as the Medtronic lead connections were not known to be compatible with other manufacturer's devices. The PCD Device was explanted and a second Model 7217B PCD device was implanted without difficulty. This patient has done well since the second implant procedure. No further device performance issues such as this one have been reported in this patient or other implanted devices.

Analysis of the explanted unit indicated that arcing occurred between the conductors inside the hermetically

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enclosed brazed ring of the high power hybrid. As a result, high voltage was momentarily applied to the low power circuitry, including the low power hybrid. This low power hybrid lost function including the capability to pace and transmit telemetry due to excessive voltage applied. The mechanism that initiated the arcing could not be identified.

Even though the arcing mechanism could not be identified, it is important to note that the hybrid manufacturing procedure has processing steps to ensure that arcing does not occur. Traceability data on this unit indicated there were no processing anomalies related to this hybrid.

Since this was the only device that exhibited this type of failure in the field and the hybrid manufacturing process has demonstrated that it will screen out infant mortality, this is considered a random component failure.

F. Clinical Conclusions

The overall clinical experience with the PCD Transvene System indicates that the system performed according to design and specification. The reported clinical complications and patient deaths are appropriately addressed in the required labelling for the system and the patient selection criteria for implant of the device is appropriate.

The following can be drawn from this analysis of the data collected in this clinical study from the 757 patients with a mean follow-up of 11.7 months:

Patient Deaths

- The projected one year survival probabilities for Sudden Cardiac Death, Non-Sudden Cardiac Death, all Cardiac Deaths and Noncardiac Death were found to be 99.5%, 96.2%, 95.8%, and 98.1%, respectively.

  The incorporation of programmable VT/VF detection and therapies has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

- The sudden cardiac death survival of 99.5% at one year is comparable to that of the AICD patient population 98.0%.

- There have been no deaths due to a PCD Device malfunction.

Complications/Observations

- Complications were reported in 19.4% of the patient population and observations were reported in 23.8% of the patient population.

- The incidence of complications was comparable to that of the market released AICD system in the categories of ineffective VT/VF therapy, pocket infection, and pocket erosion and was lower than the AICD in the category of inappropriate delivery of VT/VF therapy.

Patient Indications

- All of the 757 patients who received a 3 lead system in this clinical evaluation met at least one of the primary indications. Sudden cardiac death (SCD) was the primary indication in 37.1% of the patients, recurrent ventricular tachycardia (VT) was the primary indication in 49.8 % of the patients and SCD/VT was the primary indication in 13.1% of the patients.

- The number of patients (60.5%) receiving VT/VF therapy for spontaneous episodes of ventricular arrhythmias supports the conclusion that the patient selection criteria are appropriate and that the PCD Transvene System was implanted in patients who benefit from this therapy.

- The one year sudden cardiac death survival rates for the SCD patient group was 100.0%, for the VT patient group 99.4% and the SCD/VT patient group 98.6%.

VT/VF Detection and Therapy Performance

- The PCD Transvene System properly detects and treats VT as demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VT was 98.4%.

B

- The PCD Transvene System properly detects and treats VF as demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VF was 98.4%.

- There were no reported patient deaths due to the nondetection of a spontaneous VT or VF episode by the PCD Transvene System.

PCD Transvene System Performance

- The PCD Transvene System components (Model 7216A/7217B and Model 6884/6966, 6881/6963, 6895/6999 Transvene leads) have performed according to design and specification and are, therefore, considered safe and effective in the indicated patient population.

Medtronic asserts and the PCD Transvene investigators unanimously agree that the findings of the clinical study support the conclusion that the Medtronic Tachyarrhythmia Control System and the Transvene Cardioversion and Defibrillation Electrodes are safe and effective in the indicated patient population.

II Complications + Observations

A

II. Complications and Observations

A. Therapy Related

1. Increased Defibrillation Requirements

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	2/28/92	3/4/92	(b)(4), (b)(6)
Complication	(b)(6),	4/20/92	7/6/92	(b)(6), (b)(4)
Complication		2/5/91	3/8/91	(b)(6), (b)(4)
Complication		7/12/91	7/15/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(4), (	11/15/91	12/15/92	(b)(6), (b)(4)
Complication		12/5/91	9/15/92	
Complication		7/3/91	7/10/91	
Complication		4/8/91	4/11/91	
Complication	(b)(4), (b)(6)	11/6/91	1/8/92	(b)(6), (b)(4)
Observation		7/25/91	6/25/92	
Observation		11/26/91	9/3/92	
Observation		12/23/91	5/13/92	
Observation		12/23/91	10/18/92	
Observation		11/10/89	12/11/89	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6),	9/3/90	1/13/91	(b)(6), (b)(4)
Observation	(b)(6), (b)(4)	1/25/91	2/8/91	(b)(6), (b)(4)
Observation		6/26/91	7/23/91	

2. Inappropriate VT Therapy

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6),	11/29/90	12/14/90	(b)(6), (b)(4)
Observation		7/31/91	9/19/91	
Observation	(b)(6), (b)(4)	10/10/91	11/11/91	(b)(6), (b)(4)
Observation		2/27/90	5/2/90	
Observation		9/20/90	9/27/90	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6), (b)(4)	10/22/90	6/11/91	(b)(6), (b)(4)
Observation		1/31/91	5/3/91	
Observation		5/16/91	5/27/91	
Observation		4/24/91	5/21/91	
Observation		5/14/91	8/8/91	
Observation		9/4/91	9/6/91	
Observation		4/5/91	9/30/91	
Observation		6/27/91	7/19/91	
Observation		11/6/91	11/11/91	

3. **Inappropriate VF Therapy**

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6), (b)(4)	1/14/92	1/22/92	(b)(6), (b)(4)
Observation		1/27/92	1/30/92	
Observation		1/29/92	1/31/92	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6),	11/16/90	11/28/90	(b)(6), (b)(4)
Observation		11/29/90	9/24/91	
Observation		2/7/91	3/11/91	
Observation		2/14/91	1/3/92	
Observation		2/27/91	3/4/91	
Observation		7/24/91	12/27/91	
Observation		7/31/91	5/19/92	
Observation		8/21/91	12/26/91	
Observation		9/10/91	6/3/92	
Observation		10/3/91	10/31/91	
Observation		11/8/91	12/16/91	
Observation		11/7/91	12/3/91	
Observation		11/26/91	11/28/91	
Observation		12/11/91	5/18/92	

(b)(6), (b)(4)

(b)(6), (b)(4)

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6), (b)(4)	12/20/91	2/17/92	(b)(6), (b)(4)
Observation		1/17/92	2/26/92	
Observation		10/31/89	8/31/90	
Observation		11/21/89	2/25/90	
Observation		11/10/89	2/23/90	
Observation		2/15/90	10/18/90	
Observation		3/6/90	6/21/90	
Observation		9/27/90	10/18/91	
Observation		4/17/90	10/19/90	
Observation		5/3/90	10/22/90	
Observation		8/30/90	9/2/91	
Observation		10/22/90	6/11/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6),	10/5/90	5/13/91	(b)(6), (b)(4)
Observation		11/12/90	11/19/91	
Observation		2/28/91	4/9/91	
Observation (2 events)		2/21/91	10/10/91 4/29/92	
Observation		11/28/90	1/8/91	
Observation		12/3/90	1/9/91	
Observation		2/21/91	10/25/91	
Observation		1/31/91	5/3/91	
Observation		3/25/91	5/6/91	
Observation (2 events)		3/27/91	2/26/92 9/9/92	
Observation		4/9/91	7/18 /91	
Observation		3/19/91	3/25/91	

(b)(6), (b)(4)

(b)(6), (b)(4)

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6), (b)(4)	6/17/91	7/23/91	(b)(6), (b)(4)
Observation		2/27/91	10/24/91	
Observation		5/15/91	2/10/92	
Observation		3/13/91	9/27/91	
Observation		5/16/91	6/18/91	
Observation		4/29/91	5/3/91	
Observation		4/24/91	5/21/91	
Observation		7/8/91	11/1/91	
Observation		4/5/91	9/30/91	
Observation		7/22/91	1/10/92	
Observation		9/19/91	5/14/92	
Observation		9/25/91	11/21/91	
Observation		8/23/91	4/10/92	
Observation		6/27/91	7/19/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6), (b)(4)	10/25/91	1/23/92	(b)(6), (b)(4)
Observation		9/26/91	11/19/91	

4. Loss of Capture

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6), (b)(4)	2/14/92	2/18/92	(b)(6), (b)(4)
Complication		8/30/91	9/3/91	
Complication		11/6/91	11/19/91	
Complication		12/26/91	1/7/92	
Complication		9/13/90	9/21/90	
Complication		8/26/91	8/30/91	
Observation		2/10/92	3/11/92	
Observation		8/21/91	10/2/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation (2 events)	(b)(6),	12/23/91	1/8/92 10/21/92	(b)(6), (b)(4)
Observation		12/17/91	12/11/92	
Observation		10/31/89	11/22/90	
Observation		1/19/90	11/26/91	
Observation		4/11/91	6/26/92	
Observation		6/12/91	12/8/92	
Observation		5/28/91	7/2/91	
Observation		10/2/91	11/26/91	
Observation		10/23/91	10/28/91	

(b)(6), (b)(4)

(b)(6), (b)(4)

B. Sensing Related

1. Oversensing

Complication /Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6),	1/20/92	8/12/92	(b)(6), (b)(4)
Observation		1/14/92	4/22/92	
Observation		12/30/91	2/10/92	
Observation		1/10/92	2/14/92	
Observation		2/10/92	6/24/92	
Observation		2/4/92	4/7/92	

(b)(6), (b)(4)

(b)(6), (b)(4)

Complication /Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6),	3/2/92	12/30/92	(b)(6), (b)(4)
Observation		2/24/92	4/8/92	
Observation		4/3/92	5/26/92	
Observation		11/19/90	2/6/91	
Observation (2 events)		2/7/91	5/21/91 11/3/92	
Observation		7/10/91	7/15/91	
Observation		8/1/91	4/2/92	
Observation		8/12/91	8/21/91	
Observation		9/4/91	9/9/91	
Observation		9/10/91	6/3/92	
Observation		9/13/91	2/3/92	
Observation		9/20/91	6/23/92	
Observation		10/23/91	10/30/91	
Observation		10/23/91	4/23/92	
Observation		11/5/91	12/9/91	
Observation		10/31/91	11/1/91	
Observation		11/7/91	5/4/92	

(b)(6), (b)(4)

(b)(6), (b)(4)

Complication /Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6),	11/26/91	1/9/92	(b)(6), (b)(4)
Observation		11/19/91	6/24/92	
Observation		11/25/91	11/27/91	
Observation		12/9/91	12/12/91	
Observation		1/7/92	2/2/92	
Observation		12/23/91	6/23/92	
Observation		12/17/91	6/22/92	
Observation		12/16/91	1/4/92	
Observation		10/24/90	6/5/92	
Observation	(b)(6), (b)(4)	10/5/90	12/20/91	(b)(6), (b)(4)
Observation		11/13/90	11/12/91	
Observation		2/21/91	2/21/92	
Observation		4/19/91	5/19/92	
Observation		6/5/90	11/27/90	
Observation (2 events)		3/27/92	6/16/92 9/9/92	
Observation		6/17/91	10/19/92	
Observation		5/15/91	2/10/92	
Observation		5/14/91	8/8/91	
Observation		5/15/91	2/21/92	

Complication /Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6)	9/19/91	5/14/92	(b)(6), (b)(4)
Observation		4/18/91	4/25/91	
Observation		4/24/91	5/15/91	
Observation		7/4/91	12/19/91	
Observation		9/17/91	10/21/91	
Observation		8/23/91	8/28/91	
Observation		9/25/91	2/28/92	
Observation		8/23/91	4/10/92	
Observation		11/6/91	5/4/92	
Observation		10/25/91	11/19/91	

(b)(6), (b)(4)

(b)(6), (b)(4)

2. Undersensing

There have been no reports of undersensing in VF, VT or sinus rhythm.

C. Pocket Related

1. Skin Erosion

Complication /Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	2/22/91	4/17/91	(b)(4), (b)(6)
Observation		9/24/91	12/2/91	
Complication		5/30/90	2/17/92	

(b)(6)

(b)(4), (b)(6)

Complication	(b)(6), (b)(4)	11/13/90	1/14/92	(b)(6), (b)(4)
Complication		4/5/91	6/4/92	
Complication		9/17/91	1/22/92	

2. Pocket Infection

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6), (b)(4)	12/23/91	2/19/92	(b)(6), (b)(4)
Complication		2/5/92	3/20/92	
Complication		2/11/92	10/30/92	
Complication		3/6/92	8/24/92	
Complication		4/11/91	3/20/91	
Complication		2/26/91	5/16/91	
Complication		4/1/92	5/7/92	
Complication		4/27/92	6/4/92	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6), (	7/18/91	8/11/91	(b)(6), (b)(4)
Complication		7/31/91	9/19/91	
Complication		8/9/91	8/30/91	
Complication		11/14/91	2/7/92	
Complication		2/2/90	9/8/90	
Complication		4/12/90	10/8/90	
Complication		5/2/90	9/5/90	
Complication		5/10/90	8/12/90	
Complication		5/3/90	2/17/92	
Complication		4/5/91	6/4/92	
Complication		4/2/91	5/7/91	

(b)(6), (b)(4)

(b)(6), (b)(4)

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6),	4/25/91	8/12/91	(b)(6), (b)(4)
Complication		10/9/91	11/22/91	
Complication		10/21/91	1/15/92	
Complication		11/22/91	5/30/92	
Complication		9/24/91	3/19/92	
Observation		2/24/92	4/7/92	
Observation	(b)(6), (b)(4)	3/16/92	4/16/92	(b)(6), (b)(4)
Observation		2/22/91	3/28/91	
Observation		6/28/91	10/16/91	
Observation		7/29/91	8/29/91	
Observation		8/28/91	9/24/91	
Observation		11/1/91	12/6/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6),	10/31/89	11/28/89	(b)(6), (b)(4)
Observation	(b)(6), (b)(4)	7/13/90	2/25/92	(b)(6), (b)(4)
Observation		4/25/91	8/9/91	

3. **Seroma**

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6),	1/15/92	2/10/92	(b)(6), (b)(4)
Complication		1/30/92	3/2/92	
Complication		1/17/92	2/19/92	
Complication		12/23/91	10/21/92	
Complication		3/8/91	3/19/91	
Complication		9/17/91	10/21/91	
Observation		3/3/92	3/19/92	
Observation		11/26/90	12/13/90	
Observation		8/30/90	9/29/90	
Observation	(b)(6), (b)(4)	7/13/90	2/1/91	(b)(6), (b)(4)
Observation		11/26/90	12/13/90	
Observation		11/26/90	12/7/90	
Observation		3/26/91	4/9/91	
Observation		4/20/91	5/15/91	
Observation		6/12/91	7/5/91	
Observation		6/10/91	1/23/92	
Observation		6/18/91	7/1/91	
Observation		10/10/91	11/1/91	
Observation		4/25/91	8/9/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6), (b)(4)	10/27/91	11/18/91	(b)(6), (b)(4)

4. Hematoma

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6), (b)(4)	4/27/92	6/4/92	(b)(6), (b)(4)
Complication		8/16/91	9/17/91	
Complication		8/19/91	9/15/91	
Complication		10/24/91	11/22/91	
Complication		9/17/91	1/22/92	
Complication		10/21/91	10/24/91	
Observation		2/13/92	3/10/92	
Observation		1/22/92	2/13/92	
Observation		2/11/92	3/27/92	
Observation		2/11/92	2/19/92	
Observation		2/20/92	3/23/92	
Observation		4/3/92	5/6/92	
Observation		6/5/90	6/12/90	
Observation		7/4/90	7/31/90	
Observation		11/22/90	1/3/91	
Observation		2/25/91	3/6/91	
Observation		3/25/91	4/17/91	
Observation		4/24/91	4/29/91	
Observation		10/21/91	10/24/91	
Observation		7/2/91	8/5/91	
Observation		5/4/91	6/10/91	
Observation		9/17/91	10/29/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6), (b)(4)	7/18/91	8/15/91	(b)(6), (b)(4)

D. Lead Related

1. Pneumothorax

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6), (b)(4)	11/6/91	11/8/91	(b)(6), (b)(4)
Complication		11/23/90	11/30/90	
Observation		10/16/90	10/22/90	

2. Perforation

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6), (b)(4)	11/5/90	11/7/90	(b)(6), (b)(4)
Complication		8/8/91	8/8/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6),	10/31/91	11/29/91	(b)(6), (b)(4)
Complication	(b)(6), (b)(4)	11/6/91	5/6/92	(b)(6), (b)(4)
Complication		7/5/91	7/5/91	
Complication		8/26/91	9/2/91	

3. Subclavian Vein Thrombosis

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6),	11/8/91	1/29/92	(b)(6), (b)(4)
Observation	(b)(6), (b)(4)	2/5/92	3/5/92	(b)(6), (b)(4)

Observation	(b)(6), (b)(4)	12/26/91	4/6/92	(b)(6), (b)(4)
Observation		10/5/90	1/11/91	

4. Lead Fracture

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6), (b)(4)	3/4/92	7/27/92	(b)(6), (b)(4)
Complication		4/20/92	11/9/92	
Complication		2/11/91	8/5/91	
Complication		8/7/91	4/17/92	
Complication		11/1/91	5/20/92	
Complication		5/3/90	6/24/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6),	12/3/90	5/16/91	(b)(6), (b)(4)
Complication	(b)(6), (b)(4)	8/9/91	8/17/92	(b)(6), (b)(4)
Complication		7/23/91	2/10/92	

5. Subcutaneous Patch Crinkling

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6),	11/26/90	12/13/90	(b)(6), (b)(4)
Complication		4/25/91	5/2/91	
Complication		5/17/91	6/25/91	
Complication	(b)(6), (b)(4)	8/9/91	12/4/91	(b)(6), (b)(4)
Complication		6/28/91	10/24/91	
Complication		1/29/92	4/5/92	
Complication		7/22/91	10/18/91	
Observation		2/11/92	3/27/92	

Observation	(b)(6),	11/19/90	6/26/91	(b)(6), (b)(4)
Observation		12/11/91	6/17/92	
Observation	(b)(6), (b)(4)	6/1/90	9/17/90	(b)(6), (b)(4)
Observation		4/25/91	5/2/91	

6. Lead Dislodgement

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6),	1/15/92	2/03/92	(b)(6), (b)(4)
Complication		12/23/91	2/19/92	
Complication	(b)(6), (b)(4)	1/7/92	10/21/92	(b)(6), (b)(4)
Complication		1/23/92	2/7/92	
Complication (2 events)		1/30/92	8/7/92* 8/10/92	
Complication		2/25/92	3/24/92	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6),	3/3/92	3/6/92	(b)(6), (b)(4)
Complication		2/28/92	4/2/92	
Complication		3/16/92	4/16/92	
Complication		3/12/92	4/16/92	
Complication		4/20/92	6/17/92 6/18/92	
Complication	(b)(6), (b)(4)	11/21/89	11/30/89	(b)(6), (b)(4)
Complication		11/7/90	2/13/91	
Complication		10/26/90	11/5/90	
Complication		11/16/90	12/11/90	
Observation		*11/28/90*	*1/10/91*	
Complication		2/2/91	2/2/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6),	2/15/91	7/20/92	(b)(6), (b)(4)
Complication		2/26/91	3/22/91	
Complication		7/19/91	9/26/91	
Complication		7/1/91	5/18/92	
Complication		7/23/91	7/29/91	
Complication		7/29/91	11/3/92	
Complication	(b)(6), (b)(4)	7/3/91	9/9/91	(b)(6), (b)(4)
Observation		*7/31/91*	*9/4/91*	
Complication		3/30/92	3/31/92	
Complication		8/28/91	10/9/91	
Complication (2 events)		8/26/91	9/12/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6),	8/15/91	8/19/91	(b)(6), (b)(4)
Complication		8/28/91	12/23/91	
Complication		8/30/91	9/3/91	
Complication		9/3/91	9/6/91	
Complication		9/3/91	10/14/91	
Complication		9/3/91	9/9/91	
Complication		9/6/91	12/21/91	
Complication		9/11/91	10/16/91	
Complication		9/16/91	9/19/91	
Complication		10/1/91	10/8/91	
Complication		10/4/91	10/5/92	
Observation		*10/10/91*	*11/11/91*	

(b)(6), (b)(4)

(b)(6), (b)(4)

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication (2 events)	(b)(6),	10/11/91	10/15/91 3/9/92	(b)(6), (b)(4)
Complication		10/23/91	10/30/91	
Complication		10/24/91	12/6/91	
Complication		10/30/91	11/20/91	
Complication (2 events)	(b)(6), (b)(4)	11/1/91	12/9/91 1/27/92	(b)(6), (b)(4)
Complication		11/7/91	12/13/91	
Complication		11/6/91	5/6/92	
Observation		*11/26/91*	*12/2/91*	
Complication		11/14/91	11/18/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6),	11/19/91	11/27/91	(b)(6), (b)(4)
Complication		11/26/91	11/29/91	
Complication		12/5/91	1/9/92	
Observation		*11/27/91*	*1/10/92*	
Complication		12/9/91	2/12/92	
Complication		12/11/91	1/14/92	
(b)(6), (b)(4)				(b)(6), (b)(4)
Observation		*12/12/91*	*12/16/91*	
Complication		12/19/91	2/18/92	
Complication		12/26/91	1/7/92	
Complication		12/20/91	1/14/92	
Complication		11/26/90	12/13/90	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6), (	10/3/89	11/10/89	(b)(6), (b)(4)
Complication		1/19/90	3/15/90	
Observation		*9/27/90*	*6/21/91*	
Complication		5/4/90	5/9/90	
Complication		5/25/90	2/28/91	
Complication	(b)(6), (b)(4)	8/31/90	12/3/90	(b)(6), (b)(4)
Complication		9/13/90	10/16/90	
Complication		10/5/90	1/11/91	
Complication		11/13/90	3/14/91	
Complication		11/28/90	1/8/91	
Complication		2/5/91	2/11/91	
Complication		11/23/90	12/4/90	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6),	*2/14/91*	*2/21/91*	(b)(6), (b)(4)
Observation		*4/15/91*	*10/25/91*	
Complication		4/11/91	5/3/91	
Complication		4/2/91	4/16/91	
Complication		5/13/91	5/17/91	
Complication	(b)(6), (b)(4)	3/13/91	4/11/91	(b)(6), (b)(4)
Complication		4/29/91	8/8/91	
Complication		6/7/91	8/14/91	
Complication		6/12/91	11/11/91	
Complication		8/9/91	9/20/91	
Complication		8/16/91	9/20/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6), (b	/24/91	8/12/91	(b)(6), (b)(4)
Complication		/17/91	6/21/91	
Complication		4/7/91	5/10/91	
Observation		*6/20/91*	*7/25/91*	
Complication		7/8/91	10/8/91	
Observation		*8/23/91*	*9/27/91*	
Complication	(b)(6), (b)(4)	8/29/91	9/11/91	(b)(6), (b)(4)
Complication		4/25/91	5/24/91	
Complication		10/2/91	11/26/91	
Complication		9/19/91	10/2/91	
Complication		10/2/91	10/23/91	
Complication		10/24/91	2/6/92	

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Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6),	*8/23/91*	*12/6/91*	(b)(6), (b)(4)
Complication	(b)(6), (b)(4)	4/29/91	5/6/91	(b)(6), (b)(4)
Complication		7/18/91	8/15/91	

E. Other Complications

1. Pacemaker Syndrome

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6),	11/27/90	5/16/91	(b)(6), (b)(4)
Observation	(b)(6), (b)(4)	11/26/91	2/19/92	(b)(6), (b)(4)

2. Early Device Explant

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6),	3/19/92	3/23/92	(b)(6), (b)(4)
Complication	(b)(6), (b)(4)	11/7/90	2/13/91	(b)(6), (b)(4)
Complication		11/29/90	1/4/91	

III

Death Summaries

A

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6), (b)(6), (b)(4)	11/25/91	1/30/92	(b)(6), (b)(6), (b)(4)

III. Death Summaries

A. Perioperative Death Summaries

Perioperative deaths include all deaths occurring within thirty days of implant. The perioperative death summaries are also included in the appropriate sections of this report discussing specific death catagories.

1. Patient (b)(6)

PCD Serial Number: (b)(4), (b)(6)
Date of Implant: (b)(4), (b)(6)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4)

(b)(4)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as periopertive, non-sudden cardiac and related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and felt that the death was related to the implant procedure and not the implanted PCD Transvene System.

2. Patient (b)(6), (b)(4)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant:
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	OFF
VT NID	OFF
VT Rx #1	OFF
VT Rx #2	OFF
VT Rx #3	OFF
VT Rx #4	OFF
FDI	320 ms
VF NID	24
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

3. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant:
Date of Death:
Death Classification: Noncardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

110

Parameter	Value
Sensitivity	0.3 mV
TDI	450 ms
VT NID	20
VT Rx #1	CV/34J/SEQ
VT Rx #2	CV/34J/SEQ
VT Rx #3	CV/34J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	380 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

4. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant:
Date of Death:
Death Classification: Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	490 ms
VT NID	12
VT Rx #1	Burst
VT Rx #2	CV/5J/SIM
VT Rx #3	CV/34J/SIM
VT Rx #4	CV/34J/SIM
FDI	320 ms
VF NID	18
VF Rx #1	18J/SIM
VF Rx #2	34J/SIM
VF Rx #3	34J/SIM
VF Rx #4	34J/SIM

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as perioperative and sudden cardiac. The relationship of the death to the implanted PCD Transvene System was classified as unknown. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

5. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant:
Date of Death:
Death Classification: Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	450 ms
VT NID	12
VT Rx #1	Ramp
VT Rx #2	CV/34J/SINGLE
VT Rx #3	CV/34J/SINGLE
VT Rx #4	CV/34J/SINGLE
FDI	300 ms
VF NID	12
VF Rx #1	34J/SINGLE
VF Rx #2	34J/SINGLE
VF Rx #3	34J/SINGLE
VF Rx #4	34J/SINGLE

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as perioperative, sudden cardiac and not related to the implanted PCD Transvene System. The investigator felt that the patient's death was related to her severe left ventricular dysfunction. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

B. Sudden Cardiac Death Summaries

1. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant:
Date of Death:
Death Classification: Sudden Cardiac

(b)(4), (b)(6)

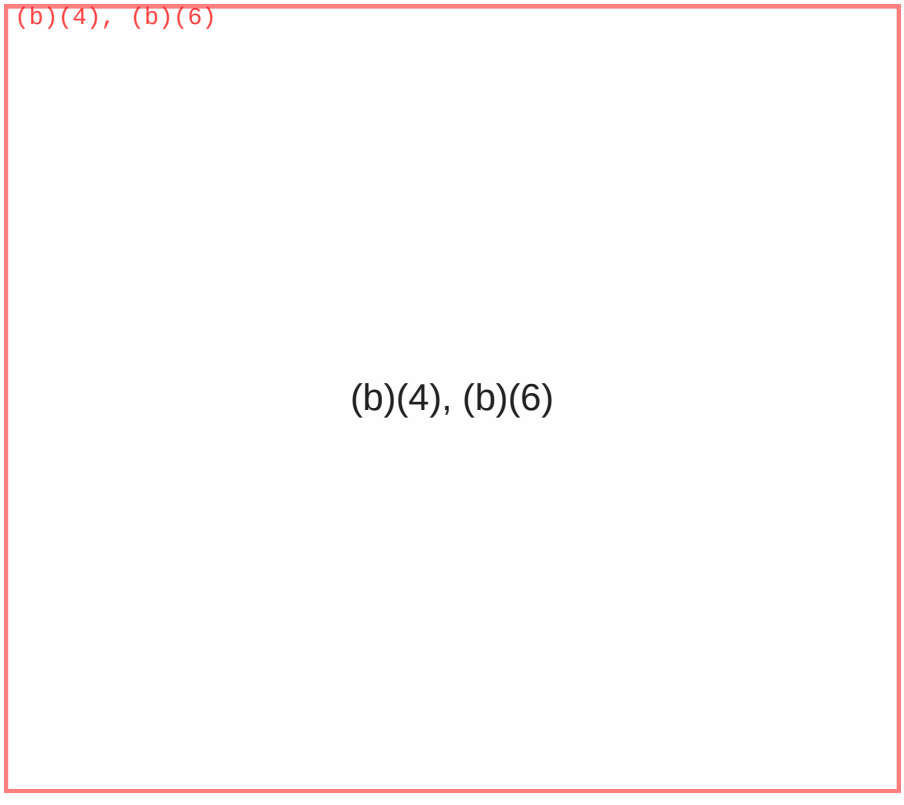
One P

(b)(4), (b)(6)

170

Parameter	Value
Sensitivity	0.3 mV
TDI	440 ms
VT NID	16
VT Rx #1	CV/34J/SEQ
VT Rx #2	CV/34J/SEQ
VT Rx #3	CV/34J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	400 ms
VF NID	30
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)



The investigator classified this patient death as sudden cardiac and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

2. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant:
Date of Death:
Death Classification: Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	490 ms
VT NID	12
VT Rx #1	Burst
VT Rx #2	CV/5J/SIM
VT Rx #3	CV/34J/SIM
VT Rx #4	CV/34J/SIM
FDI	320 ms
VF NID	18
VF Rx #1	18J/SIM
VF Rx #2	34J/SIM
VF Rx #3	34J/SIM
VF Rx #4	34J/SIM

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as perioperative and sudden cardiac. The relationship of the death to the implanted PCD Transvene System was classified as unknown. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

3. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	450 ms
VT NID	12
VT Rx #1	Ramp
VT Rx #2	CV/34J/SINGLE
VT Rx #3	CV/34J/SINGLE
VT Rx #4	CV/34J/SINGLE
FDI	300 ms
VF NID	12
VF Rx #1	34J/SINGLE
VF Rx #2	34J/SINGLE
VF Rx #3	34J/SINGLE
VF Rx #4	34J/SINGLE

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as perioperative, sudden cardiac and not related to the implanted PCD Transvene System. The investigator felt that the patient's death was related to her severe left ventricular dysfunction. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

4. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant:
Date of Death:
Death Classification: Sudden Cardiac

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	600
VT NID	16
VT Rx #1	burst
VT Rx #2	ramp
VT Rx #3	burst
VT Rx #4	CV, 1J
FDI	330
VF NID	18
VF Rx #1	34J, Seq
VF Rx #2	34J, Seq
VF Rx #3	34J, Seq
VF Rx #4	34J,Seq

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified the patient death as Sudden Cardiac (Witnessed) and not related to the implanted PCD Transvene System. The European CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

5. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant:
Date of Death:
Death Classification: Sudden Cardiac

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.6 mV
TDI	350
VT NID	12
VT Rx #1	Burst
VT Rx #2	18J,CV
VT Rx #3	34J,CV
VT Rx #4	34J,CV
FDI	280
VF NID	18
VF Rx #1	34J, Seq
VF Rx #2	34J, Seq
VF Rx #3	34J, Seq
VF Rx #4	34J,Seq

(b)(4), (b)(6)

(b)(4), (b)(6)

Based on the information received the investigator classified the patient death as Sudden Cardiac (Unwitnessed). The European CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

C. **Non-Sudden Cardiac**

1. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant:
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as periopertive, non-sudden cardiac and related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and felt that the death was related to the implant procedure and not the implanted PCD Transvene System.

2. Patient (b)(6)

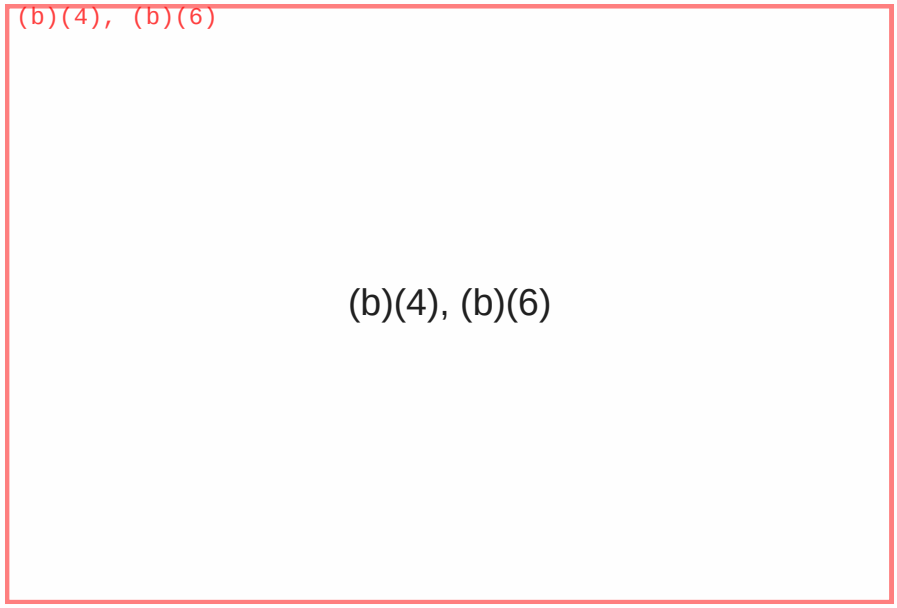
PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	420 ms
VT NID	12
VT Rx #1	Burst
VT Rx #2	Burst
VT Rx #3	CV/18J/SIM
VT Rx #4	CV/34J/SIM
FDI	320 ms
VF NID	18
VF Rx #1	18J/SIM
VF Rx #2	34J/SIM
VF Rx #3	34J/SIM
VF Rx #4	34J/SIM

(b)(4), (b)(6)



3. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-sudden Cardiac: CHF

(b)(4), (b)(6)

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	500
VT NID	16
VT Rx #1	Burst
VT Rx #2	18J,CV
VT Rx #3	34J,CV
VT Rx #4	34J,CV
FDI	350
VF NID	12
VF Rx #1	34J
VF Rx #2	34J
VF Rx #3	34J
VF Rx #4	34J

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified the patient death as non-sudden cardiac and not related to the implanted PCD Transvene System. The North American CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

4. Patient (b)(6)

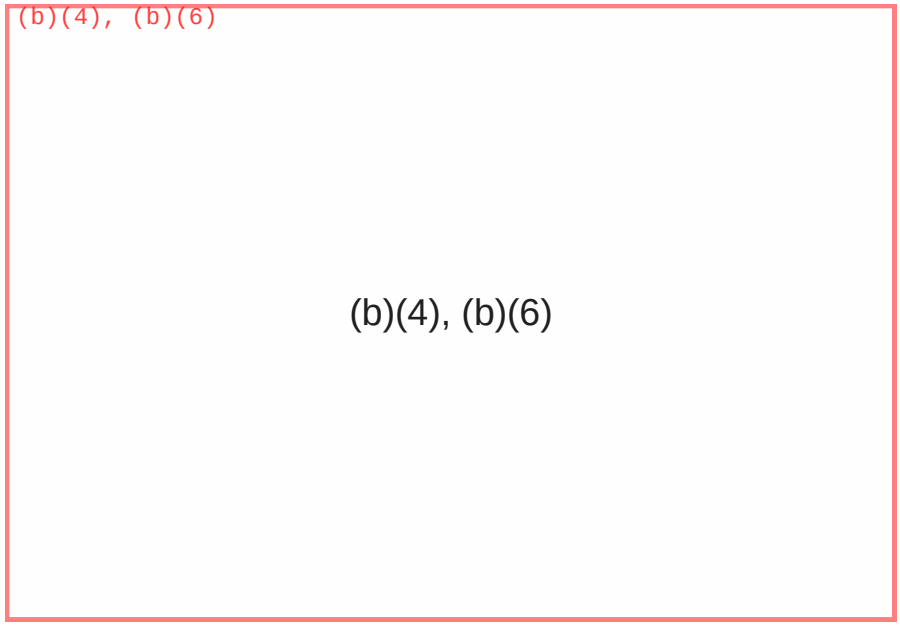
PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Noncardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.6 mV
TDI	470 ms
VT NID	16
VT Rx #1	Ramp
VT Rx #2	Ramp
VT Rx #3	CV/34J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	300 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)



(b)(4), (b)(6)

(b)(4), (b)(6)

The cause of death was reported as noncardiac secondary to brain carcinoma by the investigator and not related to the implanted PCD Transvene System. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

5. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-sudden Cardiac (Non-arrhythmic)

(b)(4), (b)(6)

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	off
VT NID	off
VT Rx #1	off
VT Rx #2	off
VT Rx #3	off
VT Rx #4	off
FDI	320
VF NID	12
VF Rx #1	34J, SEQ
VF Rx #2	34J, SEQ
VF Rx #3	34J, SEQ
VF Rx #4	34J, SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified the patient death as non-sudden cardiac (non-arrhythmic) and not related to the implanted PCD Transvene System. The North American CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

6. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	420 ms
VT NID	16
VT Rx #1	Ramp
VT Rx #2	CV,34J,Seq
VT Rx #3	CV,34J,Seq
VT Rx #4	CV,34J,Seq
FDI	320 ms
VF NID	18
VF Rx #1	34J,Seq
VF Rx #2	34J,Seq
VF Rx #3	34J,Seq
VF Rx #4	34J,Seq

(b)(4), (b)(6)

(b)(4), (b)(6)

7. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

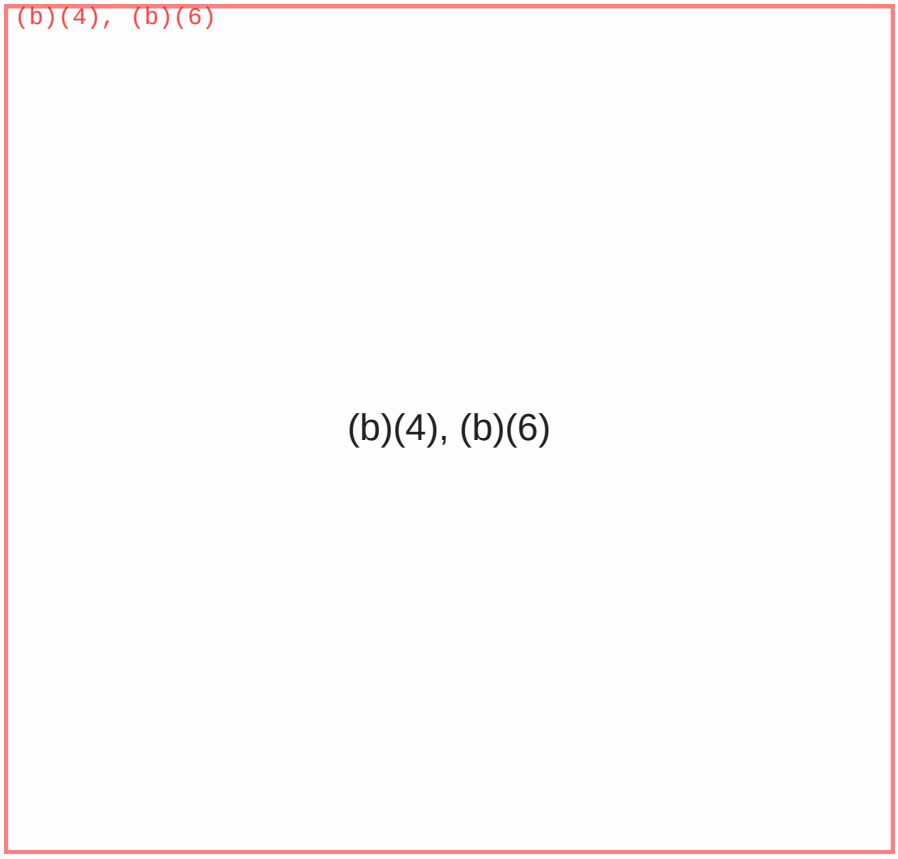
(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

300

Parameter	Value
Sensitivity	0.3 mV
TDI	350
VT NID	16
VT Rx #1	Ramp
VT Rx #2	CV, 5J
VT Rx #3	CV, 34J
VT Rx #4	CV, 34J
FDI	270
VF NID	18
VF Rx #1	18J, sim
VF Rx #2	34J, sim
VF Rx #3	34J, sim
VF Rx #4	34J, sim

(b)(4), (b)(6)



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(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator originally classified the patient death as non-cardiac and not related to the implanted PCD Transvene System. However, the North American CERC commitee recommended reclassification of the death to non-sudden cardiac after full review of the circumstances surrounding the patient's death.

8. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

the last follow-up visit was as follows:

Parameter	Value
Sensitivity	0.6 mV
TDI	350 ms
VT NID	16
VT Rx #1	CV/34J/SEQ
VT Rx #2	CV/34J/SEQ
VT Rx #3	CV/34J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	300 ms
VF NID	18
VF Rx #1	18J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

9. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	OFF
VT NID	OFF
VT Rx #1	OFF
VT Rx #2	OFF
VT Rx #3	OFF
VT Rx #4	OFF
FDI	350 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

The cause of death was reported as non-sudden cardiac secondary to end stage heart failure by the investigator and not related to the implanted PCD Transvene System. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

10. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The PCD device programmed status at the last follow-up visit was as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	OFF
VT NID	OFF
VT Rx #1	OFF
VT Rx #2	OFF
VT Rx #3	OFF
VT Rx #4	OFF
FDI	320 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

11. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

09

(b)(4), (b)(6)

(b)(4), (b)(6)

The PCD device programmed status at the time of the patient's death was as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	480 ms
VT NID	16
VT Rx #1	CV/1.0J/SEQ
VT Rx #2	CV/34J/SEQ
VT Rx #3	CV/34J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	320 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

The CERC reviewed the circumstances of this patient death and classified this patient death as perioperative and

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procedure related. The CERC also indicated that the increased frequency in spontaneous VT/VF episodes may have been related to the increased number of inductions during the implant procedure.

12. Patient (b)(6)

PCD Serial Number:	(b)(6), (b)(4)
Date of Implant:	
Date of Death:	
Death Classification:	Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

The PCD device programmed status at this time was as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	380 ms
VT NID	16
VT Rx #1	CV/10J/SEQ
VT Rx #2	CV/34J/SEQ
VT Rx #3	CV/34J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	290 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

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(b)(4), (b)(6)

(b)(4), (b)(6)

The cause of death was reported as non-sudden cardiac secondary to intractable VT by the investigator and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of the patient death and agreed with the investigator's classification.

13. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant:
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	OFF
VT NID	OFF
VT Rx #1	OFF
VT Rx #2	OFF
VT Rx #3	OFF
VT Rx #4	OFF
FDI	320 ms
VF NID	24
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

14. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	500
VT NID	16
VT Rx #1	Burst
VT Rx #2	Burst
VT Rx #3	Burst
VT Rx #4	34J,CV
FDI	320
VF NID	18
VF Rx #1	34J, seq
VF Rx #2	34J, seq
VF Rx #3	34J, seq
VF Rx #4	34J, seq

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified the patient death as Non-Sudden - Cardiac and not related to the implanted PCD Transvene System. The North American CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

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15. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	450
VT NID	12
VT Rx #1	Ramp
VT Rx #2	2J,CV
VT Rx #3	34J,CV
VT Rx #4	34J,CV
FDI	330
VF NID	12
VF Rx #1	34J, sim
VF Rx #2	34J, sim
VF Rx #3	34J, sim
VF Rx #4	34J, sim

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified the patient death as non-sudden cardiac and not related to the implanted PCD Transvene System. The North American CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

16. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant:
Date of Death:
Death Classification: Non-sudden Cardiac

(b)(4), (b)(6)

episode – 12.7 seconds).

The programmed parameters at last known follow-up are as follows:

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Parameter	Value
Sensitivity	0.3 mV
TDI	500
VT NID	24
VT Rx #1	Burst
VT Rx #2	CV, 0.6J
VT Rx #3	CV, 30J
VT Rx #4	CV, 34 J
FDI	360
VF NID	18
VF Rx #1	34J, seq
VF Rx #2	34J, seq
VF Rx #3	34J, seq
VF Rx #4	34J, seq

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified the patient death as non-sudden cardiac and not related to the implanted PCD Transvene System. The North American CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

17. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant:
Date of Death:
Death Classification: Non-sudden Cardiac

(b)(4), (b)(6)

parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	440 ms
VT NID	16
VT Rx #1	Ramp
VT Rx #2	CV,8J,Seq
VT Rx #3	CV,34J,Seq
VT Rx #4	CV,34J,Seq
FDI	330 ms
VF NID	18
VF Rx #1	34J,Seq
VF Rx #2	34J,Seq
VF Rx #3	34J,Seq
VF Rx #4	34J,Seq

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified the patient death as non-sudden cardiac (Non arrhythmic) and not related to the implanted PCD Transvene System. The North American CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

18. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

failure. The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	430 ms
VT NID	20
VT Rx #1	Burst
VT Rx #2	CV,10J,Seq
VT Rx #3	CV,34J,Seq
VT Rx #4	CV,34J,Seq
FDI	320
VF NID	18
VF Rx #1	34J,Seq
VF Rx #2	34J,Seq
VF Rx #3	34J,Seq
VF Rx #4	34J,Seq

(b)(4), (b)(6)

(b)(4), (b)(6)

19. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.6 mV
TDI	430 ms
VT NID	16
VT Rx #1	Ramp
VT Rx #2	Burst
VT Rx #3	CV, 15J, Seq
VT Rx #4	CV, 15J, Seq
FDI	290 ms
VF NID	18
VF Rx #1	34J, Seq
VF Rx #2	34J, Seq
VF Rx #3	34J, Seq
VF Rx #4	34J, Seq

(b)(4), (b)(6)

(b)(4), (b)(6)

CERC agreed The investigator classified the patient death as Non-sudden Cardiac (non-arrhythmic) and not related to the implanted PCD Transvene System. The North American CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

20. Patient (b)(6)

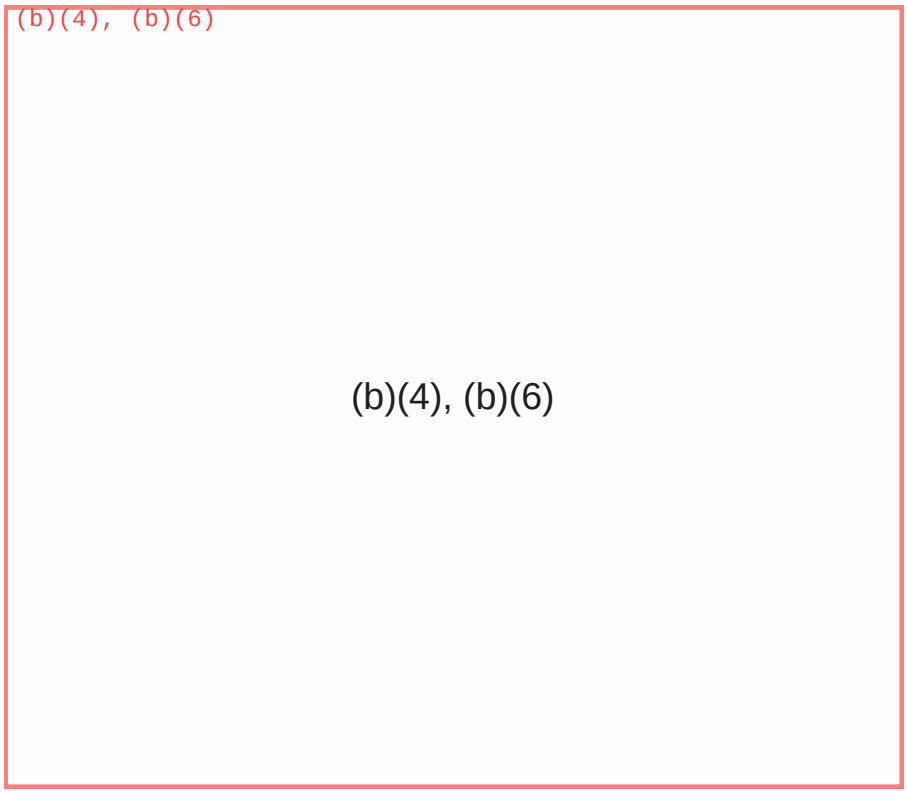
PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	OFF
VT NID	-
VT Rx #1	OFF
VT Rx #2	-
VT Rx #3	-
VT Rx #4	-
FDI	330 ms
VF NID	12
VF Rx #1	18J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)



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(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as non-sudden cardiac however it was related to an arrhythmic event. In addition, the investigator indicated that this death was not related to the implanted PCD Transvene System. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

21. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.6 mV
TDI	400
VT NID	16
VT Rx #1	off
VT Rx #2	off
VT Rx #3	off
VT Rx #4	off
FDI	340
VF NID	18
VF Rx #1	34J
VF Rx #2	34J
VF Rx #3	34J
VF Rx #4	34J

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(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified the patient death as Non-Sudden: Cardiac and not related to the implanted PCD Transvene System. The North American CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

22. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

35

(b)(4), (b)(6)

(b)(4), (b)(6)

status was as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	440 ms
VT NID	12
VT Rx #1	Burst
VT Rx #2	CV/10J/SIM
VT Rx #3	CV/20J/SIM
VT Rx #4	CV/34J/SIM
FDI	330 ms
VF NID	18
VF Rx #1	34J/SIM
VF Rx #2	34J/SIM
VF Rx #3	34J/SIM
VF Rx #4	34J/SIM

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as non-sudden cardiac and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

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23. Patient (b)(6), (b)(4)

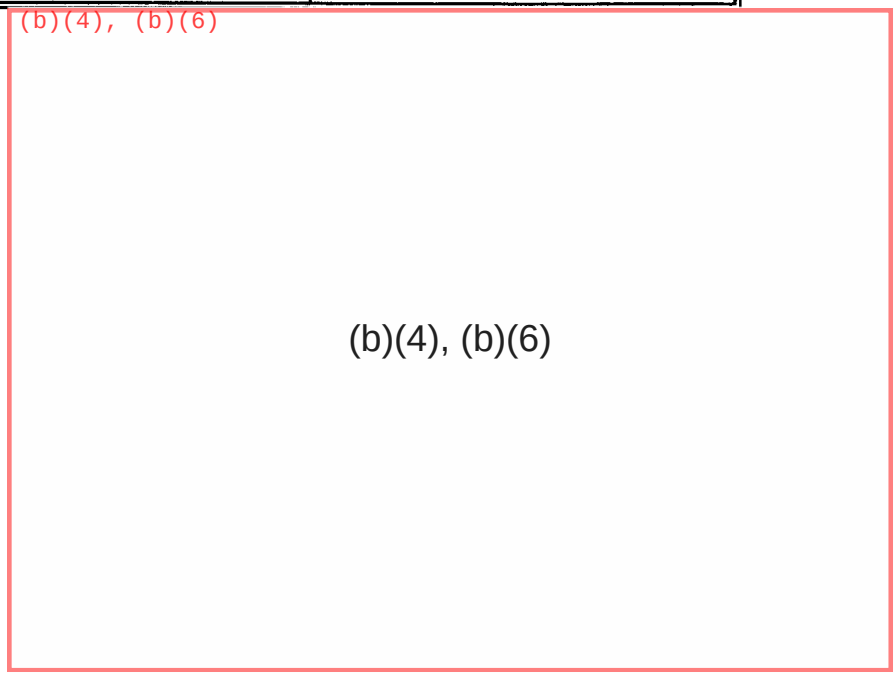
PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.6 mV
TDI	OFF
VT NID	--
VT Rx #1	OFF
VT Rx #2	OFF
VT Rx #3	OFF
VT Rx #4	OFF
FDI	370 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)



The investigator classified this patient death as cardiac, non-sudden and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigators classification.

24. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

follow-up prior to the patient's death was as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	OFF
VT NID	--
VT Rx #1	OFF
VT Rx #2	OFF
VT Rx #3	OFF
VT Rx #4	OFF
FDI	400 ms
VF NID	12
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	

H

25. Patient (b)(6)

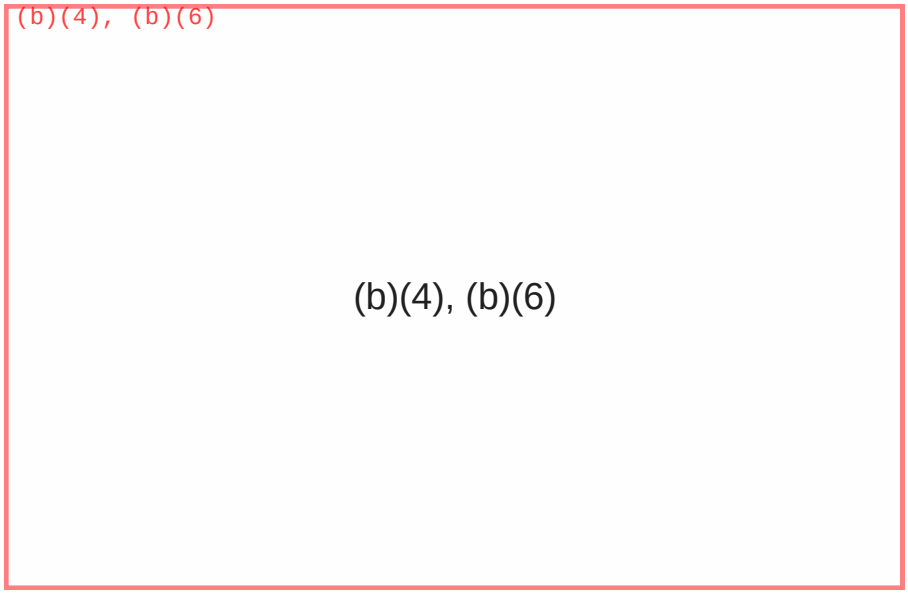
PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	400 ms
VT NID	16
VT Rx #1	Burst
VT Rx #2	CV/5J/SEQ
VT Rx #3	CV/20J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	320 ms
VF NID	24
VF Rx #1	18J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)



The primary investigator classified this patient death as non-sudden cardiac and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigators classification.

26. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	400 ms
VT NID	16
VT Rx #1	Burst
VT Rx #2	Burst
VT Rx #3	CV/18J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	370 ms
VF NID	24
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

The primary investigator classified this patient death as non-sudden cardiac due to end stage heart failure and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

27. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	400 ms
VT NID	16
VT Rx #1	Ramp
VT Rx #2	Burst
VT Rx #3	CV/15J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	320 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

The primary investigator classified this patient death as non-sudden cardiac due to end stage heart failure with associated pulmonary embolus. The death was also classified as not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

28. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.6 mV
TDI	400
VT NID	12
VT Rx #1	Ramp
VT Rx #2	18J,CV
VT Rx #3	18J,CV
VT Rx #4	34J,CV
FDI	280
VF NID	18
VF Rx #1	34J, Seq
VF Rx #2	34J, Seq
VF Rx #3	34J, Seq
VF Rx #4	34J,Seq

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified the patient death as non-sudden cardiac and not related to the PCD system. The European CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

29. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

350

Parameter	Value
Sensitivity	0.3 mV
TDI	400 ms
VT NID	24
VT Rx #1	CV,22J,Seq
VT Rx #2	CV,34J,Seq
VT Rx #3	CV,34J,Seq
VT Rx #4	CV,34J,Seq
FDI	360 ms
VF NID	12
VF Rx #1	22J,Seq
VF Rx #2	34J,Seq
VF Rx #3	34J,Seq
VF Rx #4	34J,Seq

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified the patient death as non-sudden cardiac (Non-arrhythmic) and not related to the implanted PCD Transvene System. The North American CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

30. Patient (b)(6)

PCD Serial Number: (b)(4), (b)(6)
Date of Implant:
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	440 ms
VT NID	16
VT Rx #1	Ramp
VT Rx #2	CV,2J,Seq
VT Rx #3	CV,10J,Seq
VT Rx #4	CV,34J,Seq
FDI	330 ms
VF NID	18
VF Rx #1	34J,Seq
VF Rx #2	34J,Seq
VF Rx #3	34J,Seq
VF Rx #4	34J,Seq

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified the patient death as Sudden Cardiac (Witnessed) and not related to the implanted PCD Transvene System. The North American CERC committee reviewed the circumstances of this patient's death reclassified the death non-sudden cardiac. The implanting investigator agreed with the reclassification.

31. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	---
VT NID	--
VT Rx #1	OFF
VT Rx #2	OFF
VT Rx #3	OFF
VT Rx #4	OFF
FDI	320
VF NID	18
VF Rx #1	34J,Siml
VF Rx #2	34J,Siml
VF Rx #3	34J,Siml
VF Rx #4	34J,Siml

(b)(4), (b)(6)

(b)(4), (b)(6)

Based on the information received, the investigator classified the patient's death as non-sudden cardiac and not related to the PCD system. The European CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

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D. Non-Cardiac

1. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	off
VT NID	off
VT Rx #1	off
VT Rx #2	off
VT Rx #3	off
VT Rx #4	off
FDI	320
VF NID	18
VF Rx #1	34 J, Seq
VF Rx #2	34 J, Seq
VF Rx #3	34 J, Seq
VF Rx #4	34 J, Seq

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified the patient death as non-cardiac and not related to the implanted PCD Transvene System. The U.S. CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

2. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	350 ms
VT NID	16
VT Rx #1	Ramp
VT Rx #2	CV,34J,Sgl
VT Rx #3	CV,34J,Sgl
VT Rx #4	CV,34J,Sgl
FDI	300 ms
VF NID	12
VF Rx #1	34J,Sgl
VF Rx #2	34J,Sgl
VF Rx #3	34J,Sgl
VF Rx #4	34J,Sgl

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified the patient death as non-cardiac and not related to the implanted PCD Transvene System. The U.S. CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

3. Patient (b)(6)

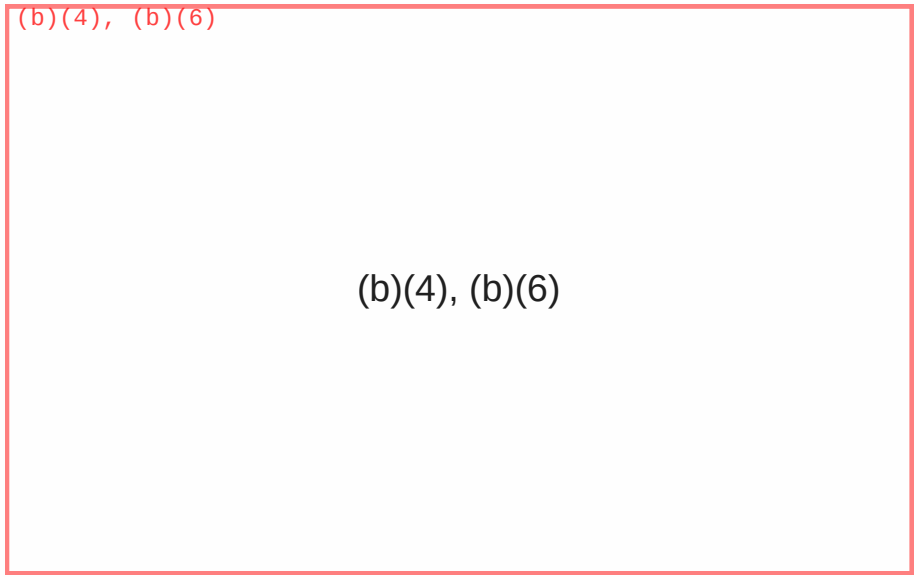
PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Noncardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.6 mV
TDI	OFF
VT NID	OFF
VT Rx #1	OFF
VT Rx #2	OFF
VT Rx #3	OFF
VT Rx #4	OFF
FDI	340 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)



The cause of death was reported as noncardiac secondary to renal failure by the investigator and not related to the implanted PCD Transvene System. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

4. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Noncardiac

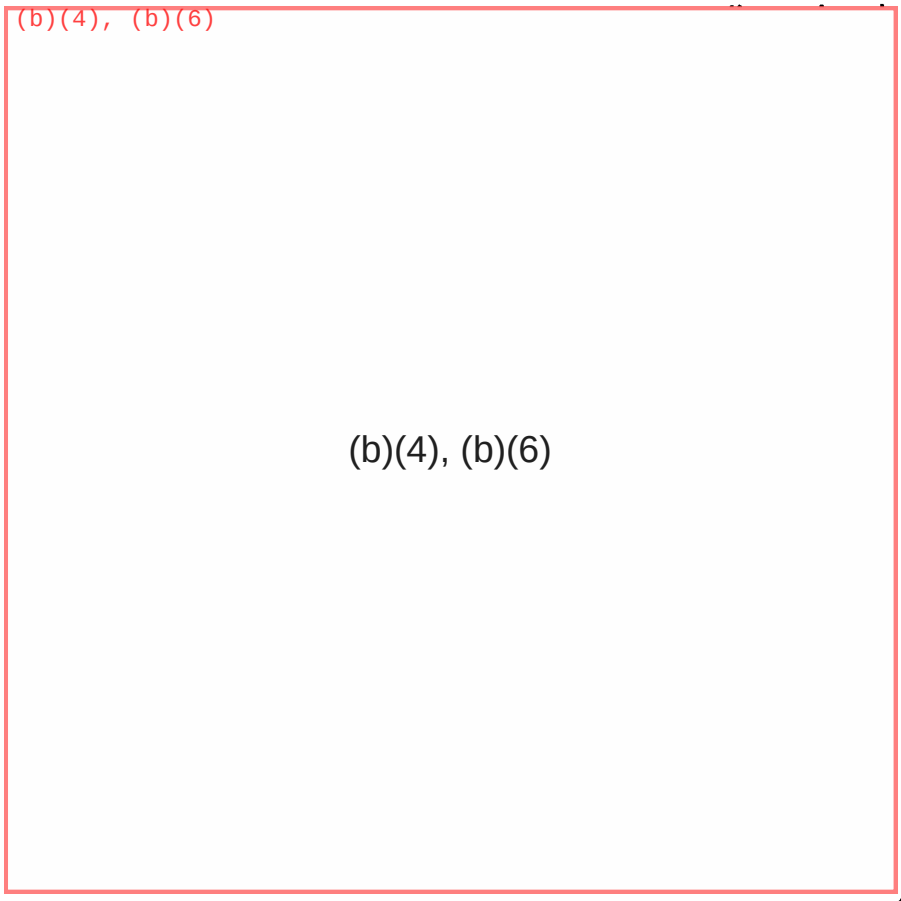
(b)(4), (b)(6)

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	600
VT NID	16
VT Rx #1	Burst
VT Rx #2	Burst
VT Rx #3	Burst
VT Rx #4	Burst
FDI	400
VF NID	18
VF Rx #1	34J, SQ
VF Rx #2	34J, SQ
VF Rx #3	34J, SQ
VF Rx #4	34J, SQ

(b)(4), (b)(6)



(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified the patient death as noncardiac and not related to the implanted PCD Transvene System. The U.S. CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

5. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	380 ms
VT NID	24
VT Rx #1	Ramp
VT Rx #2	Burst
VT Rx #3	CV,34J,Seq
VT Rx #4	CV,34J,Seq
FDI	320
VF NID	18
VF Rx #1	34J,Seq
VF Rx #2	34J,Seq
VF Rx #3	34J,Seq
VF Rx #4	34J,Seq

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified the patient death as non-cardiac and not related to the implanted PCD Transvene System. The U.S. CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

6. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	520 ms
VT NID	16
VT Rx #1	Burst
VT Rx #2	Burst
VT Rx #3	CV,15J,Seq
VT Rx #4	CV,34J,Seq
FDI	320
VF NID	18
VF Rx #1	34J,Seq
VF Rx #2	34J,Seq
VF Rx #3	34J,Seq
VF Rx #4	34J,Seq

The investigator classified the patient death as non-cardiac and not related to the implanted PCD Transvene System. The U.S. CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

7. Patient (b)(6), (b)(4)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.6 mV
TDI	460 ms
VT NID	16
VT Rx #1	Ramp
VT Rx #2	CV,1J,Seq
VT Rx #3	CV,5J,Seq
VT Rx #4	CV,34J,Seq
FDI	280 ms
VF NID	18
VF Rx #1	34J,Seq
VF Rx #2	34J,Seq
VF Rx #3	34J,Seq
VF Rx #4	34J,Seq

The investigator classified the patient death as non cardiac and not related to the implanted PCD Transvene System. The U.S. CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

8. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-cardiac

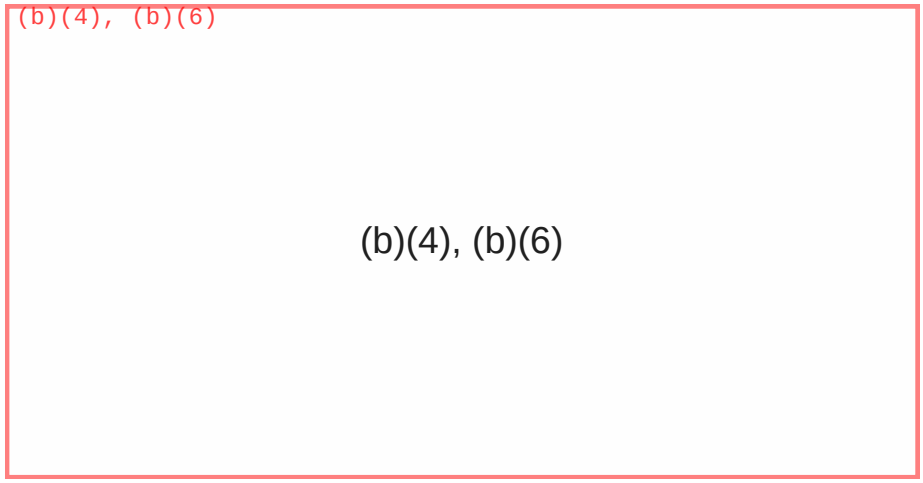
(b)(4), (b)(6)

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	350 ms
VT NID	8
VT Rx #1	Burst
VT Rx #2	CV,34J, Seq
VT Rx #3	CV,34J, Seq
VT Rx #4	CV,34J, Seq
FDI	270 ms
VF NID	12
VF Rx #1	34J, Seq
VF Rx #2	34J, Seq
VF Rx #3	34J, Seq
VF Rx #4	34J, Seq

(b)(4), (b)(6)



The investigator classified the patient death as non-cardiac and not related to the implanted PCD Transvene System. The U.S. CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

9. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Noncardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	450 ms
VT NID	20
VT Rx #1	CV/34J/SEQ
VT Rx #2	CV/34J/SEQ
VT Rx #3	CV/34J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	380 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified the patient death as perioperative, noncardiac and not related to the implanted PCD Transvene System. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

10. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	360 ms
VT NID	20
VT Rx #1	CV, 34J
VT Rx #2	CV, 34J
VT Rx #3	CV, 34J
VT Rx #4	CV, 34J
FDI	300 ms
VF NID	18
VF Rx #1	34J
VF Rx #2	34J
VF Rx #3	34J
VF Rx #4	34J

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified the patient death as non-cardiac and not related to the implanted PCD Transvene System. The U.S. CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

11. Patient (b)(6)

PCD Serial Number:	(b)(6), (b)(4)
Date of Implant:	(b)(6), (b)(4)
Date of Death:	
Death Classification:	Noncardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

device delivered 5 cardioversion therapies of 5 Joules each. The PCD device programmed status was as follows:

Parameter	Value
Sensitivity	0.6 mV
TDI	400 ms
VT NID	16
VT Rx #1	CV/5J/SEQ
VT Rx #2	CV/34J/SEQ
VT Rx #3	CV/34J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	300 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

The cause of death was reported as non-cardiac, specifically respiratory arrest, by the investigator and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

380

12. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	340
VT NID	24
VT Rx #1	OFF
VT Rx #2	34J,CV
VT Rx #3	34J,CV
VT Rx #4	34J,CV
FDI	300
VF NID	18
VF Rx #1	34J, Seq
VF Rx #2	34J, Seq
VF Rx #3	34J, Seq
VF Rx #4	34J,Seq

(b)(4), (b)(6)

(b)(4), (b)(6)

Based on the information received the investigator classified the patient death as non-cardiac and not related to the implanted PCD Transvene System. The European CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

13. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	360 ms
VT NID	24
VT Rx #1	CV,18J,Seq
VT Rx #2	CV,18J,Seq
VT Rx #3	CV,18J,Seq
VT Rx #4	CV,18J,Seq
FDI	320 ms
VF NID	18
VF Rx #1	34J,Seq
VF Rx #2	34J,Seq
VF Rx #3	34J,Seq
VF Rx #4	34J,Seq

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified the patient death as non-cardiac and not related to the implanted PCD Transvene System. The U.S. CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

14. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-cardiac

(b)(6)

(b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.3 Mv
TDI	400
VT NID	16
VT Rx #1	34J,CV
VT Rx #2	34J,CV
VT Rx #3	34J,CV
VT Rx #4	34J,CV
FDI	320
VF NID	18
VF Rx #1	34J,SIML
VF Rx #2	34J,SIML
VF Rx #3	34J,SIML
VF Rx #4	34J,SIML

(b)(6)

(b)(6)

The investigator classified the patient death as non-cardiac and not related to the PCD system. The European CERC committee reviewed the circumstances of this patient's death and agreed with the investigator's classification.

15. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The programmed parameters at last known follow-up are as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	380
VT NID	16
VT Rx #1	Burst
VT Rx #2	34J,CV
VT Rx #3	34J,CV
VT Rx #4	34J,CV
FDI	300
VF NID	18
VF Rx #1	34J,Siml
VF Rx #2	34J,Siml
VF Rx #3	34J,Siml
VF Rx #4	34J,Siml

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified the patient death as non-cardiac. The European CERC has reviewed this death.

E

E. Deaths: Non-standard Lead Configurations and Epicardial Implants

Non-Standard:

1. Patient (b)(6)

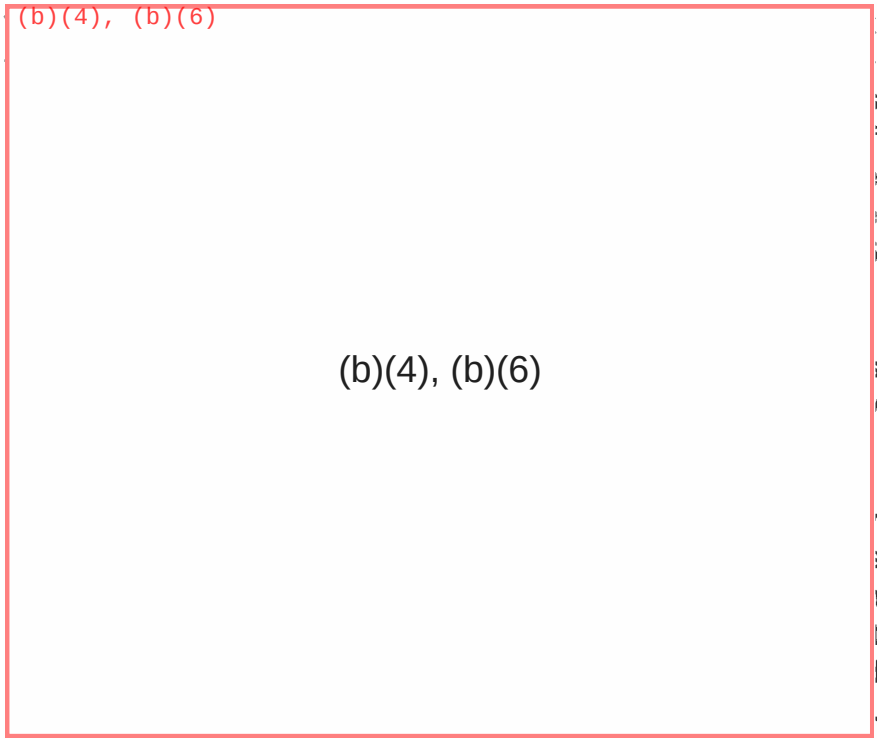
PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.6 mV
TDI	420 ms
VT NID	12
VT Rx #1	Ramp
VT Rx #2	CV/34J/SIM
VT Rx #3	CV/34J/SIM
VT Rx #4	CV/34J/SIM
FDI	300 ms
VF NID	12
VF Rx #1	34J/SIM
VF Rx #2	34J/SIM
VF Rx #3	34J/SIM
VF Rx #4	34J/SIM

(b)(4), (b)(6)



The investigator classified this patient death as non-sudden cardiac and not related to the implanted PCD Transvene

System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

2. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Noncardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as perioperative, noncardiac and not related to the implanted

PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

Epicardial System

1. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Noncardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	500 ms
VT NID	20
VT Rx #1	Burst
VT Rx #2	CV/5J/SIN
VT Rx #3	CV/34J/SIN
VT Rx #4	CV/34J/SIM
FDI	320 ms
VF NID	12
VF Rx #1	34J/SIN
VF Rx #2	34J/SIN
VF Rx #3	34J/SIN
VF Rx #4	34J/SIN

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as perioperative, noncardiac and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

2. Patient (b)(6)

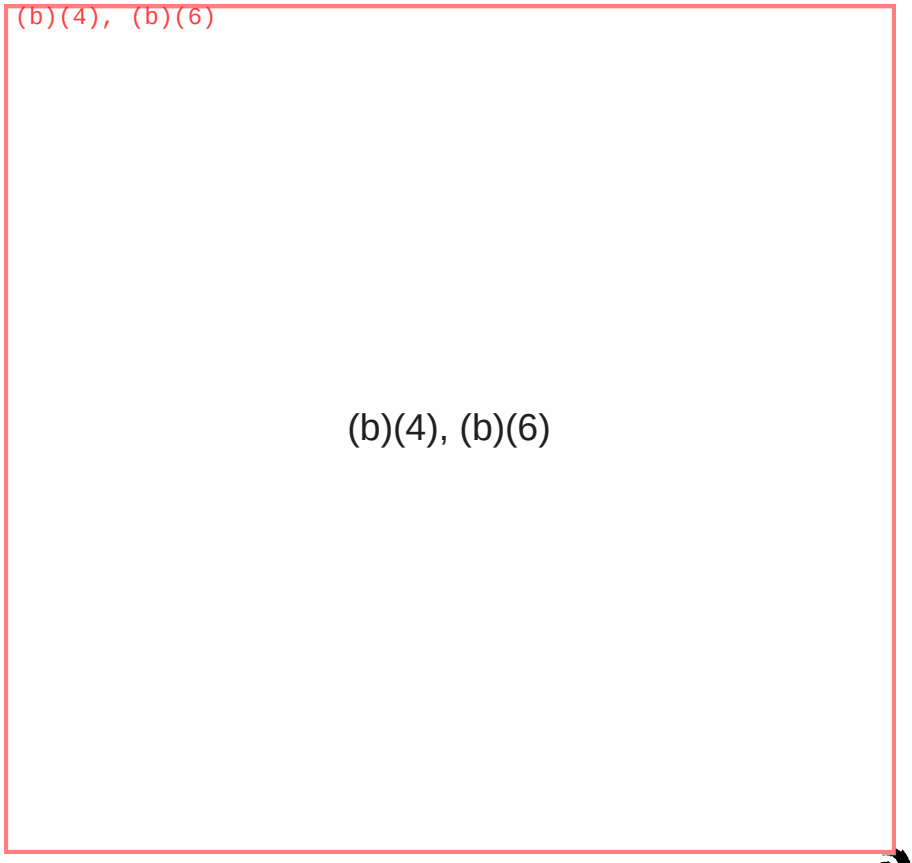
PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	OFF
VT NID	-
VT Rx #1	-
VT Rx #2	-
VT Rx #3	-
VT Rx #4	-
FDI	350 ms
VF NID	12
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)



(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as perioperative, non-sudden cardiac and related to an ventricular arrhythmia episode. The investigator indicated that the patient death was not related to the implanted PCD System. The CERC reviewed the circumstances of this patient death and agreed with investigator's classification.

3. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

300

Parameter	Value
Sensitivity	0.6 mV
TDI	450 ms
VT NID	16
VT Rx #1	Ramp
VT Rx #2	Burst
VT Rx #3	CV/34/SIN
VT Rx #4	CV/34/SIN
FDI	340 ms
VF NID	18
VF Rx #1	34J/SIN
VF Rx #2	34J/SIN
VF Rx #3	34J/SIN
VF Rx #4	34J/SIN

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as perioperative, non-sudden cardiac and not related to the implanted PCD System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

4. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The primary investigator classified the death nonsudden cardiac, perioperative and not related to the implanted PCD system. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

5. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

The CERC reviewed the circumstances of this patient death and agreed with the primary investigator's classification. In addition, the death was classified as procedure related due to the fact the patient underwent both a nonthoracotomy and epicardial lead evaluation.

6. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Noncardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

The CERC reviewed the circumstances of this patient death and agreed with the primary investigator's classification. In addition, the death was classified as perioperative and procedure related due to cerebrovascular accident that occurred during surgical procedure.

7. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The PCD Device programmed status was:

Parameter	Value
Sensitivity	0.6 mV
TDI	OFF
VT NID	-
VT Therapy #1	OFF
VT Therapy #2	OFF
VT Therapy #3	OFF
VT Therapy #4	OFF
FDI	320 ms
VF NID	18
VF Therapy #1	34J SIM
VF Therapy #2	34J SIM
VF Therapy #3	34J SIM
VF Therapy #4	34J SIM

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

The CERC reviewed the circumstances of this patient death and agreed with the primary investigator's classification. In addition, this death was classified as perioperative and procedure related due to both a nonthoracotomy and epicardial lead evaluation being performed.

8. Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Non-Sudden Cardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

The final programmed status of PCD Device was as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	OFF
VT NID	-
VT Therapy #1	-
VT Therapy #2	-
VT Therapy #3	-
VT Therapy #4	-
FDI	320 ms
VF NID	18
VF Therapy #1	34J/SIN
VF Therapy #2	34J/SIN
VF Therapy #3	34J/SIN
VF Therapy #4	34J/SIN

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as perioperative, non-sudden cardiac and not related to the implanted PCD System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

IX Summary of Additional Implants

A

13

IV. Summary of Additional Implants

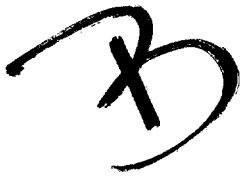
A. Overview

(b)(4), (b)(6)

(b)(4), (b)(6)

PCD Transvene System Data Summary of Updated Population N = 1330			
Number of Patients	757	573	1330
Device Months Follow-up	8894.8	1758.9	10,653.7 mo
Mean Follow-up Time	11.7 mo	3.1 mo	8.0 mo
Maximum Follow-up Time	37.4 mo	12.5 mo	37.4 mo
Number, % Male **Number, % Female**	610 80.6% 147 19.4%	475 82.9% 98 17.1%	1085 81.6% 245 18.4%
Mean Age	59.4 yrs	61.8 yrs	60.4 yrs
Primary Indication: **SCD** **VT** **SCD/VT**	 281 37.1% 377 49.8% 99 13.1%	 182 31.8% 347 60.6% 44 7.6%	 463 34.8% 724 54.4% 143 10.8%
Coronary Artery Disease	561 74.1%	453 79.1%	1014 73.4%
Mean Ejection Fraction	688 35.6%	506 32.5%	1194 34.3%
Defibrillation Pathway: **Sequential** **Simultaneous** **Single**	 574 75.3% 178 23.4% 10 1.3%	 406 70.9% 163 28.4% 4 0.7%	 980 73.4% 341 25.5% 14 1.1%
Mean LED	16.0J (N = 702)	17.0J (N = 534)	16.4J (N = 1236)
Mean DFT	14.8J (N = 316)	16.4J (N = 180)	15.4J (N = 496)
Spontaneous VT: **Number of Patients** **Number of Episodes** **% Success**	 316 9864/10027 98.4%	 108 1487/1550 96.0%	 424 11577 98.1%
Spontaneous VF: **Number of Patients** **Number of Episodes** **% Success**	 317 1951/1982 98.4%	 110 468/471 99.4%	 427 2453 98.6%
One Year SCD Survival	99.5%	98.3%	99.3%
Overall Survival	93.3%	93.4%	93.0%

Table IVA-1: PCD Transvene System: Data Summary - Updated Pts. (1330) - 2/1/93



B. Complications and Observations

(b)(4)

(b)(4)

(b)(4)

(b)(4) **None of the reported complications or observations have resulted in a patient death.**

PCD Transvene System Reported Complications By Category			
Category	757	573	1330
	Num (% of Pts)	Num (% of Pts)	Num (% of Pts)
Increased Defibrillation Requirements	9 (1.2%)	5 (0.9%)	14 (1.1%)
Inappropriate VF Therapy Delivery	-	-	-
Inappropriate VT Therapy Delivery	-	-	-
Loss of Capture	6 (0.8%)	-	6 (0.5%)
Oversensing	-	1 (0.2%)	1 (0.1%)
Undersensing	-	-	-
Skin Erosion	5 (0.7%)	-	5 (0.4%)
Pocket Infection	24 (3.2%)	6 (1.0%)	30 (2.3%)
Seroma	6 (0.8%)	4 (0.7%)	10 (0.8%)
Hematoma	6 (0.8%)	6 (1.0%)	12 (0.9%)
Pneumothorax	2 (0.3%)	-	2 (0.2%)
Pacemaker Syndrome	-	-	-
Perforation	6 (0.8%)	1 (0.2%)	7 (0.5%)
Subclavian Vein Thrombosis	1 (0.1%)	-	1 (0.1%)
Lead Fracture	9 (1.2%)	-	9 (0.7%)
Subcutaneous Patch Crinkling	7 (0.9%)	-	7 (0.5%)
Early Device Explant	4 (0.5%)	-	4 (0.3%)
Total Lead Dislodgement (n=1330)	91 (12.0%)	26 (4.5%)	117 (8.8%)
Total	176	49	225

Table IVB-2: PCD Transvene System: Reported Complications/ Observations (n = 1330) - 2/1/93

18

PCD Transvene System Reported Observations By Category			
Category	757	573	1330
	Num (% of Pts)	Num (% of Pts)	Num (% of Pts)
Increased Defibrillation Requirements	8 (1.1%)	1 (0.2)	9 (0.7%)
Inappropriate VF Therapy Delivery	12 (1.6%)	3 (0.5%)	15 (1.1%)
Inappropriate VT Therapy Delivery	59 (7.8%)	9 (1.6%)	68 (5.1%)
Loss of Capture	14 (1.8%)	2 (0.3%)	16 (1.2%)
Oversensing	54 (7.1%)	29 (5.1%)	83 (6.2%)
Undersensing	-	-	-
Skin Erosion	1 (0.1%)	-	1 (0.1%)
Pocket Infection	10 (1.3%)	2 (0.3%)	12 (0.9%)
Seroma	14 (1.8%)	6 (1.0%)	20 (1.5%)
Hematoma	17 (2.2%)	6 (1.0%)	23 (1.7%)
Pneumothorax	1 (0.1%)	-	1 (0.1%)
Pacemaker Syndrome	2 (0.3%)	-	2 (0.2%)
Perforation	-	-	-
Subclavian Vein Thrombosis	3 (0.4%)	3 (0.5%)	6 (0.5%)
Lead Fracture	-	-	-
Subcutaneous Patch Crinkling	5 (0.7%)	-	5 (0.4%)
Early Device Explant	-	-	-
Total Lead Dislodgement	12 (1.6%)	-	12 (0.9%)
Total	212	61	273

Table IVB-3: PCD Transvene System: Reported Observations - 2/1/93

(b)(4), (b)(6)

(b)(4), (b)(6)

PCD Transvene System
Reported Complications/Observations
Lead Dislodgements (b)(4), (b)(6)

Category	Complications	Observations
	Num (% of Pts)	
(b)(4)		

(b)(4)

Table IVB-4: PCD Transvene System: Lead Dislodgements (b)(4) 2/1/93

(b)(4)

(b)(4)

(b)(4)

320

(b)(4)

(b)(4)

C. Patient Deaths

(b)(4)

(b)(4)

Non-Cardiac:	Deaths that occurred where the primary cause of death was determined to be non cardiac in nature, e.g. stroke, cancer, etc.
Cardiac:	Deaths that occurred where the primary cause of death was determined to be cardiac in nature.
Non-Sudden:	Deaths that occur greater than one hour after the onset of symptoms.
Sudden:	Deaths that occur within one hour of the onset of symptoms or where the death is unwitnessed. Sudden cardiac deaths were also categorized as being **Witnessed** or **Unwitnessed**.
Perioperative:	Deaths that occur within thirty days of implant.
System Related:	A death which results from a malfunction (operation not according to design specification) of a PCD System component, or as a result of a device induced arrhythmia, or an interaction between a PCD System component and the patient.
Procedure Related:	A death which occurs as a result of a procedure required to implant, follow or test a PCD System.

(b)(4)

(b)(4)

PCD Transvene System Summary of Death Classifications (b)(4) (b)(4)	
Classifications	(b)(4)
Sudden Cardiac	
Non-Sudden Cardiac	
Noncardiac	
TOTAL	

Table IVC-1: PCD Transvene System - Summary of Death Classifications (b)(4) (b)(4)

None of the patient deaths were attributed to a malfunction of the PCD Transvene System.

(b)(4)

(b)(4)

(b)(4)

PCD Transvene System One Year Actuarial Survival	
	(b)(4)
Sudden Cardiac Death	
Non-Sudden Cardiac	
All Cardiac	
Noncardiac	
Perioperative	
Overall	

Table IVC-2: PCD Transvene System - One Year Actuarial Survival - 2/1/93

(b)(4)

(b)(4)

24

V

Explants

A

V. Explants

A. Transvene Lead Performance

(b)(4)

(b)(4)

Detailed Analysis Results

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Conclusions

(b)(4)

(b)(4)

330

B. PCD Devices

(b)(4)

(b)(4)

PCD Transvene System Reasons for PCD Device Explant n = 762	
Reason	All Models
Patient Death	(b)(4)
Infection	
Cardiac Transplant	
Low Battery Voltage Measurement	
PCD Device Performance Issues	
L23	
Lead Issues	
Total	

Table VB-1 Reasons for PCD Device Explant - 2/1/93

(b)(4)

(b)(4)

PCD Transvene System Final Analysis on Explanted PCD Devices (N = 762)	
Within Normal Specifications	(b)(4)
Hermetic Leakage at IC	
Random Component Failure	
Shorted on Pulse 2 Output	
L23	
Analysis Pending	
Total	

Table IB-2: Final Analysis on Explanted PCD Devices - 2/1/93

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

VI Non-Clinical Testing

A

2

P920015/AC2r3

A. Laboratory (Bench) Testing of the Non-Thoracotomy Lead System

1. Model 6963

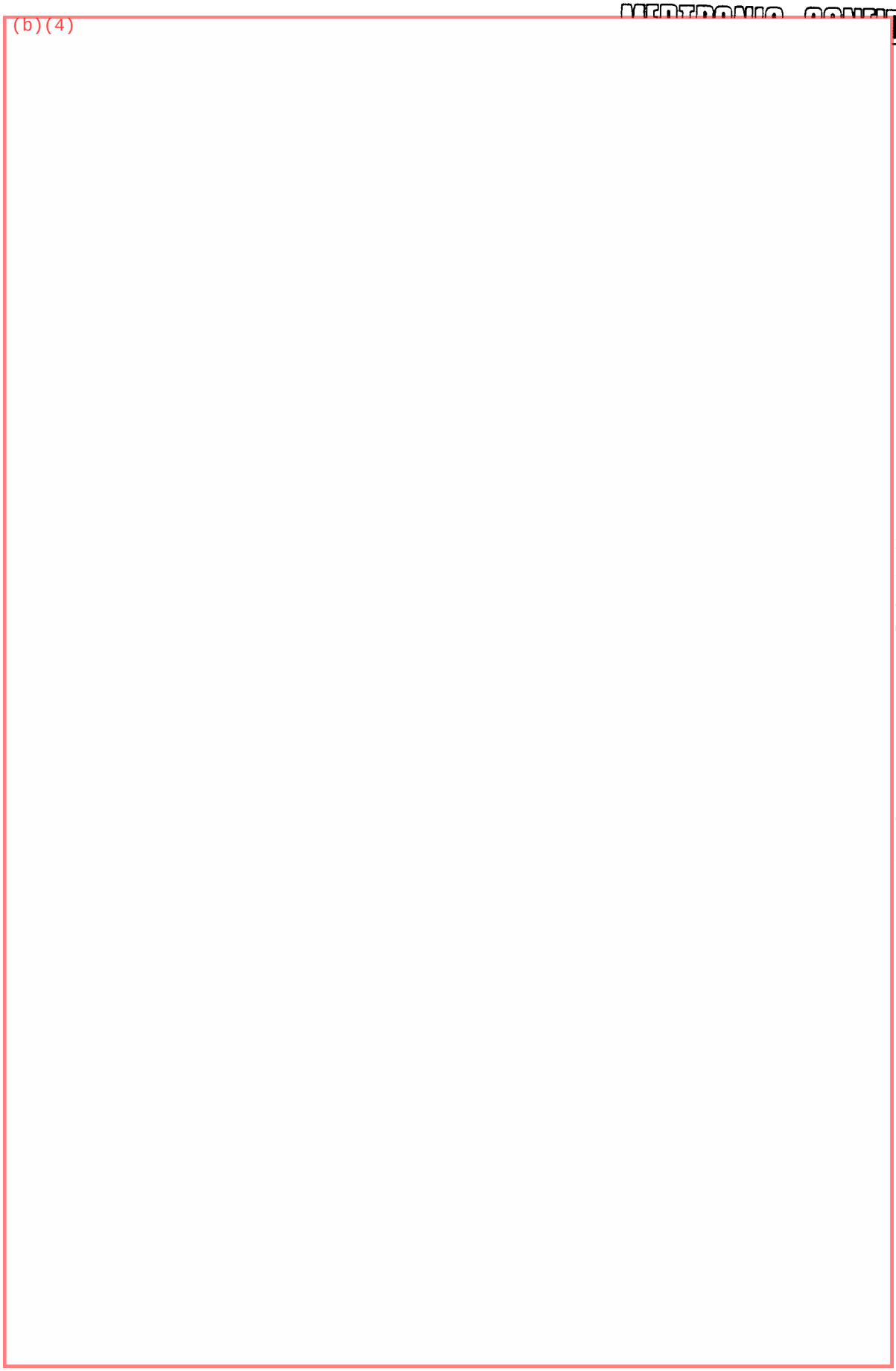
(b)(4)

Parameter	Model 6963
(b)(4)	

(b)(4)

3

(b)(4)



a. Model 6963 Electrical Testing

Electrical Testing

1) D.C. Resistance

a) Test Method

(b)(4)

(b)(4)

b) Rationale

(b)(4)

(b)(4)

c) Test Equipment

(b)(4)

(b)(4)

d) Samples Tested

(b)(4)

(b)(4)

e) Results

Distal End of Defibrillation Coil to Connector Pin

(b)(4)

(b)(4)

b. Environmental Testing

1) Thermal Shock

a) Test Method

(b)(4)

(b)(4)

b) Rationale

(b)(4)

(b)(4)

c) Test Equipment

(b)(4)

(b)(4)

d) Samples Tested

(b)(4)

(b)(4)

e) Results

(b)(4)

(b)(4)

c. Mechanical Testing

(b)(4)

(b)(4)

1) Flex Testing of Insulated Conductor Coils and Non-insulated Electrode Coils*

a) Test Method

(b)(4)

(b)(4)

b) Rationale

(b)(4)

(b)(4)

c) Test Equipment

(b)(4)

(b)(4)

d) Insulated Conductor Coil

i. Samples Tested

(b)(4)

(b)(4)

Model 6963
Insulated Lead Body

(b)(4)

(b)(4)

* See Appendix 2 for additional information regarding development of the Medtronic flex test and information relative to the Transvene lead system.

ii. Results

(b)(4)

(b)(4)

e) Electrode Coil

i. Samples Tested

(b)(4)

(b)(4)

ii. Results

(b)(4)

(b)(4)

2) Lead Joint Tensile Strengths

(b)(4)

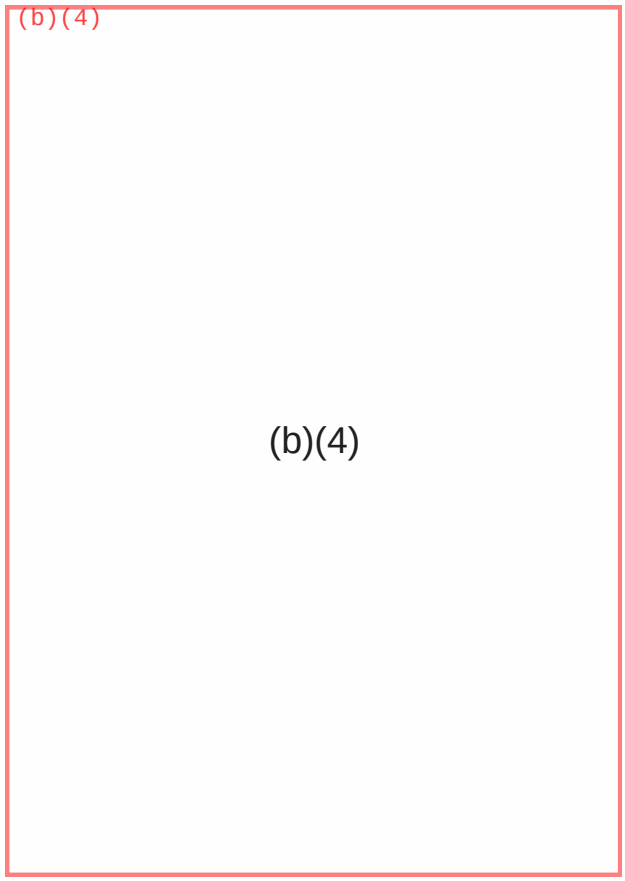
(b)(4)

a) Composite Pull Strength

(b)(4)

(b)(4)

(b)(4)

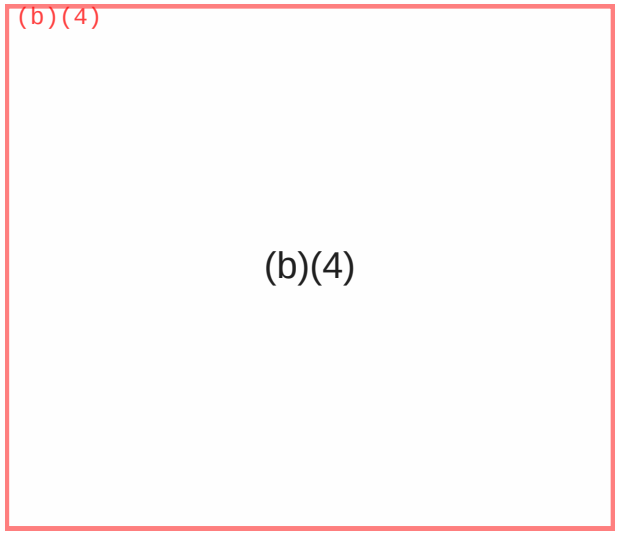


Distal Proximal

(b)(4)

(b)(4)

(b)(4)



b) Crimp/Weld Pull Strengths

(b)(4)

(b)(4)

(b)(4)

(b)(4)

10

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

3) Lead Stiffness

(b)(4)

(b)(4)

4) Anchoring Sleeve Testing

(b)(4)

(b)(4)

Sliding Force

(b)(4)

(b)(4)

Suture Force

(b)(4)

(b)(4)

d. Biostability Testing

1) Historical Overview

(b)(4)

(b)(4)

(b)(4)

(b)(4)

2) Rationale for Using Silicone Rubber

(b)(4)

(b)(4)

3) Biostability of Silicone Rubber Leads

a) Analysis of Canine Explants

i. Test Methods

(b)(4)

(b)(4)

(b)(4)

(b)(4)

ii. Rationale

(b)(4)

(b)(4)

iii. Test Equipment

- (b)(4)
- (b)(4)

iv. Samples Tested

(b)(4)

(b)(4)

v. Results

(b)(4)

(b)(4)

vi. Conclusion

(b)(4)

(b)(4)

b) Analysis of Human Explants

i. Test Methods

(b)(4)

(b)(4)

ii. Rationale

(b)(4)

(b)(4)

iii. Test Equipment

- (b)(4)

(b)(4)

iv. Samples Tested

(b)(4)

(b)(4)

v. Results

(b)(4)

(b)(4)

vi. Conclusion

(b)(4)

(b)(4)

4) Biostability of Silicone Rubber Under Strain

a) Test Methods

(b)(4)

(b)(4)

b) Rationale

(b)(4)

(b)(4)

18

(b)(4)

(b)(4)

c) Test Equipment

- (b)(4)
- (b)(4)
-

d) Samples Tested

(b)(4)

(b)(4)

e) Results

(b)(4)

(b)(4)

f) Overall Conclusion

(b)(4)

(b)(4)

2. Model 6966

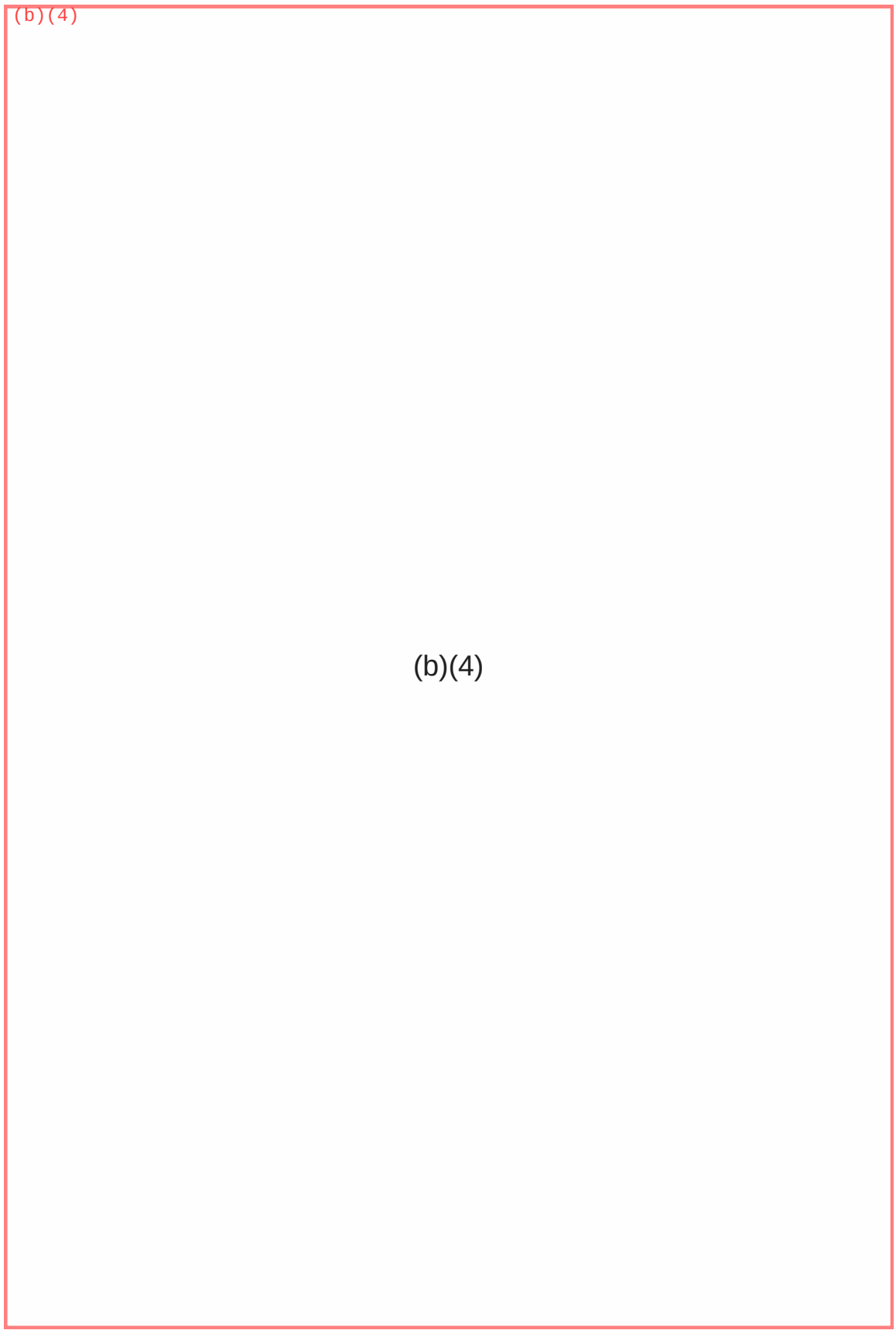
(b)(4)

(b)(4)

Parameter	Model 6966
(b)(4)	(b)(4)

Parameters	Model 6966
(b)(4)	(b)(4)

(b)(4)



MODEL 6966 RIGHT VENTRICULAR LEAD
DISTAL END

23

(b)(4)

(b)(4)

MODEL 6966 RIGHT VENTRICULAR LEAD
PROXIMAL END

a. Model 6966 Electrical Testing

Electrical Testing

1) D.C. Resistance

a) Test Method

(b)(4)

(b)(4)

b) Rationale

(b)(4)

(b)(4)

c) Test Equipment

(b)(4)

(b)(4)

d) Samples Tested

(b)(4)

(b)(4)

e) Results

Inner Coil Assembly (pacing helix)

(b)(4)

(b)(4)

Middle Coil Assembly (sensing ring)

(b)(4)

(b)(4)

Outer Coil Assembly (defibrillation coil)

(b)(4)

(b)(4)

b. Environmental Testing

1) Thermal Shock

a) Test Method

(b)(4)

(b)(4)

b) Rationale

(b)(4)

(b)(4)

c) Test Equipment

(b)(4)

(b)(4)

d) Samples Tested

(b)(4)
(b)(4)

e) Results

(b)(4)
(b)(4)

c. Mechanical Testing

(b)(4)
(b)(4)

1) Flex Testing of Insulated Conductor Coils and Non-insulated Electrode Coils*

a) Test Method

(b)(4)
(b)(4)

b) Rationale

(b)(4)
(b)(4)

c) Test Equipment

(b)(4)
(b)(4)

* See Appendix 2 for additional information regarding development of the Medtronic flex test and information relative to the Transvene lead system.

d) Insulated Conductor Coils

i. Samples Tested

(b)(4)

(b)(4)

Model 6966
Insulated Conductor Coil

(b)(4)

(b)(4)

ii. Results

(b)(4)

(b)(4)

1.
2.
3.
4.
5.
6.

(b)(4)

(b)(4)

7.
8.
9.
10.
11.

(b)(4)

(b)(4)

e) Electrode Coil

i. Samples Tested

(b)(4)

(b)(4)

ii. Results

(b)(4)

(b)(4)

2) Lead Joint Tensile Strengths

(b)(4)

(b)(4)

a) Composite Pull Strength

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Distal Proximal

(b)(4)

(b)(4)

b) Crimp/Weld Pull Strengths

(b)(4)

(b)(4)

(b)(4)

(b)(4)

31

(b)(4)

(b)(4)

(b)(4)

(b)(4)

3) Lead Stiffness

(b)(4)

(b)(4)

4) Anchoring Sleeve Testing

(b)(4)

(b)(4)

Sliding Force

(b)(4)

(b)(4)

Suture Force

(b)(4)

(b)(4)

(b)(4)

(b)(4)

5) Leak Test--Lead Body

a) Test Method

(b)(4)

(b)(4)

b) Rationale

(b)(4)

(b)(4)

c) Test Equipment

(b)(4)

(b)(4)

d) Samples Tested

(b)(4)

(b)(4)

e) Results

(b)(4)

(b)(4)

6) Leak Test--Sleeve Head

a) Test Method

(b)(4)

(b)(4)

b) Rationale

(b)(4)

(b)(4)

c) Test Equipment

(b)(4)

(b)(4)

d) Samples Tested

(b)(4)

(b)(4)

e) Results

(b)(4)

(b)(4)

d. Model 6966 Biostability Testing

1) Background

(b)(4)

(b)(4)

2) Test Method/Rationale

(b)(4)

(b)(4)

3) Test Equipment

(b)(4)

(b)(4)

4) Samples Tested

(b)(4)

(b)(4)

5) Results

(b)(4)

(b)(4)

6) Conclusion

(b)(4)

(b)(4)

3. Model 6999

(b)(4)

(b)(4)

Parameter	Model 6999
(b)(4)	(b)(4)

(b)(4)

(b)(4)

a. Model 6999 Electrical Testing

Electrical Testing

1) D.C. Resistance

a) Test Method

(b)(4)

(b)(4)

b) Rationale

(b)(4)

(b)(4)

c) Test Equipment

(b)(4)

(b)(4)

d) Samples Tested

(b)(4)

(b)(4)

e) Results

Lead Body

(b)(4)

(b)(4)

Distal End of Electrode Coils to Connector Pin

Inner Electrode

(b)(4)

(b)(4)

b. Environmental Testing

1) Thermal Shock

a) Test Method

(b)(4)

(b)(4)

b) Rationale

(b)(4)

(b)(4)

c) Test Equipment

(b)(4)

(b)(4)

d) Samples Tested

(b)(4)

(b)(4)

e) Results

(b)(4)

(b)(4)

c. Mechanical Testing

(b)(4)

(b)(4)

1) Flex Testing of Insulated Conductor Coils and Non-insulated Electrode Coils*

a) Test Method

(b)(4)

(b)(4)

b) Rationale

(b)(4)

(b)(4)

c) Test Equipment

(b)(4) (b)(4)

d) Insulated Conductor Coils

i. Samples Tested

(b)(4)

(b)(4)

Model 6999
Insulated Lead Body

(b)(4)

(b)(4)

* See Appendix 2 for additional information regarding the development of the Medtronic flex test and information relative to the Transvene lead system.

ii. Results

(b)(4)

(b)(4)

e) Electrode Coil

i. Samples Tested

(b)(4)

(b)(4)

ii. Results

(b)(4)

(b)(4)

1. (b)(4)
2. (b)(4)
3. (b)(4)
4. (b)(4)
5. (b)(4)
6. (b)(4)
7. (b)(4)
8. (b)(4)
9. (b)(4)
10. (b)(4)
11. (b)(4)

(b)(4)

(b)(4)

2) Lead Joint Tensile Strengths

(b)(4)

(b)(4)

a) Composite Pull Strength

(b)(4)

(b)(4)

Distal	Proximal
(b)(4)	

(b)(4)

b) Crimp Pull Strengths

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

d. Biostability Testing

1) Historical Overview

(b)(4)

(b)(4)

(b)(4)

(b)(4)

2) Rationale for Using Silicone Rubber

(b)(4)

(b)(4)

3) Biostability of Silicone Rubber Leads

a) Analysis of Canine Explants

i. Test Methods

(b)(4)

(b)(4)

(b)(4)

(b)(4)

ii. Rationale

(b)(4)

(b)(4)

iii. Test Equipment

- (b)(4)
- (b)(4)

iv. Samples Tested

(b)(4)

(b)(4)

v. Results

(b)(4)
(b)(4)

vi. Conclusion

(b)(4)
(b)(4)

b) Analysis of Human Explants

i. Test Methods

(b)(4)
(b)(4)

ii. Rationale

(b)(4)
(b)(4)

iii. Test Equipment

- (b)(4)
(b)(4)

iv. Samples Tested

(b)(4)
(b)(4)

v. Results

(b)(4)

(b)(4)

vi. Conclusion

(b)(4)

(b)(4)

4) Biostability of Silicone Rubber Under Strain

a) Test Methods

(b)(4)

(b)(4)

b) Rationale

(b)(4)

(b)(4)

(b)(4)

(b)(4)

c) Test Equipment

- (b)(4)

(b)(4)

d) Samples Tested

(b)(4)

(b)(4)

e) Results

(b)(4)

(b)(4)

f) Overall Conclusion

(b)(4)

(b)(4)

4. Biocompatibility Testing

a) Model 6963 and 6999 Leads

Materials Used

(b)(4)

(b)(4)

- (b)(4)

Rationale

(b)(4)

(b)(4)

Conclusion

(b)(4)

(b)(4)

b. Model 6966 Lead

Materials Used

The following is a list of materials previously tested and used in the Model 6966 right ventricular lead:

- (b)(4)

(b)(4)

- (b)(4)
- (b)(4)
- (b)(4)
- (b)(4)
- (b)(4)
- (b)(4)

Rationale

(b)(4)

(b)(4)

Conclusion

All materials were found to be biocompatible and therefore are considered suitable for human implant. See the Biocompatibility Table following this section.

BIOCOMPATIBILITY TEST DATA FOR NON-THORACOTOMY (TRANSVENE) LEADS

(b)(4)

(b)(4)

The biocompatibility testing performed on the non-thoracotomy leads was in accordance with the Office of Device Evaluation, Division of Cardiovascular Devices' Implantable Pacemaker Lead Testing Guidance for the Submission of a 510(k) Notification. September 1989. In this guidance, the following biocompatibility tests are stated as being considered necessary to satisfy the biocompatibility of the implanted materials:

- (b)(4)

Therefore, the above-listed tests which were performed are considered adequate to assess the biocompatibility of the material used in the non-thoracotomy leads. This testing performed is consistent with the biocompatibility testing that has been performed for all of Medtronic's pacing lead products.

In addition, the following rationale is provided as to why we did not perform specific tests of the Tripartite Biocompatibility Guidance for Medical Devices:

SUBCHRONIC AND CHRONIC TOXICITY

(b)(4)

(b)(4)

(b)(4)

(b)(4)

PHARMACOKINETICS

(b)(4)

(b)(4)

CARCINOGENICITY

(b)(4)

(b)(4)

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Raw Material Test Data for Implantable PCD Leads (includes patches and transvenous leads)

(b)(4)

5. Lead System (Life) Testing

a. High-Voltage Testing

1) Test Method

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

b) Rationale

(b)(4)

(b)(4)

c) Test Equipment

(b)(4)

(b)(4)

d) Samples Tested

(b)(4)

(b)(4)

e) Results

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Model 6963 D.C. Resistance Specification

(b)(4)

(b)(4)

Model 6966 D.C. Resistance Specification

(b)(4)

(b)(4)

Model 6968 D.C. Resistance Specification

(b)(4)

(b)(4)

Model 6999 D.S. Resistance Specification

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Addtional Testing for R & D

(b)(4)

(b)(4)

b. Crush Testing

1) Test Method

(b)(4)

(b)(4)

2) Rationale

(b)(4)

(b)(4)

3) Test Equipment

- (b)(4)
- (b)(4)
- (b)(4)

4) Samples Tested

(b)(4)
(b)(4)

5) Results

(b)(4)
(b)(4)

(b)(4)

(b)(4)

(b)(4)

Figure 5

c. Insertion/Withdrawal Testing

1) Test Method

(b)(4)

(b)(4)

2) Rationale

(b)(4)

(b)(4)

3) Test Equipment

(b)(4)

(b)(4)

4) Samples Tested

(b)(4)

(b)(4)

5) Results

	Insertion	Withdrawal
(b)(4)	(b)(4)	

Model 6966

(b)(4)

(b)(4)

Model 6999

(b)(4)

(b)(4)

The results are within the specified limits and therefore are considered acceptable.

d. AC Impedance/Leakage Testing

1) Test Method

(b)(4)

(b)(4)

2) Rationale

(b)(4)

(b)(4)

3) Test Equipment

(b)(4)

(b)(4)

4) Samples Tested

(b)(4)

(b)(4)

5) Results

(b)(4)

(b)(4)

6. Related System Components

(b)(4)

(b)(4)

(b)(4)

(b)(4)

1. EXECUTIVE SUMMARY OF THE ANIMAL TESTING

The information presented in this section is an accumulation of several studies, some of which FDA has previously reviewed in IDE submissions (G870102). These studies demonstrate the safety of the Transvene lead Models 6963, 6966 and 6999.

A variety of non-thoracotomy leads were evaluated in a series of four canine studies. Descriptions of the leads, as well as the study number(s) (1, 2, 3 or 4) in which they were evaluated, are presented below.

Description: Non-thoracotomy Leads

CORONARY SINUS/SUPERIOR VENA CAVA LEADS

Model 6963, evaluated in Study No. 4, is a silicone, unipolar, coronary sinus or superior vena cava lead with a 6.5 mm connector and platinum alloy electrode for delivery of cardioversion and defibrillation therapies.

Model 6881, evaluated in Study Nos. 2, 3 and 4 is functionally equivalent to the Model 6963 except the 6881 has a 3.2 mm connector.

Model 10285, evaluated in Study No. 1, is the temporary version of the Model 6963/6881.

RIGHT VENTRICULAR LEADS

Model 6966, evaluated in Study No. 4, is a polyurethane, tripolar, extendable/retractable, screw-in lead with a 6.5 mm connector and platinum alloy electrode for delivery of cardioversion and defibrillation therapies. Additionally, the 6966 has a 3.2 mm connector for pacing and sensing.

Model 6884, evaluated in Study Nos. 2 and 3, is functionally equivalent to the Model 6966 except the 6884 has a 3.2 mm connector in place of the 6.5 mm connector for the cardioversion-defibrillation electrode.

Model 10284, evaluated in Study No. 1, is the temporary version of the Model 6966/6884.

SUBCUTANEOUS PATCH LEADS

Model 6999, evaluated in Study No. 4, is a silicone, unipolar, oval, subcutaneous patch with a 6.5 mm connector and platinum alloy electrode coils that are partially embedded in the silicone patch for delivery of cardioversion and defibrillation therapies. Additionally, the patch is embedded with (b)(4) (b)(4)

Model 6895, evaluated in Study Nos. 2 and 3, is functionally equivalent to the Model 6999 except the 6895 has a 3.2 mm connector and is covered with (b)(4) (b)(4)

Model 10317, evaluated in Study No. 3, is functionally equivalent to the 6895 except it is embedded on the outer edge with (b)(4) (b)(4)

Although model numbers differ, all leads in each of the three groups are functionally equivalent. The various model numbers reflect an evolution of temporary to transvenous lead development, as well as minor changes, such as the connector pin modification from 3.2 mm to 6.5 mm.

Additional devices were used to evaluate the non-thoracotomy lead studies in canines. These are described below.

External Devices for Implant Support

Model 5355 External Tachyarrhythmia Control Device (ETCD)

The Model 5355 ETCD provides the same detection capabilities as the implantable Model 7217B PCD Device. Therapies are identical except that the maximum output energy is 40 joules (J) and automatic defibrillation and cardioversion are not available in the Model 5355. The Model 5355 ETCD provides measurement and display of output waveform parameters and ETCD status, an isolated electrogram signal, and passthrough connections of pacing and sensing electrodes to external instrumentation.

Model 2394 External Cardioverter/Defibrillator (ECVD)

The Model 2394 ECVD instrument can deliver: (1) a single stimulation pulse on one output channel, or (2) a pair of pulses, delivered individually on the two different output channels. Monophasic and biphasic pulses are provided, output capacitance can be varied between 10 and 150 microFarads (mf) depending on which external capacitor modules are used, and pulse width can be specified as a fixed duration (0.1-19.9 ms) or "tilt" (10-90%).

between 50 and 1090 volts and may be delivered asynchronously (upon manual command) or synchronized with an intrinsic sensed event.

Model 2376 External Cardioverter/Defibrillator (ECVD)

The output stimulation parameters of the Model 2376 are very similar to those of the Model 2394 except for the following modifications:

- All pulses are monophasic, truncated, exponential waveforms.
- Output capacitance is fixed at 50 microFarads and pulse width is determined by a fixed pulse duration only.
- Pulse output voltages can range between 50 and 1090 volts and may be delivered asynchronously (upon manual command) or synchronized with an intrinsic sensed event.

Study Methods

All canine studies were conducted according to the 1966 and 1970 Animal Welfare Acts, 1985 NIH Laboratory Animal Use and Care Guidelines and GLP regulations. Adult mongrel canines were used for all studies. The dogs weighed 20 kg or more.

Specific details of each study are presented in the following "Animal Studies/Results" section.

Each study is briefly described below. Both acute and chronic studies were performed to assess the toxicity of the non-thoracotomy lead system as well as its stability over time.

Study #1: Acute Toxicity Testing of Non-thoracotomy Leads

The objective of this study was to quantify the amount and nature of shock-induced damage to the myocardial tissue resulting from multiple, high energy defibrillation shocks delivered through transvenous defibrillation leads and a subcutaneous patch. This information has previously been submitted to the agency in the Non-Thoracotomy IDE, reference Document Control Number G870102/S23; FDA Approved October 4, 1990. Lead models evaluated in this study are functionally equivalent to the Models 6963, 6966 and 6999. Results of these studies revealed only minimal shock-induced necrosis (<0.1-0.5 percent by weight), which did not result in functional impairment of the cardiac tissue. Therefore, the use of the Model 6963, 6966 and 6999 leads did not result in significant myocardial damage in canines and could be safely implanted in humans.

Study #2: Model 6881, 6884 and 6895 Chronic Lead Evaluation

The objective of this study was to evaluate the suitability of the lead system for human clinical use. Lead models evaluated in this study are functionally equivalent to the Models 6963, 6966 and 6999. Study results demonstrate that the performance of the non-thoracotomy lead system when used with the PCD and ETCD devices is in conformance with system design and expected operation.

Study #3: Model 6881, 6884 and 6895 Chronic Lead Defibrillation Study

This study is an evaluation of the chronic stability of the non-thoracotomy lead system via the monitoring of defibrillation and pacing thresholds. In addition, histopathological examinations have been performed to assess the amount and nature of shock-induced damage to the myocardial tissue resulting from defibrillation shocks. Lead models evaluated in this study are functionally equivalent to the Models 6963, 6966 and 6999. Results demonstrate stable pacing, sensing and defibrillation thresholds over time. Additionally, histopathology analysis shows no cardiac tissue damage due to delivery of defibrillation shocks.

Study #4: Model 6963, 6966 and 6999 Chronic Lead Defibrillation Study

This study is an ongoing evaluation of the non-thoracotomy lead system to assess chronic defibrillation threshold stability, pacing thresholds, intracardiac sensing capabilities and tissue damage. Results indicate the lead system performs as intended; DFTs and pacing thresholds have remained stable throughout the study (40 weeks) and intracardiac sensing is appropriate. Additionally there is minimal localized trauma to the cardiac tissue (<0.05 percent by weight).

Conclusion

All of these canine studies have demonstrated that the non-thoracotomy lead system, which includes the Model 6963 CS/SVC lead, 6966 RV lead and 6999 SQ patch lead, functions safely and is therefore appropriate for human use.

2. ANIMAL STUDIES/RESULTS

In this section each study (1-4) is described in detail and includes the study objectives, methods, relevance and conclusions.

A brief abstract prefaces each chronic study report.

Study No. 1

Acute Toxicity Testing

Study Objectives

(b)(4)

(b)(4)

Study Methods and Materials

(b)(4)

(b)(4)

Defibrillator

(b)(4)

(b)(4)

Lead System

(b)(4)

(b)(4)

Protocol

(b)(4)

(b)(4)

Results

Gross Pathology

(b)(4)

(b)(4)

Histopathology

(b)(4)

(b)(4)

Summary and Conclusions

(b)(4)

(b)(4)

Table VI-B-1(a)

LEAD COMPARISON

The following tables provide side-by-side comparisons of the leads used in the acute toxicity studies and the leads used in the non-thoracotomy lead clinical investigation.

	Model 10285 Temporary Coronary Sinus Lead	Model 6963 Permanent Coronary Sinus Lead
Outer insulation:	(b)(4)	
Inner conductor:		
External coil electrode:		
External coil electrode length:		
Electrode Shadow area*:		
Conductive surface area:		
Lead diameter:		
Lead Length:		
Pacing/sensing rings:		

(b)(4)

* The shadow area is the surface area, or silhouette, covered by the electrode.

Table VI-B-1(b)

LEAD COMPARISON

	Model 6966 Permanent RV Lead	Model SP2100-5 Permanent RV Lead	Model 10284 Temporary RV Lead
Outer insulation:	(b)(4)	(b)(4)	(b)(4)
Inner conductor:			
External coil:			
External coil electrode length:			
Electrode Shadow area*:			
Conductive surface area:			
Lead diameter:			
Lead length:			
Pacing/sensing rings:			

\+ The Model SP2100-5 is a screw-in lead where the screw acts as the pacing electrode; sensing is achieved from the screw to the defibrillation coil.

* The shadow area is the surface area, or silhouette, covered by the electrode.

Table VI-B-2

Shock History

Canine	Leads	Shock Type	Shock #1/Shock #2	Voltage	Cumulative Energy Delivered
(b)(4)					

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Table VI-B-3

SHOCK INDUCED NECROSIS

Canine	Heart Weight	Necrosis
(b)(4)	(b)(4)	

Study No. 2

Abstract

Study Objective

(b)(4)

(b)(4)

Study Materials and Methods

(b)(4)

(b)(4)

Pulse Type: Sequential

(b)(4)

(b)(4)

Study Results

(b)(4)

(b)(4)

Study Relevance/Significance

(b)(4)

(b)(4)

Study No. 2

Model 6881, 6884 and 6895 Chronic Lead Evaluation

Introduction

(b)(4)

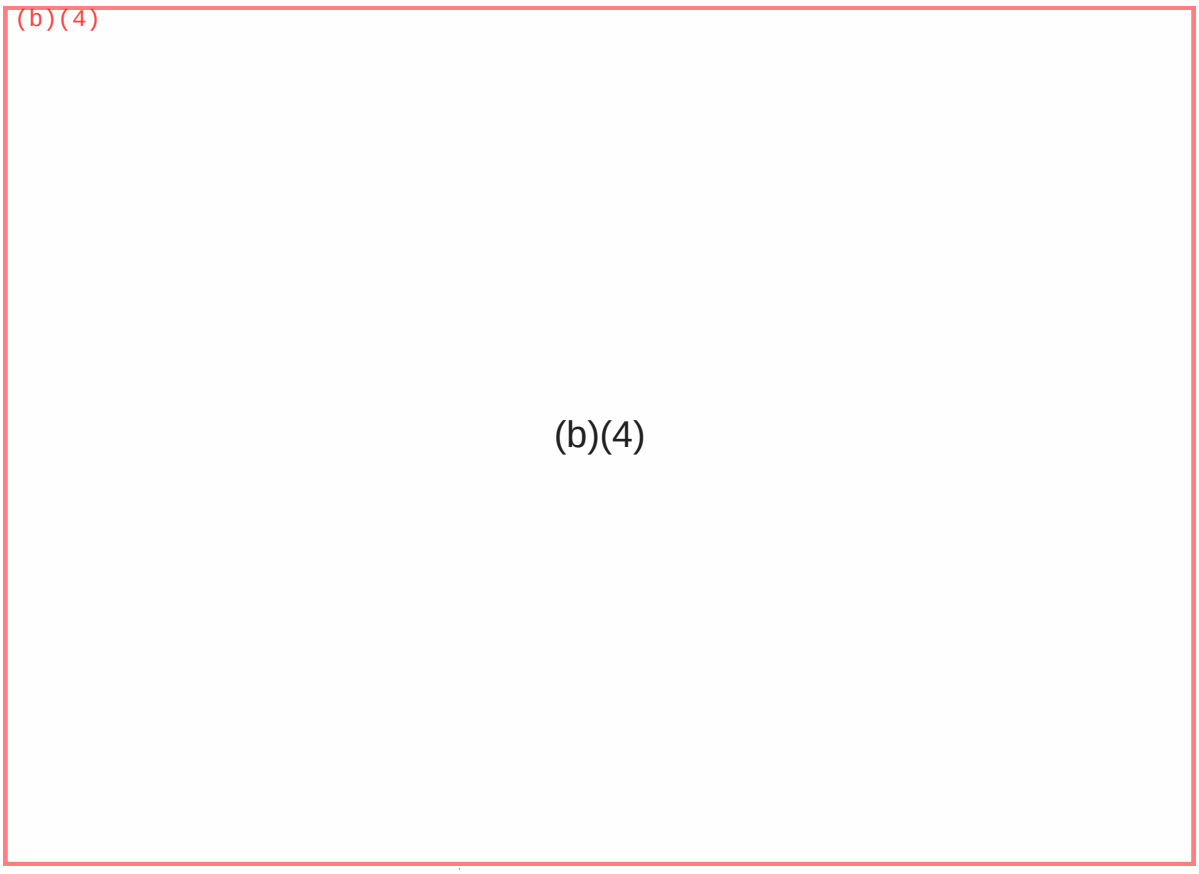
(b)(4)

Study Methods and Materials

(b)(4)

(b)(4)

(b)(4)



Results

Defibrillation and Pacing Thresholds at Implant

(b)(4)

(b)(4)

Lead Implant Summary Table

			Defibrillation Threshold				Pacing and Sensing	
Canine No.	Lead Configuration	Lead Model	Stored Energy (Joules)	Delivered Energy	PULSE1 (Ohms)	PULSE2 (Ohms)	Pacing Threshold at 0.5 ms P.W. (Volts)	R-wave Amp. (mV)

(b)(4)

(b)(4)

Model 5355 ETCD Testing (Prior to Model 7217B Implant)

(b)(4)

(b)(4)

Model 5355 ETCD Cardioversion and Defibrillation Therapy Summary
(Right Ventricle, Subcutaneous, Coronary Sinus)

Canine No.	Monitor	Therapy/ Joules	Pulse Path	Comments	Measured Energy Delivered (Joules)	Measured Impedance PULSE1 (Ohms)	Measured Impedance PULSE2 (Ohms)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Model 5355 ETCD Cardioversion and Defibrillation Therapy Summary
(Right Ventricle, Subcutaneous, Superior Vena Cava)

Canine No.	Monitor	Therapy/ Joules	Pulse Path	Comments	Measured Energy Delivered (Joules)	Measured Impedance PULSE1 (Ohms)	Measured Impedance PULSE2 (Ohms)
(b)(4)							

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Testing of the Non-thoracotomy Lead System with Model 7217B PCD

(b)(4)

(b)(4)

Model 7217B PCD Cardioversion and Defibrillation Therapy Summary

Canine No.	Monitor	Therapy (Joules)	Pulse Path	Charge Time (Sec)	Comments
(b)(4)					

(b)(4)

(b)(4)

(b)(4)

Model 7217B PCD Cardioversion and Defibrillation Therapy Summary

Canine No.	Monitor	Therapy/ Joules	Pulse Path	Charge Time (Sec)	Comments
(b)(4)					

(b)(4)

Model 7217B PCD Cardioversion and Defibrillation Therapy Summary

Canine No.	Monitor	Therapy/ Joules	Pulse Path	Charge Time (Sec)	Comments
(b)(4)					

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Discussion

(b)(4)

(b)(4)

Conclusion

(b)(4)

(b)(4)

Study No. 3

Abstract

Study Objective

(b)(4)

(b)(4)

Study Methods and Materials

(b)(4)

(b)(4)

Defibrillation Electrodes

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Study Results

(b)(4)

(b)(4)

Study Relevance/Significance

(b)(4)

(b)(4)

No. 3

Model 6881/6884/6895 Chronic Lead Defibrillation Study

Introduction

(b)(4)

(b)(4)

Study Objectives

(b)(4)

(b)(4)

- (b)(4)
- (b)(4)
- (b)(4)

Methods and Materials

(b)(4)

(b)(4)

Defibrillator

(b)(4)

(b)(4)

Lead System

(b)(4)

(b)(4)

- (b)(4)
-
-

Protocol

(b)(4)

(b)(4)

Table VI-B-4. Placement of Model 6881 defibrillation lead and models chosen for SQ and RV placement.

Canine #	Model 6881 Position	SQ Model	RV Model
(b)(4)			

(b)(4)

(b)(4)

(b)(4)

Data Acquisition

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Termination

(b)(4)

(b)(4)

Results

(b)(4)

(b)(4)

Gross Pathology

(b)(4)

(b)(4)

Histopathology

(b)(4)

(b)(4)

(b)(4)

(b)(4)

6884 PACING THRESHOLDS
(0.5 ms PULSE WIDTH)

(b)(4)

(b)(4)

Table VI-B-8. Summary of shock induced damage noted during histopathological study of animal hearts.

Canine	Heart Weight (gm)	Damage (% by weight)
(b)(4)	(b)(4)	

Conclusion

(b)(4)

(b)(4)

Study No. 4

Abstract

Study Objectives

(b)(4)

(b)(4)

Materials and Methods

Defibrillation Electrodes

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4) (b)(4)

Study Results

(b)(4)

(b)(4)

Study Relevance/Significance

(b)(4)

(b)(4)

Study No. 4

Model 6963/6966/6999 Chronic Lead Defibrillation Study

Introduction

(b)(4)

(b)(4)

Materials and Methods

Lead Description

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Lead Implants

(b)(4)

(b)(4)

B

Table VI-B-9. Summary of lead configurations and pulse pathways. The CS Lead dislodged at Week 8 in (b)(4) and was repositioned in the SVC. Superscript designations used in chart are explained below.

Canine No.	Pulse Pathway	RV Lead	CS Lead	SVC Lead	SQ Patch
(b)(4)					
		(b)(4)			
(b)(4)					
		(b)(4)			

Mechanical Evaluation

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Electrical Testing

(b)(4)

(b)(4)

- (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Termination

(b)(4)

(b)(4)

Study Results

Overview

(b)(4)

(b)(4)

Mechanical Evaluation

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Defibrillation Thresholds

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Canine No.	Configuration*	Pulse Path	Duration (Weeks)	Implant DFT (Joules)	Range (all monitors)	Cumulative Energy Delivered (Joules)

(b)(4)

* Bold indicates common electrode.

Chronic Defibrillation Thresholds in (b)(4)

(b)(4)

(b)(4)

Chronic Defibrillation Thresholds in (b)(4)

(b)(4)

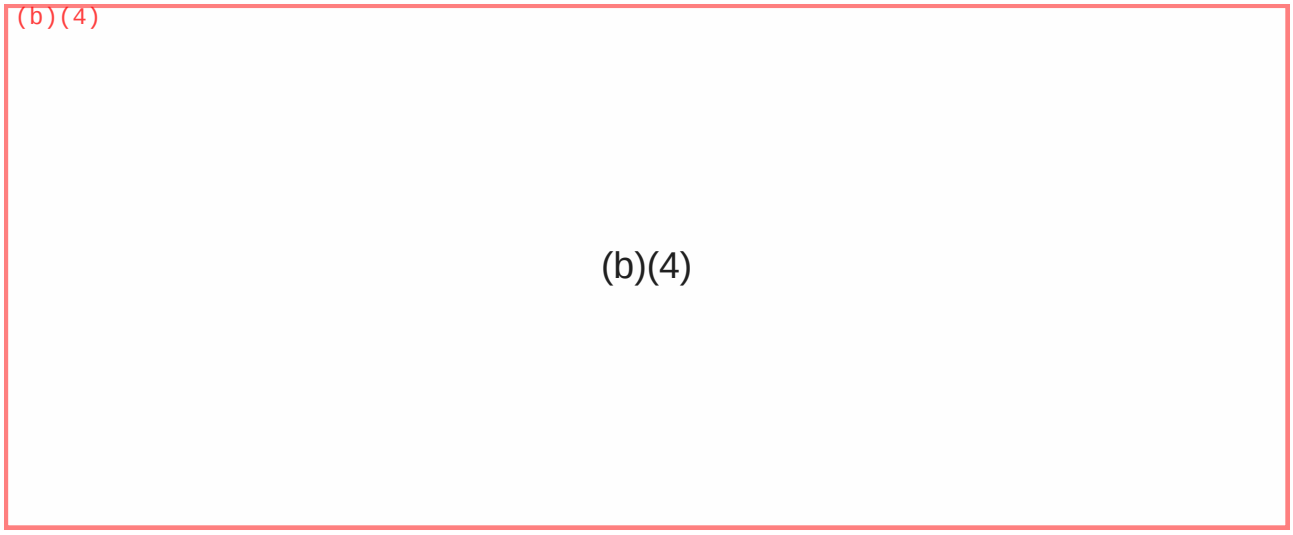
(b)(4)

Chronic Defibrillation Thresholds in (b)(4)

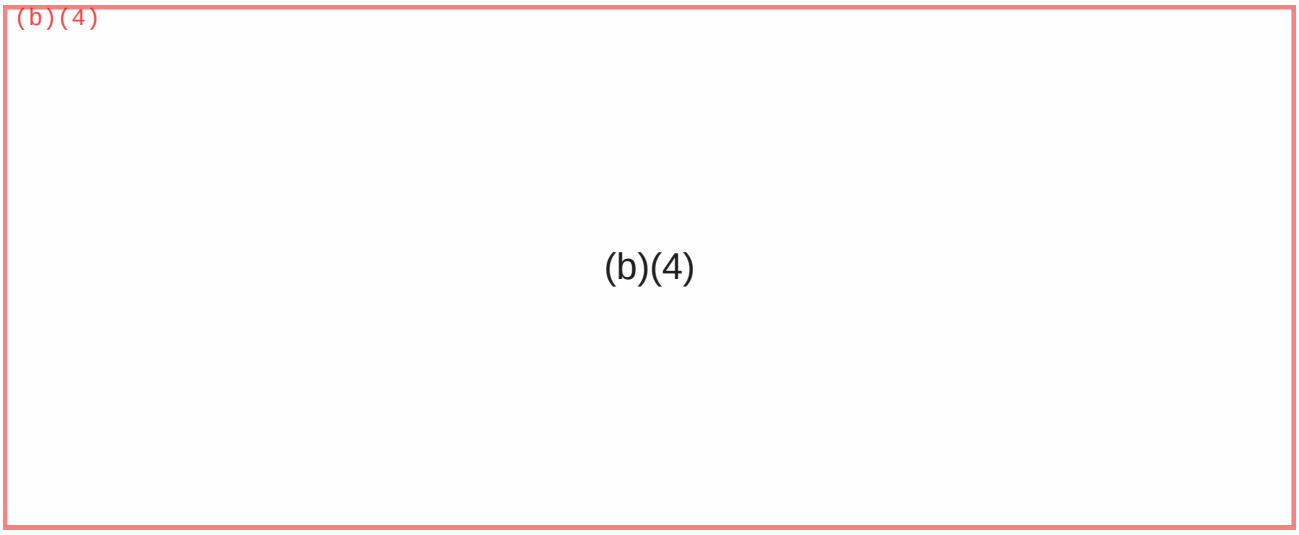
(b)(4)

(b)(4)

Chronic Defibrillation Thresholds for (b)(4)



Chronic Defibrillation Thresholds in (b)(4)



Chronic Defibrillation Thresholds in (b)(4)

(b)(4)

(b)(4)

Chronic Defibrillation Thresholds in (b)(4)

(b)(4)

(b)(4)

37

Chronic Defibrillation Thresholds in (b)(4)

(b)(4)

(b)(4)

Chronic Defibrillation Thresholds in (b)(4)

(b)(4)

(b)(4)

Chronic Defibrillation Thresholds in (b)(4)

(b)(4)

(b)(4)

Chronic Defibrillation Thresholds in (b)(4)

(b)(4)

(b)(4)

Chronic Defibrillation Thresholds in (b)(4)

(b)(4)

(b)(4)

Pacing and Sensing Measurements

(b)(4)

(b)(4)

Table VI-B-11. Summary of pacing thresholds from Chronic NTL Lead Study. The data was collected using the Model 6966 RV lead in an integrated bipolar configuration. The common defibrillation electrode (pacing anode) is designated in bold print.

			Measured Pacing Thresholds			
Canine No.	Lead System	Duration (Weeks)	Implant (volts)	Mean (volts)	Standard Deviation	Peak (volts)
(b)(4)						

(b)(4)

Pacing Thresholds for Model 6966 RV Lead

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Table VI-B-12. Summary of sensing data from Chronic NTL Lead Study. The data was collected using the Model 6966 RV Lead in a standard bipolar sensing configuration. Data designated as (b)(4) were greater than the sensing capabilities of the Model 5311 Pacing System Analyzer.

Canine No.	Lead System	Measured Sensing Amplitudes		
		Implant (volts)	Mean (volts)	Range (volts)
(b)(4)				

(b)(4)

Sensing Amplitude for Model 6966 RV Leads

(b)(4)

(b)(4)

Gross Pathology and Histopathology

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Discussion

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Clinical Appendix

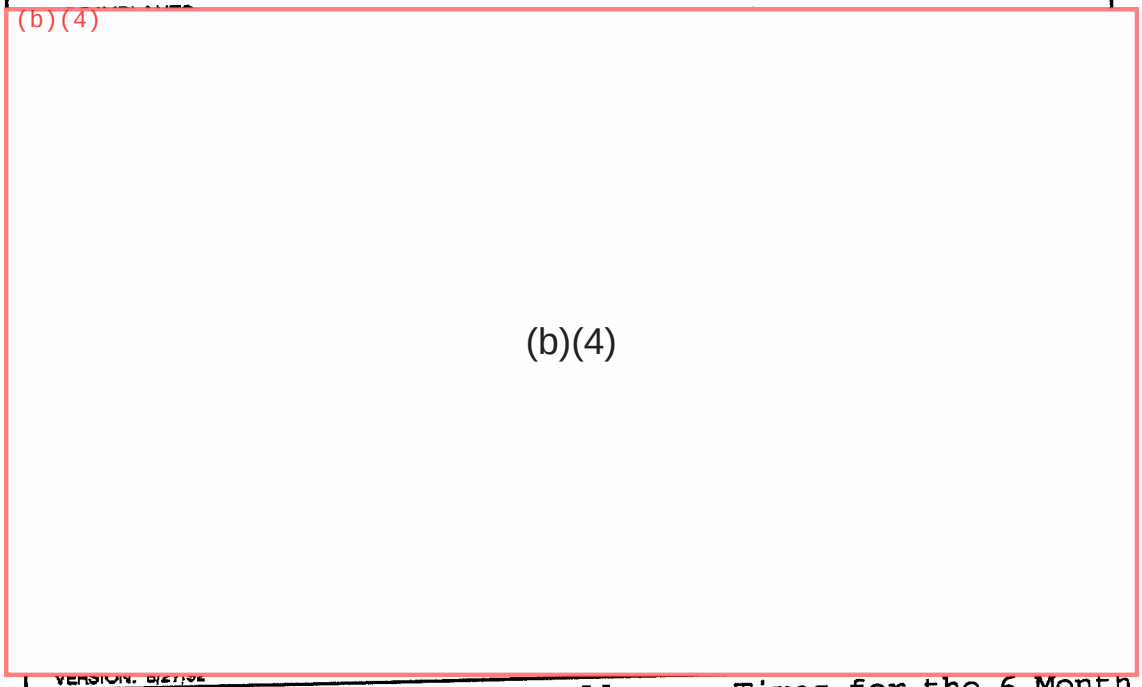
P920015/A C1 V3

Appendix A: Follow-up Time

PCD TRANSVENE SYSTEM

PATIENTS WITH 6 MONTHS OF FOLLOW-UP

(b)(4)



VERSION: 8/27/92

Figure 1: Distribution of Follow-up Times for the 6 Month Follow-up

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PCD TRANSVENE SYSTEM

PATIENTS WITH 12 MONTHS OF FOLLOW-UP

(b)(4)

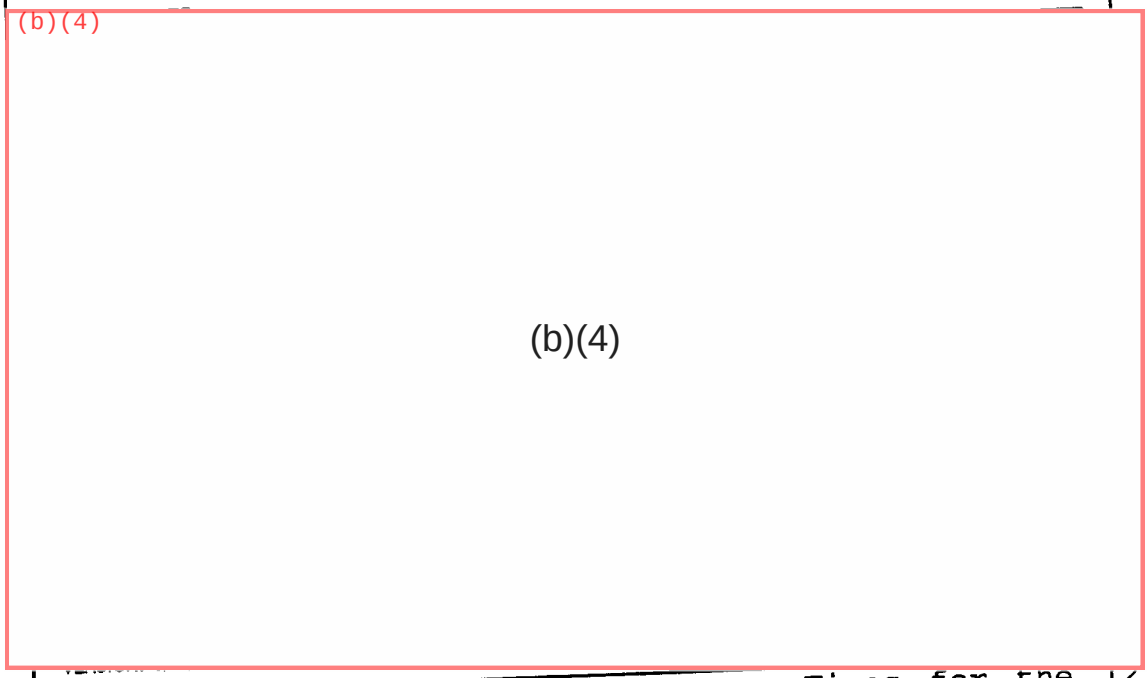
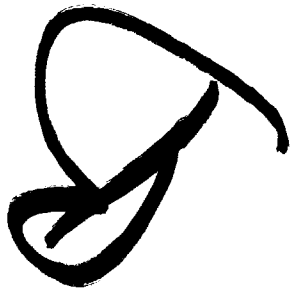


Figure 2: Distribution of Follow-up Times for the 12 Month Follow-up

Compliance



Appendix B: Compliance

(b)(4)

(b)(4)

(b)(4)

(b)(4)

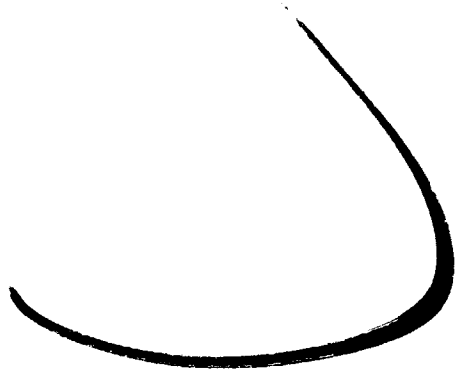
PCD™ Transvene™ System Patient Compliance									
Follow-up Visit Status	1 Month	3 Month	6 Month	9 Month	12 Month	15 Month	18 Month	21 Month	24 Month
Follow-up in on time									
Follow-up not yet due									
Patient discontinued before F.U. date									
Follow-up not in but subsequent one in									
SUBTOTAL - IN COMPLIANCE									
Lost to Follow-up									
Follow-up in early									
Follow-up in late									
Follow-up missing									
SUBTOTAL - OUT OF COMPLIANCE									
TOTAL									
COMPLIANCE RATE									

(b)(4)

(b)(4)

Table B: Follow-up Compliance Report - PCD™ Transvene™ System Worldwide Experience as of 9/16/92

MEDTRONIC CONFIDENTIAL 4641



Appendix C: Complications and Observations

PCD Transvene System Reported Complications and Observations and Corresponding Treatments

All complications and observations reported as of June 24, 1992 are presented in Tables Appendix C-1 and C-2. A total of 757 patients have received a PCD Transvene System.

Complications have been reported in 138 patients and clinical observations have been reported in 157 patients. The reported clinical complication incidence in this patient population is 18.2% (138/757). The reported clinical observation incidence in this patient population is 20.8% (157/757).

The following tables provide clinical summaries of the complications and observations reported in the PCD Transvene System patient population.

PCD Transvene System Reported Complications/Observations By Category 6/24/92		
Category	**Complications**	**Observations**
Increased Defibrillation Requirements	0.8%	0.5%
Inappropriate Therapy Delivery	-	8.2%
Pace/Sense Performance Related	0.8%	4.1%
Infection Related - Explant Required	2.0%	-
Infection Related	1.5%	4.9%
Lead Related	12.4%	2.6%
Device Related	0.5%	-

Table Appendix C-1: PCD Transvene System Complications and Observations by Category - 6/24/92

PCD Transvene System Reported Complications and Observations 6/24/92		
Category	**Complications**	**Observations**
Increased Defibrillation Requirements	6	4
Inappropriate VF Therapy Delivery	-	13
Inappropriate VT Therapy Delivery	-	49
Loss of Capture	6	7
Oversensing	-	24
Undersensing	-	-
Skin Erosion	2	1
Pocket Infection	15	8
Seroma	5	11
Hematoma	4	17
Pneumothorax	2	1
Pacemaker Syndrome	-	2
Right Ventricular Perforation	5	-
Subclavian Vein Thrombosis	1	3
Lead Fracture	4	-
Subcutaneous Patch Crinkling	7	5
Total Lead Dislodgement	77	12
RV Lead Dislodgement	21	1
CS Lead Dislodgement	19	4
SVC Lead Dislodgement	37	7
Early Device Explant	4	-
TOTAL	**138**	**157**

Table Appendix C-2: PCD Transvene System Reported Complications and Observations - 6/24/92

INCREASED DEFIBRILLATION REQUIREMENTS

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	2/28/92	3/4/92	(b)(4), (b)(6)
Complication	(b)(6)	2/5/91	3/8/91	(b)(4), (b)(6)
Complication		7/12/91	7/15/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	7/3/91	7/10/91	(b)(4), (b)(6)
Complication		4/8/91	4/11/91	
Complication		11/6/91	1/8/92	
Observation		11/10/89	12/11/89	
Observation		9/3/90	1/13/91	
Observation		1/25/91	2/8/91	
Observation		6/26/91	7/23/91	

(b)(6)
(b)(4), (b)(6)

INAPPROPRIATE VF THERAPY DELIVERY

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6)	11/29/90	12/14/90	(b)(4), (b)(6)
Observation		7/31/91	9/19/91	
Observation		10/10/91	11/11/91	
Observation		2/27/90	5/2/90	
Observation		9/20/90	9/27/90	
Observation		10/22/90	6/11/91	
Observation		1/31/91	5/3/91	
Observation		5/16/91	5/27/91	
Observation		4/24/91	5/21/91	
Observation		9/4/91	9/6/91	

(b)(6)

(b)(4), (b)(6)

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6)	4/5/91	9/39/91	(b)(4), (b)(6)
Observation		6/27/91	7/19/91	
Observation		11/6/91	11/11/91	

INAPPROPRIATE VT THERAPY DELIVERY

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6)	1/14/92	1/22/92	(b)(4), (b)(6)
Observation		1/27/92	1/30/92	
Observation		1/29/92	1/31/92	
Observation		11/16/90	11/28/90	
Observation		11/29/90	9/24/91	
Observation		2/14/91	1/3/92	
Observation		2/27/91	3/4/91	
Observation		2/7/91	3/11/91	
Observation		7/24/91	12/27/91	
Observation		8/21/91	12/26/91	
Observation		10/3/91	10/31/91	
Observation		11/8/91	12/16/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6)	11/7/91	12/3/91	(b)(4), (b)(6)
Observation		11/26/91	11/28/91	
Observation		12/20/91	2/17/92	
Observation		1/17/92	2/26/92	
Observation		10/31/89	8/31/90	
Observation		11/21/89	2/25/90	
Observation		11/10/89	2/23/90	
Observation		2/15/90	10/18/90	
Observation		3/6/90	6/21/90	
Observation		9/27/90	10/18/91	
Observation		4/17/90	10/19/90	
Observation		5/3/90	10/22/90	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6)	8/30/90	9/2/91	(b)(4), (b)(6)
Observation		10/22/90	6/11/91	
Observation		10/5/90	5/13/91	
Observation		11/12/90	11/19/91	
Observation		2/28/91	4/9/91	
Observation		11/28/90	1/8/91	
Observation		12/3/90	1/9/91	
Observation		1/31/91	5/3/91	
Observation		3/25/91	5/6/91	
Observation		3/27/91	2/26/92	
Observation		4/9/91	7/18 /91	
Observation		3/19/91	3/25/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6)	6/17/91	7/23/91	(b)(4), (b)(6)
Observation		2/27/91	10/24/91	
Observation		3/13/91	9/27/91	
Observation		5/16/91	6/18/91	
Observation		4/29/91	5/3/91	
Observation		4/24/91	5/21/91	
Observation		7/8/91	11/1/91	
Observation		4/5/91	9/30/91	
Observation		7/22/91	1/10/92	
Observation		9/25/91	11/21/91	
Observation		6/27/91	7/19/91	
Observation		10/25/91	1/23/92	
Observation		9/26/91	11/19/91	

LOSS OF CAPTURE

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	2/14/92	2/18/92	(b)(4), (b)(6)
Complication		8/30/91	9/3/91	
Complication		11/6/91	11/19/91	
Complication		12/26/91	1/7/92	
Complication		9/13/90	9/21/90	
Complication		8/26/91	8/30/91	
Observation		2/10/92	3/11/92	
Observation		8/21/91	10/2/91	
Observation		12/23/91	1/8/92	
Observation		10/31/89	11/22/90	
Observation		1/19/90	11/26/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6) (b)(6)	5/28/91	7/2/91	(b)(6) (b)(4), (b)(6)
Observation		10/23/91	10/28/91	

OVERSENSING

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6)	12/30/91	2/10/92	(b)(4), (b)(6)
Observation		1/10/92	2/14/92	
Observation		2/24/92	4/8/92	
Observation		11/19/90	2/6/91	
Observation		2/7/91	5/21/91	
Observation		7/10/91	7/15/91	
Observation		8/1/91	4/2/92	
Observation		8/12/91	8/21/91	
Observation		9/4/91	9/9/91	
Observation		9/13/91	2/3/92	
Observation		10/23/91	10/30/91	
Observation		11/5/91	12/9/91	
Observation		10/31/91	11/1/91	
Observation		11/26/91	1/9/92	
Observation		11/25/91	11/27/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6)	12/9/91	12/12/91	(b)(4), (b)(6)
Observation		1/7/92	2/2/92	
Observation		12/16/91	1/4/92	
Observation		6/5/90	11/27/90	
Observation		4/18/91	4/25/91	
Observation		4/24/91	5/15/91	
Observation		7/4/91	12/19/91	
Observation		9/17/91	10/21/91	
Observation		8/23/91	8/28/91	

UNDERSENSING

There have been no reports of undersensing in VF, VT or sinus rhythm.

SKIN EROSION

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	2/22/91	4/17/91	(b)(4), (b)(6)
Complication	(b)(6)	9/17/91	1/22/92	(b)(4), (b)(6)
Observation	(b)(6)	9/24/91	12/2/91	(b)(4), (b)(6)

POCKET INFECTION

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	12/23/91	2/19/92	(b)(4), (b)(6)
Complication		2/5/92	3/20/92	
Complication		2/11/91	3/20/91	
Complication		2/26/91	5/16/91	
Complication		7/18/91	8/11/91	
Complication		7/31/91	9/19/91	
Complication		8/9/91	8/30/91	
Complication		2/2/90	9/8/90	
Complication		3/12/90	10/8/90	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	5/2/90	9/5/90	(b)(4), (b)(6)
Complication		5/10/90	8/12/90	
Complication		4/2/91	5/7/91	
Complication		4/25/91	8/12/91	
Complication		10/9/91	11/22/91	
Complication		10/21/91	1/15/92	
Observation		2/24/92	4/7/92	
Observation		3/16/92	4/16/92	
Observation		2/22/91	3/28/91	
Observation		6/28/91	10/16/91	
Observation		7/29/91	8/29/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6)	8/28/91	9/24/91	(b)(4), (b)(6)
Observation		10/31/89	11/28/89	
Observation		4/25/91	8/9/91	

SEROMA

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	1/15/92	2/10/92	(b)(4), (b)(6)
Complication		1/30/92	3/2/92	
Complication		1/17/92	2/19/92	
Complication		3/8/91	3/19/91	
Complication		9/17/91	10/21/91	
Observation		11/26/90	12/13/90	
Observation		8/30/90	9/29/90	
Observation	(b)(6)	7/13/90	2/1/91	
Observation		11/26/90	12/13/90	
Observation		11/26/90	12/7/90	
Observation		3/26/91	4/9/91	
Observation		4/20/91	5/15/91	
Observation		6/12/91	7/5/91	
Observation		6/18/91	7/1/91	
Observation		10/10/91	11/1/91	
Observation		4/25/91	8/9/91	

HEMATOMA

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	8/16/91	9/17/91	(b)(6), (b)(4)
Complication		8/19/91	9/15/91	
Complication		10/24/91	11/22/91	
Complication		10/21/91	10/24/91	
Observation		2/13/92	3/10/92	
Observation		1/22/92	2/13/92	
Observation		2/11/92	3/27/92	
Observation		2/11/92	2/19/92	
Observation		2/20/92	3/23/92	
Observation	(b)(6)	4/3/92	5/6/92	(b)(6), (b)(4)
Observation		6/5/90	6/12/90	
Observation		7/4/90	7/31/90	
Observation		11/22/90	1/3/91	
Observation		2/25/91	3/6/91	
Observation		3/25/91	4/17/91	
Observation		4/24/91	4/29/91	
Observation		10/21/91	10/24/91	
Observation		7/2/91	8/5/91	
Observation		6/4/91	6/10/91	
Observation		9/17/91	10/29/91	
Observation		7/18/91	8/15/91	

PNEUMOTHORAX

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	11/6/91	11/8/91	(b)(6), (b)(4)
Complication	(b)(6)	11/23/90	11/30/90	(b)(6), (b)(4)
Observation	(b)(6)	10/16/90	10/22/90	(b)(6), (b)(4)

PACEMAKER SYNDROME

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6)	11/27/90	5/16/91	(b)(6), (b)(4)
Observation	(b)(6)	11/26/91	2/19/92	(b)(6), (b)(4)

RIGHT VENTRICLE PERFORATION

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	11/5/90	11/7/90	(b)(6), (b)(4)
Complication		8/8/91	8/8/91	
Complication		10/31/91	11/29/91	
Complication		7/5/91	7/5/91	
Complication		8/26/91	9/2/91	

SUBCLAVIAN VEIN THROMBOSIS

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	11/8/91	1/29/92	(b)(6), (b)(4)
Observation	(b)(6)	2/5/92	3/5/92	(b)(6), (b)(4)
Observation	(b)(6)	12/26/91	4/6/92	(b)(6), (b)(4)
Observation	(b)(6)	10/5/90	1/11/91	(b)(6), (b)(4)

LEAD FRACTURE

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	2/11/91	8/5/91	(b)(6), (b)(4)
Complication	(b)(6)	5/3/90	6/24/91	(b)(6), (b)(4)
Complication	(b)(6)	12/3/90	5/16/91	(b)(6), (b)(4)
Complication	(b)(6)	7/23/91	2/10/92	(b)(6), (b)(4)

SUBCUTANEOUS PATCH CRINKLING

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	11/26/90	12/13/90	(b)(6), (b)(4)
Complication		4/25/91	5/2/91	
Complication		5/17/91	6/25/91	
Complication		8/9/92	12/4/91	
Complication		6/28/91	10/24/91	
Complication		1/29/92	4/5/92	
Complication		7/22/91	10/18/91	
Observation		2/11/92	3/27/92	
Observation		11/19/90	6/26/90	
Observation		12/11/91	6/17/92	
Observation		6/1/90	9/17/90	
Observation		4/25/91	5/2/91	

LEAD DISLODGEMENT

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	1/15/92	2/03/92	(b)(6), (b)(4)
Complication		12/23/91	2/19/92	
Complication		1/23/92	2/7/92	
Complication		3/3/92	3/6/92	
Complication		3/16/92	4/16/92	
Complication		11/21/89	11/30/89	
Complication		11/7/90	2/13/91	
Complication		10/26/90	11/5/90	
Complication		11/16/90	12/11/90	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6)	11/28/90	1/10/91	(b)(6), (b)(4)
Complication		2/2/91	2/2/91	
Complication		2/26/91	3/22/91	
Complication		7/2/91	7/31/91	
Complication		7/19/91	9/26/91	
Complication		7/23/91	7/29/91	
Complication		7/3/91	9/9/91	
Observation		7/31/91	9/4/91	
Complication		3/30/92	3/31/92	
Complication		8/28/91	10/9/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	8/26/91	9/12/91	(b)(6), (b)(4)
Complication		8/15/91	8/19/91	
Complication		8/26/91	9/5/91	
Complication		8/28/91	12/23/91	
Complication		8/30/91	9/3/91	
Complication		9/3/91	9/6/91	
Complication	(b)(6)	9/3/91	10/14/91	(b)(6), (b)(4)
Complication		9/3/91	9/9/91	
Complication		9/6/91	12/21/91	
Complication		9/11/91	10/16/91	
Complication		9/16/91	9/19/91	
Complication		10/1/91	10/8/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6)	10/10/91	11/11/91	(b)(6), (b)(4)
Complication		10/11/91	10/15/91	
Complication		10/23/91	10/30/91 11/8/91	
Complication		10/24/91	12/6/91	
Complication		10/30/91	11/20/91	
Complication	(b)(6)	10/31/91	11/16/91	(b)(6), (b)(4)
Complication		11/1/91	12/9/91	
Complication		11/7/91	12/13/91	
Observation		11/26/91	12/2/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	11/14/91	11/18/91	(b)(6), (b)(4)
Complication		11/19/91	11/27/91	
Complication		11/26/91	11/29/91	
Complication		12/5/91	1/9/92	
Observation		11/27/91	1/10/92	
Complication		12/9/91	2/12/92	
Complication		12/11/91	1/14/92	
Observation		12/12/91	12/16/91	
Complication		12/26/91	1/7/92	
Complication		12/20/91	1/14/92	
Complication		11/26/90	12/13/90	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	10/3/89	11/10/89	(b)(6), (b)(4)
Complication		11/19/90	3/15/90	
Observation		9/27/90	6/21/91	
Complication		5/4/90	5/9/90	
Complication		5/25/90	2/28/91	
Complication		8/31/90	12/3/90	
Complication		9/13/90	10/16/90	
Complication		10/5/90	1/11/91	
Complication		11/13/90	3/14/91	
Complication		11/28/90	1/8/91	
Complication		2/5/91	2/11/91	
Complication		11/23/90	12/4/90	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Observation	(b)(6)	2/14/91	2/21/91	(b)(6), (b)(4)
Observation		4/15/91	10/25/91	
Complication		4/11/91	5/3/91	
Complication		4/2/91	4/16/91	
Complication		5/13/91	5/17/91	
Complication		3/13/91	4/11/91	
Complication		4/29/91	8/8/91	
Complication		6/7/91	8/14/91	
Complication		6/12/91	11/11/91	
Complication		9/8/91	9/20/91	
Complication		8/16/91	9/20/91	

MEDTRONIC CONFIDENTIAL

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	5/24/91	8/12/91	(b)(6), (b)(4)
Complication		5/17/91	6/21/91	
Complication		4/7/91	5/10/91	
Observation		6/20/91	7/25/91	
Complication		7/8/91	10/8/91	
Observation		8/23/91	9/27/91	
Complication	(b)(6)	8/29/91	9/11/91	(b)(6), (b)(4)
Complication		4/25/91	5/24/91	
Complication		10/2/91	11/26/91	
Complication		9/19/91	10/2/91	
Observation		8/23/91	12/6/91	
Complication		4/29/91	5/6/91	

Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	7/18/91	8/15/91	(b)(6), (b)(4)

EARLY DEVICE EXPLANT

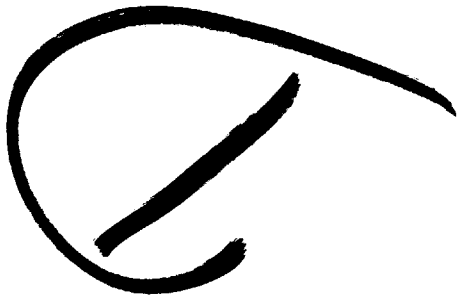
Complication/ Observation	ID#	Implant Date	Event Date	Resolution/Outcome
Complication	(b)(6)	3/19/92	3/23/92	(b)(6), (b)(4)
Complication		11/7/90	2/13/91	
Complication		11/29/90	1/4/91	
Complication		11/25/91	1/30/92	

(b)(6)

(b)(6), (b)(4)

Patient Deaths

5



PCD Transvene System Death Summaries

There have been 34 reported patient deaths in patients who were screened for a PCD Transvene System implant as of June 24, 1992. A description of each of these deaths is provided in the following discussion.

There are **twenty-two (22) patient deaths** in patients who received a PCD Transvene System. Three of these deaths were classified as sudden cardiac; sixteen were classified as non-sudden cardiac; and the remaining three patient deaths were classified as noncardiac. There were 5 perioperative patient deaths in this group.

There have been **two (2) patient deaths** in patients who have received "Other Lead Systems". One death was classified as non-sudden cardiac due to CHF and septicemia and the other was classified as perioperative, noncardiac due to sepsis.

There have been **eight (8) patient deaths** in patients who were screened for a PCD Transvene System but ultimately received a PCD Epicardial System. Two of the deaths were classified as sudden cardiac, four were classified as non-sudden cardiac and the remaining two deaths were classified as noncardiac. All of the patient deaths were classified as perioperative.

There have been **two (2) patient deaths** in patients who were screened for a PCD Transvene System who did not meet the implant criteria and received no PCD System. Both of these deaths were classified as non-sudden cardiac and neither occurred in the perioperative period.

All of the patient deaths have been reviewed by a committee compromised of PCD Device investigators and other physicians (Clinical Event Review Committee). The primary purpose of these reviews was to determine whether the PCD device system was related to the deaths that have occurred, and if so what changes are required to prevent such events in the future.

There have been no patient deaths reported secondary to ineffective defibrillation of a spontaneous episode of VF, lead dislodgement or lead fracture.

Patients Received PCD Transvene System

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant:
Date of Death:
Death Classification: **Noncardiac**

(b)(4), (b)(6)

Device programmed status was as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	450 ms
VT NID	20
VT Rx #1	CV/34J/SEQ
VT Rx #2	CV/34J/SEQ
VT Rx #3	CV/34J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	380 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified the patient death as perioperative, noncardiac and not related to the implanted PCD Transvene System. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

Device programmed status was as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	490 ms
VT NID	12
VT Rx #1	Burst
VT Rx #2	CV/5J/SIM
VT Rx #3	CV/34J/SIM
VT Rx #4	CV/34J/SIM
FDI	320 ms
VF NID	18
VF Rx #1	18J/SIM
VF Rx #2	34J/SIM
VF Rx #3	34J/SIM
VF Rx #4	34J/SIM

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as perioperative and sudden cardiac. The relationship of the death to the implanted PCD Transvene System was classified as unknown. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

programmed status was as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	450 ms
VT NID	12
VT Rx #1	Ramp
VT Rx #2	CV/34J/SINGLE
VT Rx #3	CV/34J/SINGLE
VT Rx #4	CV/34J/SINGLE
FDI	300 ms
VF NID	12
VF Rx #1	34J/SINGLE
VF Rx #2	34J/SINGLE
VF Rx #3	34J/SINGLE
VF Rx #4	34J/SINGLE

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as perioperative, sudden cardiac and not related to the implanted PCD Transvene System. The investigator felt that the patient's death was related to her severe left ventricular dysfunction. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

programmed status was as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	OFF
VT NID	-
VT Rx #1	OFF
VT Rx #2	-
VT Rx #3	-
VT Rx #4	-
FDI	330 ms
VF NID	12
VF Rx #1	18J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as non-sudden cardiac however it was related to an arrhythmic event. In addition, the investigator indicated that this death was not related to the implanted PCD Transvene System. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as periopertive, non-sudden cardiac and related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and felt that the death was related to the implant procedure and not the implanted PCD Transvene System.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

Parameter	Value
Sensitivity	0.3 mV
TDI	420 ms
VT NID	12
VT Rx #1	Burst
VT Rx #2	Burst
VT Rx #3	CV/18J/SIM
VT Rx #4	CV/34J/SIM
FDI	320 ms
VF NID	18
VF Rx #1	18J/SIM
VF Rx #2	34J/SIM
VF Rx #3	34J/SIM
VF Rx #4	34J/SIM

(b)(4), (b)(6)

(b)(4), (b)(6)

The cause of death was reported as non-sudden cardiac secondary to end stage heart failure by the investigator and not related to the implanted PCD Transvene System. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Noncardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.6 mV
TDI	470 ms
VT NID	16
VT Rx #1	Ramp
VT Rx #2	Ramp
VT Rx #3	CV/34J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	300 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

The cause of death was reported as noncardiac secondary to brain carcinoma by the investigator and not related to the implanted PCD Transvene System. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.6 mV
TDI	350 ms
VT NID	16
VT Rx #1	CV/34J/SEQ
VT Rx #2	CV/34J/SEQ
VT Rx #3	CV/34J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	300 ms
VF NID	18
VF Rx #1	18J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

The cause of death was reported as non-sudden cardiac secondary to end stage heart failure by the investigator and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

91

Parameter	Value
Sensitivity	0.3 mV
TDI	OFF
VT NID	OFF
VT Rx #1	OFF
VT Rx #2	OFF
VT Rx #3	OFF
VT Rx #4	OFF
FDI	350 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

The cause of death was reported as non-sudden cardiac secondary to end stage heart failure by the investigator and not related to the implanted PCD Transvene System. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

The PCD device programmed status at the last follow-up visit was as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	OFF
VT NID	OFF
VT Rx #1	OFF
VT Rx #2	OFF
VT Rx #3	OFF
VT Rx #4	OFF
FDI	320 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

The cause of death was reported as non-sudden cardiac secondary to end stage heart failure by the investigator and not related to the implanted PCD Transvene System. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

4

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

(b)(4), (b)(6)

episodes by the pacing therapy.

(b)(4), (b)(6)

(b)(4), (b)(6)

The PCD device programmed status at the time of the patient's death was as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	480 ms
VT NID	16
VT Rx #1	CV/1.0J/SEQ
VT Rx #2	CV/34J/SEQ
VT Rx #3	CV/34J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	320 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4)

(b)(4)

The CERC reviewed the circumstances of this patient death and

classified this patient death as perioperative and procedure related. The CERC also indicated that the increased frequency in spontaneous VT/VF episodes may have been related to the increased number of inductions during the implant procedure.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: Noncardiac

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.6 mV
TDI	OFF
VT NID	OFF
VT Rx #1	OFF
VT Rx #2	OFF
VT Rx #3	OFF
VT Rx #4	OFF
FDI	340 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ

VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

The cause of death was reported as noncardiac secondary to renal failure by the investigator and not related to the implanted PCD Transvene System. The CERC committee reviewed the circumstances of this patient death and agreed with the investigator's classification.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

The PCD device programmed status at this time was as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	380 ms
VT NID	16
VT Rx #1	CV/10J/SEQ
VT Rx #2	CV/34J/SEQ
VT Rx #3	CV/34J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	290 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

The cause of death was reported as non-sudden cardiac secondary to intractable VT by the investigator and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of the patient death and agreed with the investigator's classification.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	OFF
VT NID	OFF
VT Rx #1	OFF
VT Rx #2	OFF
VT Rx #3	OFF
VT Rx #4	OFF
FDI	320 ms
VF NID	24
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

Patient (b)(6)

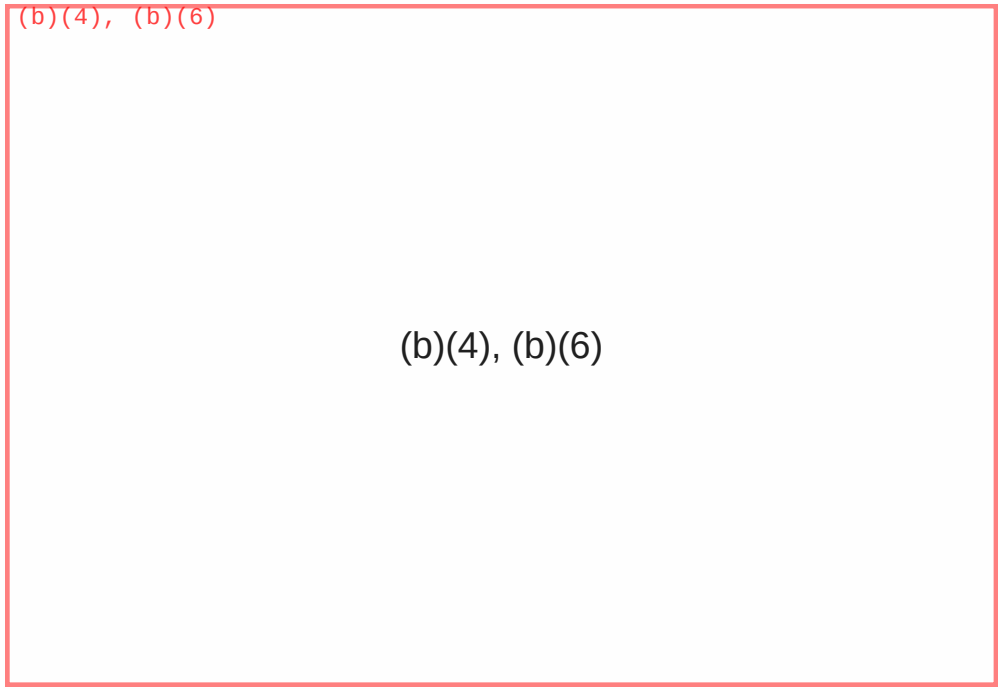
PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	440 ms
VT NID	16
VT Rx #1	CV/34J/SEQ
VT Rx #2	CV/34J/SEQ
VT Rx #3	CV/34J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	400 ms
VF NID	30
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)



The investigator classified this patient death as perioperative, sudden cardiac and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Noncardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.6 mV
TDI	400 ms
VT NID	16
VT Rx #1	CV/5J/SEQ
VT Rx #2	CV/34J/SEQ
VT Rx #3	CV/34J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	300 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

The cause of death was reported as non-cardiac, specifically respiratory arrest, by the investigator and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	440 ms
VT NID	12
VT Rx #1	Burst
VT Rx #2	CV/10J/SIM
VT Rx #3	CV/20J/SIM
VT Rx #4	CV/34J/SIM
FDI	330 ms
VF NID	18
VF Rx #1	34J/SIM
VF Rx #2	34J/SIM
VF Rx #3	34J/SIM
VF Rx #4	34J/SIM

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as non-sudden cardiac and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

Patient (b)(6)

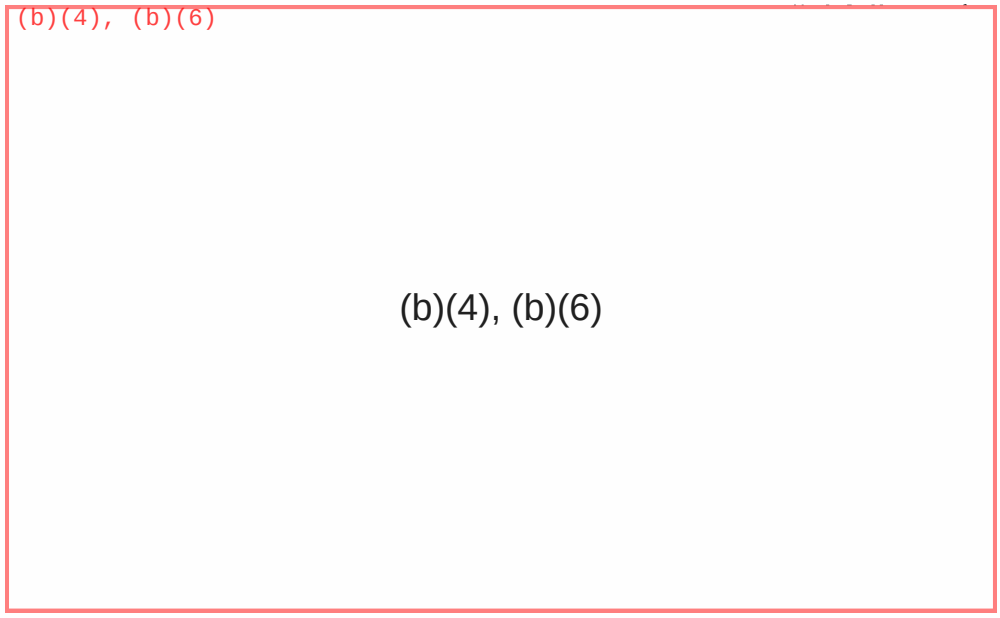
PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.6 mV
TDI	OFF
VT NID	--
VT Rx #1	OFF
VT Rx #2	OFF
VT Rx #3	OFF
VT Rx #4	OFF
FDI	370 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)



The investigator classified this patient death as cardiac, non-sudden and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigators classification.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	OFF
VT NID	--
VT Rx #1	OFF
VT Rx #2	OFF
VT Rx #3	OFF
VT Rx #4	OFF
FDI	400 ms
VF NID	12
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as cardiac, non-sudden and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	400 ms
VT NID	16
VT Rx #1	Burst
VT Rx #2	CV/5J/SEQ
VT Rx #3	CV/20J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	320 ms
VF NID	24
VF Rx #1	18J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

The primary investigator classified this patient death as non-sudden cardiac and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigators classification.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	400 ms
VT NID	16
VT Rx #1	Burst
VT Rx #2	Burst
VT Rx #3	CV/18J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	370 ms
VF NID	24
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

The primary investigator classified this patient death as non-sudden cardiac due to end stage heart failure and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	400 ms
VT NID	16
VT Rx #1	Ramp
VT Rx #2	Burst
VT Rx #3	CV/15J/SEQ
VT Rx #4	CV/34J/SEQ
FDI	320 ms
VF NID	18
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)

(b)(4), (b)(6)

The primary investigator classified this patient death as non-sudden cardiac due to end stage heart failure with associated pulmonary embolus. The death was also classified as not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

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Patients Who Received "Other" Transvene System

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

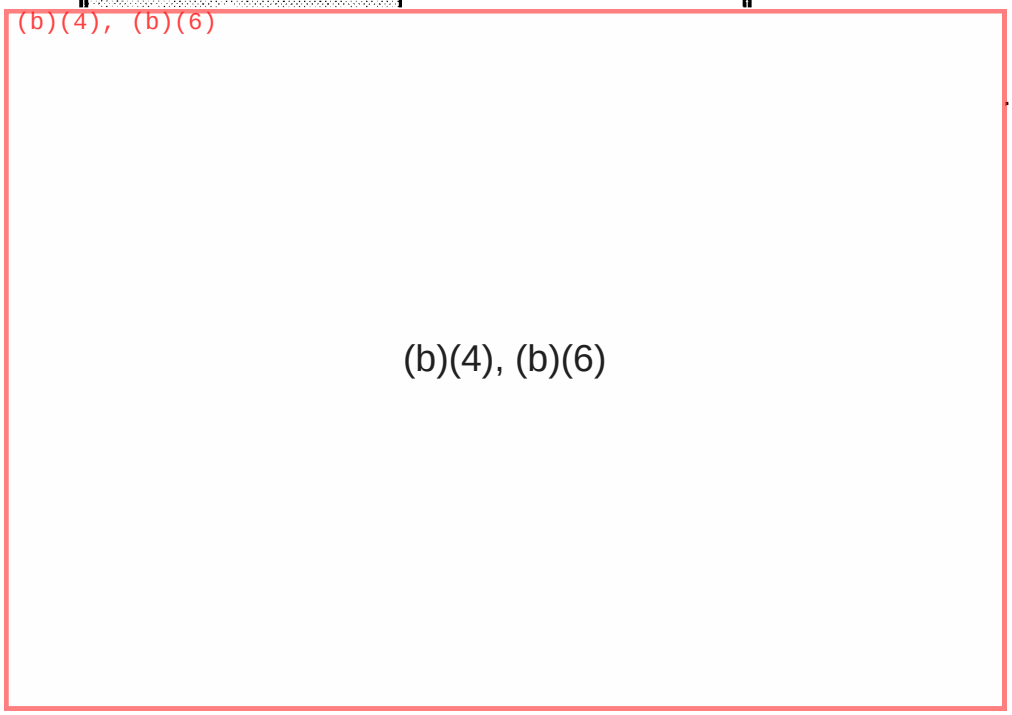
(b)(4), (b)(6)

(b)(4), (b)(6)

102

Parameter	Value
Sensitivity	0.6 mV
TDI	420 ms
VT NID	12
VT Rx #1	Ramp
VT Rx #2	CV/34J/SIM
VT Rx #3	CV/34J/SIM
VT Rx #4	CV/34J/SIM
FDI	300 ms
VF NID	12
VF Rx #1	34J/SIM
VF Rx #2	34J/SIM
VF Rx #3	34J/SIM
VF Rx #4	34J/SIM

(b)(4), (b)(6)



The investigator classified this patient death as non-sudden cardiac and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

153

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Noncardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

Patients Screened For PCD Transvene System Who Received PCD Epicardial System

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Noncardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	500 ms
VT NID	20
VT Rx #1	Burst
VT Rx #2	CV/5J/SIN
VT Rx #3	CV/34J/SIN
VT Rx #4	CV/34J/SIM
FDI	320 ms
VF NID	12
VF Rx #1	34J/SIN
VF Rx #2	34J/SIN
VF Rx #3	34J/SIN
VF Rx #4	34J/SIN

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as perioperative, noncardiac and not related to the implanted PCD Transvene System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

Patient (b)(6)

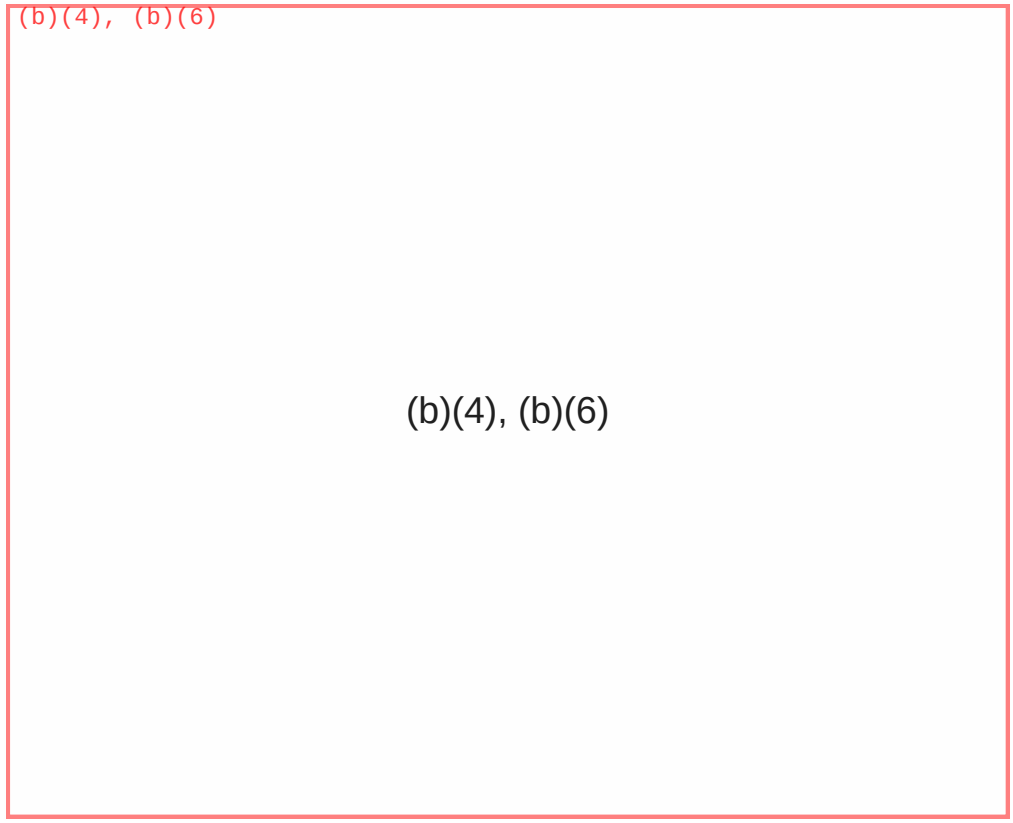
PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.3 mV
TDI	OFF
VT NID	-
VT Rx #1	-
VT Rx #2	-
VT Rx #3	-
VT Rx #4	-
FDI	350 ms
VF NID	12
VF Rx #1	34J/SEQ
VF Rx #2	34J/SEQ
VF Rx #3	34J/SEQ
VF Rx #4	34J/SEQ

(b)(4), (b)(6)



(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as perioperative, non-sudden cardiac and related to an ventricular arrhythmia episode. The investigator indicated that the patient death was not related to the implanted PCD System. The CERC reviewed the circumstances of this patient death and agreed with investigator's classification.

110

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

Parameter	Value
Sensitivity	0.6 mV
TDI	450 ms
VT NID	16
VT Rx #1	Ramp
VT Rx #2	Burst
VT Rx #3	CV/34/SIN
VT Rx #4	CV/34/SIN
FDI	340 ms
VF NID	18
VF Rx #1	34J/SIN
VF Rx #2	34J/SIN
VF Rx #3	34J/SIN
VF Rx #4	34J/SIN

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as perioperative, non-sudden cardiac and not related to the implanted PCD System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

The CERC reviewed the circumstances of this patient death and agreed with the primary investigator's classification. In addition, the death was classified as procedure related due to the fact the patient underwent both a nonthoracotomy and epicardial lead evaluation.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Noncardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

(b)(4), (b)(6)

The CERC reviewed the circumstances of this patient death and agreed with the primary investigator's classification. In addition, the death was classified as perioperative and procedure related due to cerebrovascular accident that occurred during surgical procedure.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

The PCD Device programmed status was:

Parameter	Value
Sensitivity	0.6 mV
TDI	OFF
VT NID	-
VT Therapy #1	OFF
VT Therapy #2	OFF
VT Therapy #3	OFF
VT Therapy #4	OFF
FDI	320 ms
VF NID	18
VF Therapy #1	34J SIM
VF Therapy #2	34J SIM
VF Therapy #3	34J SIM
VF Therapy #4	34J SIM

(b)(4), (b)(6)

(b)(4), (b)(6)

The primary investigator classified this patient death as sudden cardiac and not related to the implanted PCD system. The CERC reviewed the circumstances of this patient death and agreed with

the investigator's classification.

The CERC reviewed the circumstances of this patient death and agreed with the primary investigator's classification. In addition, this death was classified as perioperative and procedure related due to both a nonthoracotomy and epicardial lead evaluation being performed.

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)

The final programmed status of PCD Device was as follows:

Parameter	Value
Sensitivity	0.3 mV
TDI	OFF
VT NID	-
VT Therapy #1	-
VT Therapy #2	-
VT Therapy #3	-
VT Therapy #4	-
FDI	320 ms
VF NID	18
VF Therapy #1	34J/SIN
VF Therapy #2	34J/SIN
VF Therapy #3	34J/SIN
VF Therapy #4	34J/SIN

(b)(4), (b)(6)

(b)(4), (b)(6)

The investigator classified this patient death as perioperative, non-sudden cardiac and not related to the implanted PCD System. The CERC reviewed the circumstances of this patient death and agreed with the investigator's classification.

Patients Who Received No PCD System

Patient (b)(6)

PCD Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

(b)(4), (b)(6)

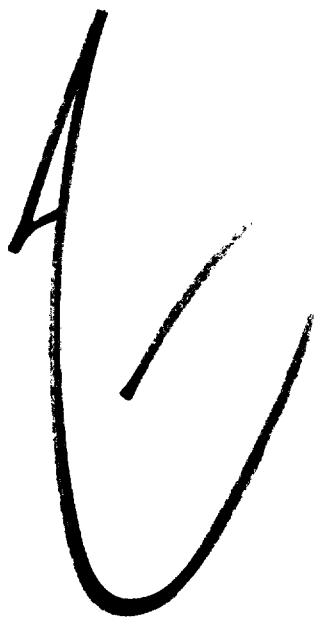
(b)(4), (b)(6)

Patient (b)(6)

PCD Device Serial Number: (b)(6), (b)(4)
Date of Implant: (b)(6), (b)(4)
Date of Death:
Death Classification: **Non-Sudden Cardiac**

(b)(4), (b)(6)

(b)(4), (b)(6)



Appendix E: Investigator List

A. U.S. Model 7216A/17B NTL Implants by Center

Center	Investigator	Number of Implants	Date of First Implant	RV-SVC-SQ	RV-CS-SQ	RV-CS-SVC	Other
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)			

CONFIDENTIAL 581

Center	Investigator	Number of Implants	Date of First Implant	RV-SVC-SQ	RV-CS-SQ	RV-CS-SVC	Other
(b)(4)							

(b)(4)

Center	Investigator	Number of Implants	Date of First Implant	RV-SVC-SQ	RV-CS-SQ	RV-CS-SVC	Other
(b)(4)							

IAI 583

Center	Investigator	Number of Implants	Date of First Implant	RV-SVC-SQ	RV-CS-SQ	RV-CS-SVC	Other
(b)(4)							

B. International Implants by Center

Center	Investigator	Number of Implants	Date of First Implant	RV-SVC-SQ	RV-CS-SQ	RV-CS-SVC	Other
(b)(4)							

(b)(4)

A1585

(b)(4)

Center	Investigator	Number of Implants	Date of First Implant	RV-SVC-SQ	RV-CS-SQ	RV-CS-SVC	Other
(b)(4)							

Center	Investigator	Number of Implants	Date of First Implant	RV-SVC-SQ	RV-CS-SQ	RV-CS-SVC	Other
(b)(4)							

(b)(4)

Center	Investigator	Number of Implants	Date of First Implant	RV-SVC-SQ	RV-CS-SQ	RV-CS-SVC	Other
(b)(4)							

(b)(4)

Appendix F: Statistical Analysis

PCD™ Transvene™ System U.S. vs Int'l Data Summary of Variables Tested				
Category	**U.S.**	**Int'l**	**Statistical Test**	**P-Value**
Mean Age	(b)(4)			
Number, % Male Number, % Female				
Mean Ejection Fraction				
Primary Indication: SCD VT SCD & VT				
NYHA Classification: I/II II/III				
Coronary Artery Disease				
Myocardial Infarction				
Congestive Heart Failure				
Cardiomyopathy				

(b)(4)

Table F1: Summary of Variables Tested for Pooling U.S. and Int'l Data - 6/24/92

(b)(4)

(b)(4)

Category	(b)(4)
Myocardial Infarction	
Congestive Heart Failure	
Sex	
NYHA Classification	
Coronary Artery Disease	
Ejection Fraction	
Cardiomyopathy	
Primary Indication	
Age	

PCD™ Transvene™ System 7216A and 7217B Summary of Variables Tested			(b)(4)
CATEGORY	**7216A**	**7217B**	
Mean Age	62.4	59.4	
Number, % Male **Number, % Female**	15 83.3% 3 16.7	595 80.5% 144 19.5%	
Mean Ejection Fraction	37.8%	35.5%	
Primary Indication: **SCD** **VT** **SCD & VT**	 5 27.8% 8 44.4% 5 27.8%	 276 37.4% 369 49.9% 94 12.7%	
NYHA Classification: **I/II** **III/IV**	 15 83.3% 3 16.7%	 594 82.7% 124 17.3%	(b)(4)
Coronary Artery Disease	83.3%	73.9%	
Myocardial Infarction	83.3%	67.8%	
Congestive Heart Failure	16.7%	33.4%	
Cardiomyopathy	11.1%	31.9%	

Table F2: Summary of Variables Tested for Pooling 7216A AND 7217B - 6/24/92

PCD™ Transvene™ System RV/SVC/SQ vs RV/CS/SQ vs RV/CS/SVC				(b)(4)
CATEGORY	**RV/SVC/SQ**	**RV/CS/SQ**	**RV/CS/SVC**	
Mean Age	59.2	60.3	57.0	
Number, % Male Number, % Female	403 82.0% 93 18.0%	182 81.3% 40 18.7%	25 64.1% 14 35.9%	
Mean Ejection Fraction	36.2%	34.0%	35.8%	
Primary Indication: SCD VT SCD & VT	 187 36.05% 114 51.4% 28 12.6%	 80 37.7% 114 49.0% 28 13.3%	 14 35.9% 20 51.3% 5 12.8%	
NYHA Classification: I/II III/IV	 396 81.7% 89 18.3%	 180 84.9% 32 15.1%	 33 84.6% 6 15.4%	
Coronary Artery Disease	75.0%	73.0%	69.2%	
Myocardial Infarction	68.0%	68.8%	61.5%	
Congestive Heart Failure	35.1%	32.3%	30.8%	
Cardiomyopathy	140 28.2%	88 39.6%	10 25.6%	

Table F3: Summary of Variables Tested on Lead Configurations - 6/24/92

(b)(4)

(b)(4)

Category	(b)(4)	(b)(4)
Primary Indication		
Congestive Heart Failure		
Coronary Artery Disease		
Myocardial Infarction	(b)(4)	(b)(4)
NYHA Classificatic		
Age		
Ejection Fraction		
Sex		
Cardiomyopathy		

APPENDIX A

INVESTIGATIONAL PLAN

G920015/Ac2v4

2

(b)(4)

(b)(4)

3

01/18/93
NTL

INVESTIGATIONAL PLAN

MODEL 7217B PCD
PACER-CARDIOVERTER-DEFIBRILLATOR WITH
NON-THORACOTOMY LEAD SYSTEMS

RECEIVED
1993 JAN 30 11
FDA/CDE/DHC

A. STUDY PURPOSE

1. Name and Intended Use of System

The Model 7217B PCD System consists of several components, including a pulse generator; various transvenous, subcutaneous, and epicardial leads; and a dedicated software cartridge used with an existing programmer system.

The Model 7217B PCD (Pacer-Cardioverter-Defibrillator) is an implantable, multiprogrammable, automatic tachyarrhythmia control device designed to detect and treat episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF) using either low energy pacing therapies or higher energy cardioversion or defibrillation therapies.

(b)(4)

(b)(4)

The Model 7217B will be used with two basic types of lead systems -

a. (b)(4)

b. (b)(4)

4

(b)(4)

(b)(4)

(b)(4)

(b)(4)

2. Study Objectives

(b)(4)

(b)(4)

a.

b.

c.

(b)(4)

(b)(4)

(b)(4)

(b)(4)

1. Epicardial

(b)(4)

(b)(4)

2. (b)(4)

3.

4.

(b)(4)

5.

6.

(b)(4)

(b)(4)

* (b)(4)

(b)(4)

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(b)(4)

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*

(b)(4)

(b)(4)

(b)(4)

3. Study Duration

(b)(4)

(b)(4)

8

B. PROTOCOL

1. Summary

a. Objective

(b)(4)

(b)(4)

b. Patients

(b)(4)

(b)(4)

c. Methods

(b)(4)

(b)(4)

9

(b)(4)

(b)(4)

d.

(b)(4)

(b)(4)

2. Methods

10

a. Investigator Selection

(b)(4)

(b)(4)

* (b)(4)

*

*

*

*

*

*

b. Supply of Study Material

11

(b)(4)

(b)(4)

c. Patient Selection Criteria

(b)(4)

(b)(4)

12

(b)(4)

(b)(4)

1) Patient History

(b)(4)

(b)(4)

a)

b)

(b)(4)

(b)(4)

13

c) (b)(4)

(b)(4)

(b)(4)

(b)(4)

14

2) Lead System Evaluation

(b)(4)

(b)(4)

15

(b)(4)

(b)(4)

3) Geographically Stable

(b)(4)

(b)(4)

4) Willing to Follow Protocol

(b)(4)

(b)(4)

16

(b)(4)

(b)(4)

d. Study Procedures: General Requirements

(b)(4)

(b)(4)

1)

2)

3)

(b)(4)

(b)(4)

e. Study Procedures

1)

(b)(4)

(b)(4)

17

(b)(4)

(b)(4)

a)

(b)(4)

(b)(4)

b)

c)

The following tests should be performed dependent on patient history:

d)

(b)(4)

(b)(4)

e)

18

(b)(4)

(b)(4)

The following is OPTIONAL information requested if available as a result of normal cardiological testing:

e) (b)(4) (b)(4)

19

f) (b)(4)

g) (b)(4)

2) Lead System Testing Procedures

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

1.

2.

3.

(b)(4)

(b)(4)

21

(b)(4)

(b)(4)

22

(b)(4)

(b)(4)

Defibrillation Efficacy Protocol
(b)(4)

(b)(4)

NOTE:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

2a) Non-Epicardial Lead System Testing

a1) (b)(4)

(b)(4)

24

(b)(4)

(b)(4)

a2)

(b)(4)

a3)

NOTE:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

a4)

(b)(4)

(b)(4)

NOTE:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

a5)

(b)(4)

(b)(4)

37

a7)

a8)

a9)

a10)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

DISCHARGES:

(b)(4)

(b)(4)

NOTE:

(b)(4)

(b)(4)

a11)

(b)(4)

(b)(4)

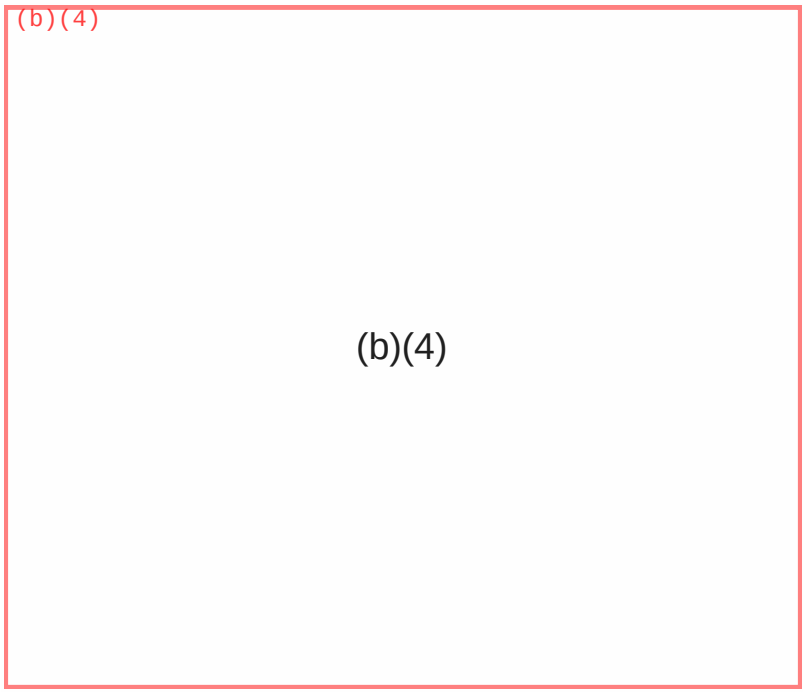
31

(b)(4)

(b)(4)

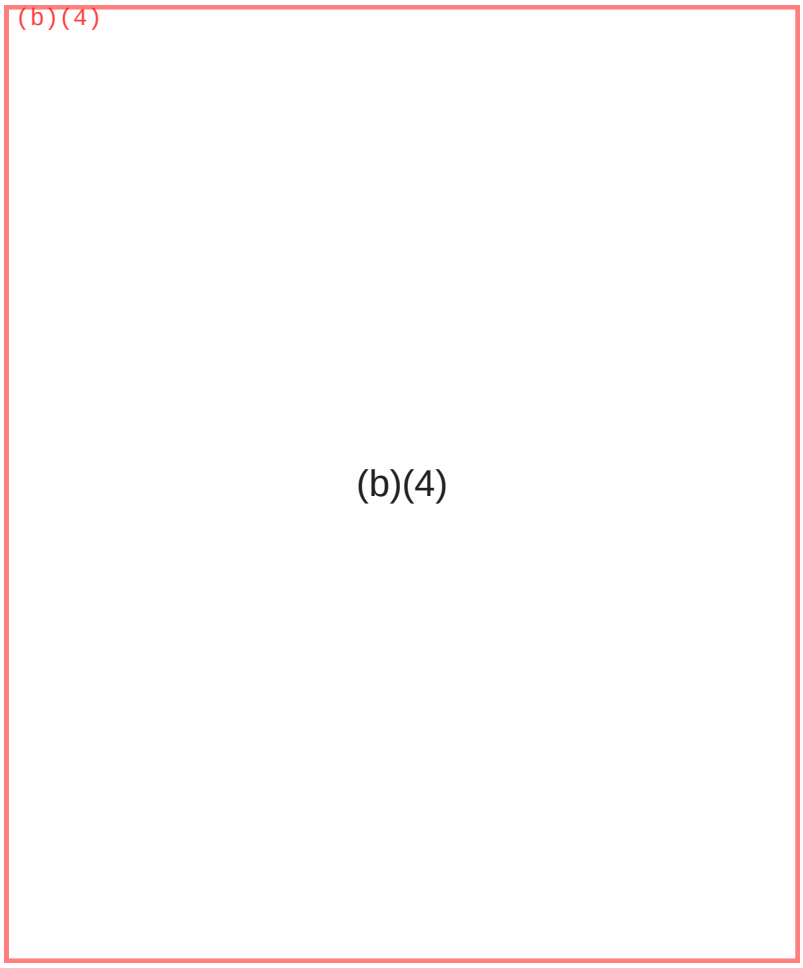
30

(b)(4)



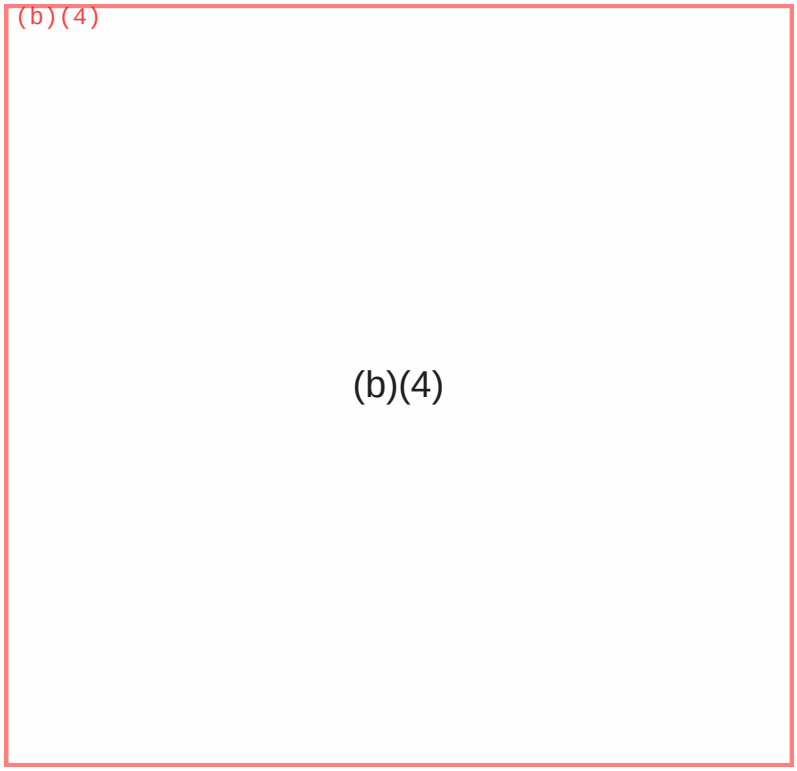
a12)

(b)(4)



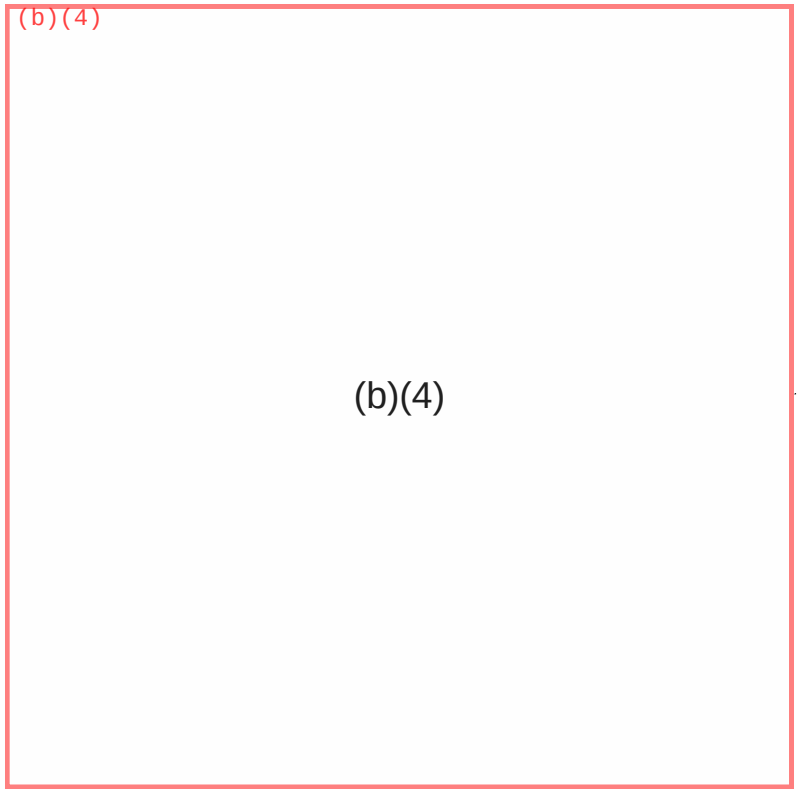
31

a13) (b)(4)



2b) Epicardial Lead System Testing

b1) (b)(4)



30

(b)(4)

b2)

(b)(4)

b3)

33

b4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

34

(b)(4)

(b)(4)

b5)

(b)(4)

(b)(4)

NOTE:

(b)(4)

(b)(4)

b6)

(b)(4)

35

(b)(4)

(b)(4)

b7)

37

b8) (b)(4)

b9)

(b)(4)

DISCHARGES:

b10) (b)(4)

(b)(4)

i) (b)(4)

ii)

(b)(4)

iii)

iv)

b11) (b)(4)

(b)(4)

39

(b)(4)

(b)(4)

NOTE:

(b)(4)

(b)(4)

b12)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

b13) (b)(4) (b)(4)

(b)(4)

(b)(4)

NOTE: (b)(4)

(b)(4)

41

(b)(4)

(b)(4)

b14) (b)(4)

(b)(4)

NOTE: (b)(4)

(b)(4)

(b)(4)

(b)(4)

3) Implantable Pulse Generator Testing

NOTE: (b)(4)

(b)(4)

a) (b)(4)

b)

(b)(4)

c)

43

i) (b)(4)

ii)

iii)

(b)(4)

d) (b)(4)

(b)(4)

NOTE: (b)(4)

(b)(4)

43

(b)(4)

(b)(4)

e)

(b)(4)

f)

g)

44

(b)(4)

(b)(4)

4) Post-Implant Hospital Monitoring/Testing

(b)(4)

(b)(4)

a)

b)

c)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

d)

(b)(4)

e)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

f) (b)(4)

(b)(4)

5) Follow-up Procedures

a) (b)(4)

(b)(4)

b)

HS

(b)(4)

(b)(4)

(b)(4)

(b)(4)

NOTE:

(b)(4)

(b)(4)

c)

(b)(4)

d)

g) (b)(4)

51

(b)(4)

h)

i) (b)(4)

52

j) (b)(4)

(b)(4)

6) Documentation

(b)(4)

(b)(4)

7) Patient Diary

(b)(4)

(b)(4)

53

(b)(4)

(b)(4)

8) Follow-up Schedule

(b)(4)

(b)(4)

9) Study Schedule

(b)(4)

(b)(4)

f. Study Design Analysis

(b)(4)

(b)(4)

54

(b)(4)

(b)(4)

(b)(4)

(b)(4)

C. RISK ANALYSIS

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Included in these risks are the following:

1) (b)(4)

2)

(b)(4)

(b)(4)

3)

4)

5)

6)

(b)(4)

7)

8)

9)

10)

58

(b)(4)

(b)(4)

54

(b)(4)

(b)(4)

D. PCD SYSTEM DESCRIPTION

(b)(4)

(b)(4)

60

(b)(4)

(b)(4)

(b)(4)

(b)(4)

E. MONITORING PROCEDURES

1. Study Monitors

(b)(4)

(b)(4)

(b)(4)

(b)(4)

2. Monitoring Procedures

a. Summary of Monitoring Procedures and Responsibilities

(b)(4)

(b)(4)

62

(b)(4)

(b)(4)

b. Pre-Study Visit/Investigator Training

(b)(4)

(b)(4)

1)

2)

3)

4)

5)

5)

6)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

c. Device Implantation/Follow-Up Support

63

(b)(4)

(b)(4)

d. Review of Completed Data Forms and Other Study Documents

(b)(4)

(b)(4)

1) Investigator Agreement

(b)(4)

(b)(4)

2) Lead System Testing/Implant Data Forms

(b)(4)

(b)(4)

3) Follow-up and Spontaneous Episode/Monitoring Data Forms

(b)(4)

(b)(4)

4) Study Monitor-Designate Reports

(b)(4)

(b)(4)

64

(b)(4)

(b)(4)

5) Other Records and Reports (see Section J).

e. On-Site Monitoring

(b)(4)

(b)(4)

f. Final Monitoring Visit/Telephone Review

(b)(4)

(b)(4)

g. Study Complications

(b)(4)

(b)(4)

(b)(4)

(b)(4)

F. LABELING

The Technical Manuals and other labeling are attached to this Investigational Plan.

G. CONSENT MATERIALS

1. (b)(4)

(b)(4)

a. (b)(4)

b.

c.

d. (b)(4)

e.

f.

(b)(4)

g. (b)(4)

h. (b)(4)

(b)(4)

(b)(4)

2. Exceptions

(b)(4)

(b)(4)

H. IRB/ETHICS COMMITTEE INFORMATION

67

(b)(4)

(b)(4)

I. OTHER INSTITUTIONS

(b)(4)

(b)(4)

J. RECORDS AND REPORTS

1. Investigator Records

(b)(4)

(b)(4)

a. (b)(4)

(b)(4)

b.

(1) (b)(4)

(2)
(3)
(4) (b)(4)
(5)

(6)

c. (b)(4)

(b)(4)

2. Investigator Reports

(b)(4)

(b)(4)

108

(b)(4)

(b)(4)

REPORT	SUBMIT TO	DESCRIPTION
(b)(4)		

(b)(4)

(b)(4)

(b)(4)

3. Medtronic Records

Medtronic will maintain the following records:

a. (b)(4)

b.

c.

d.

e. (b)(4)

f.

g.

(b)(4)

(b)(4)

4. Medtronic Reports

REPORT	SUBMIT TO	DESCRIPTION
(b)(4)	(b)(4)	

(b)(4)

(b)(4)

Record retention requirements described in Section H.1 will apply to these IRB records.

APPENDIX B

CLINICAL DATA FORMS

Version 7/16/92

Patient ID
Hospital ID
Physician ID

Medtronic

(b)(4)

(b)(4)

(b)(4)

UC9202583EN

(b)(4)

(b)(4)

Version 7/16/92

Patient ID
Hospital ID
Physician ID

Medtronic

(b)(4)

(b)(4)

(b)(4)

PATIENT NAME _____ DATE _____ LEAD SYSTEM EVALUATION DATA FORM

(b)(4)

(b)(4)

Version 7/16/92

Patient ID
Hospital ID
Physician ID

Medtronic

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Version 10/30/92

Patient ID
Hospital ID
Physician ID

Medtronic

(b)(4)

(b)(4)

(b)(4)

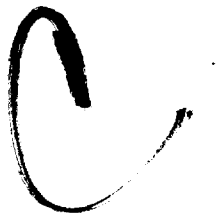
(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)



APPENDIX C

CLINICAL LITERATURE

APPENDIX C

A copy of the Bibliography provided in the original Transvene PMA application (dated March 31, 1992) is included here for convenient reference (listing of literature articles). In addition, copies of the following relevant articles are also provided.

Bardy, G.H., Hofer, B., Johnson, G., Kudenchuk, P.J., Poole, J.E., Dolack, G.L., Gleva, M., Mitchell, R., Kelso, D. "Implantable Transvenous Cardioverter-Defibrillator" Circulation Vol 87, No 4, April 1993, p. 1152-68.

Dunnett, C.W., Tamhane, A.C. "A Step-up Multiple Test Procedure" Journal of the American Statistical Association Vol. 87, No. 417, March 1992, p. 162-70.

Winkle, R.A., Mead, H., Ruder, M., Gaudiani, V.A., Smith, N.A., Buch, W.S., Schmidt, P., Shipman, T. "Long-term Outcome with the Automatic Implantable Cardioverter-Defibrillator" J Am Coll Cardiol 13(6), May 89, p. 1353-61.

Pages removed for the following reason: Copyright Materials.

BIBLIOGRAPHY

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APPENDIX D

VT/VF EPISODE DATA BY FOLLOW-UP INTERVAL

Appendix D

Table D1 contains a summary of the spontaneous and induced episodes of VT and VF at various follow-up intervals.

PCD Transvene System Data Summary		
		(b)(4)
VT		
# Patients	Induced	(b)(4)
	Spontaneous	
	Either	
# Episodes	Induced	
	Spontaneous	
	Either	
VF		
# Patients	Induced	(b)(4)
	Spontaneous	
	Either	
# Episodes	Induced	
	Spontaneous	
	Either	
VT or VF		
# Patients	Induced	(b)(4)
	Spontaneous	
	Either	
# Episodes	Induced	
	Spontaneous	
	Either	

Table D1: Induced and Spontaneous Episodes of VT/VF over Time - 2/1/93

E

APPENDIX E

STATISTICAL ANALYSIS

Appendix E: Statistical Analysis

1. Justification of Data Pooling

Table E1 contains the summary of variables tested for pooling the U.S.anf International data.

PCD Transvene System U.S. vs Int'l Data Summary of Variables Tested			(b)(4)
Category	U.S.	Int'l	
Mean Age	61.1	57.0	
Number, % Male Number, % Female	351 78.9% 94 21.1%	251 83.0% 53 17.0%	
Mean Ejection Fraction	33.6%	38.4%	
Primary Indication: SCD VT SCD & VT	 166 37.3% 240 53.9% 39 8.8%	 115 36.9% 137 43.9% 60 19.2%	(b)(4)
NYHA Classification: I/II II/III	 366 85.1% 64 14.9%	 243 79.4% 63 20.6%	
Coronary Artery Disease	347 78.0%	214 68.6%	
Myocardial Infarction	305 68.5%	211 67.6%	
Congestive Heart Failure	155 34.8%	95 30.5%	
Cardiomyopathy	162 36.4%	76 24.4%	

Table E1: Summary of Variables Tested for Pooling U.S. and Int'l Data - 2/01/93

(b)(4)

(b)(4)

Category	p-value	adjusted p-value
Myocardial Infarction	(b)(4)	(b)(4)
Congestive Heart Failure		
Sex		
NYHA Classification		
Coronary Artery Disease		
Ejection Fraction		
Cardiomyopathy		
Primary Indication		
Age		

** statistically significant at 0.05 significance level

Table E2 and Table E3 contain the summary of variable tested for pooling the 7216A and 7217B and the summary of variables tested on lead configurations, respectively.

PCD Transvene System
7216A and 7217B
Summary of Variables Tested

CATEGORY	7216A	7217B	(b)(4)
Mean Age	62.4	59.4	
Number, % Male Number, % Female	15 83.3% 3 16.7	595 80.5% 144 19.5%	
Mean Ejection Fraction	37.8%	35.5%	
Primary Indication: SCD VT SCD & VT	 5 27.8% 8 44.4% 5 27.8%	 276 37.4% 369 49.9% 94 12.7%	
NYHA Classification: I/II III/IV	 15 83.3% 3 16.7%	 594 82.7% 124 17.3%	
Coronary Artery Disease	83.3%	73.9%	
Myocardial Infarction	83.3%	67.8%	
Congestive Heart Failure	16.7%	33.4%	
Cardiomyopathy	11.1%	31.9%	

(b)(4)

Table E2: Summary of Variables Tested for Pooling 7216A AND 7217B - 2/01/93

PCD Transvene System
RV/SVC/SQ vs RV/CS/SQ vs RV/CS/SVC

CATEGORY	RV/SVC/SQ	RV/CS/SQ	RV/CS/SVC	(b)(4)
Mean Age	59.2	60.3	57.0	
Number, % Male Number, % Female	403 82.0% 93 18.0%	182 81.3% 40 18.7%	25 64.1% 14 35.9%	
Mean Ejection Fraction	36.2%	34.0%	35.8%	
Primary Indication: SCD VT SCD & VT	 187 36.05% 114 51.4% 28 12.6%	 80 37.7% 114 49.0% 28 13.3%	 14 35.9% 20 51.3% 5 12.8%	
NYHA Classification: I/II III/IV	 396 81.7% 89 18.3%	 180 84.9% 32 15.1%	 33 84.6% 6 15.4%	
Coronary Artery Disease	75.0%	73.0%	69.2%	
Myocardial Infarction	68.0%	68.8%	61.5%	
Congestive Heart Failure	35.1%	32.3%	30.8%	
Cardiomyopathy	140 28.2%	88 39.6%	10 25.6%	

(b)(4)

Table E3: Summary of Variables Tested on Lead Configurations - 2/01/93

(b)(4)

(b)(4)

Category	p-value	adjusted p-value
Primary Indication	(b)(4)	
Congestive Heart Failure		
Coronary Artery Disease		
Myocardial Infarction		
NYHA Classification		
Age		
Ejection Fraction		
Sex		
Cardiomyopathy		

(b)(4)

B. Statistical Tests used in this document

(b)(4)

(b)(4)

1. (b)(4)

2. (b)(4)

3.

3. Patient Withdrawal from analysis

(b)(4)

(b)(4)

4

APPENDIX F

RETURN PRODUCT ANALYSIS PROCEDURES

A description of the protocol for PCD device and Transvene lead analysis is presented below.

Failure Analysis Procedure: PCD Device and Transvene Leads

(b)(4)

(b)(4)

PCD Device

(b)(4)

(b)(4)

1.
2.
3.
4.
5.

(b)(4)

(b)(4)

Specialized testing may include:

1.
2.
3.
4.
5.

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5e

Destructive testing may include:

1.
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Specialized battery depletion testing may include:

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2.
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Transvene Leads

(b)(4)

(b)(4)

1.
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Specialized testing may include:

1.
2.
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58

APPENDIX G

LABELING; TECHNICAL MANUALS--
MODELS 6963, 6966, 6999

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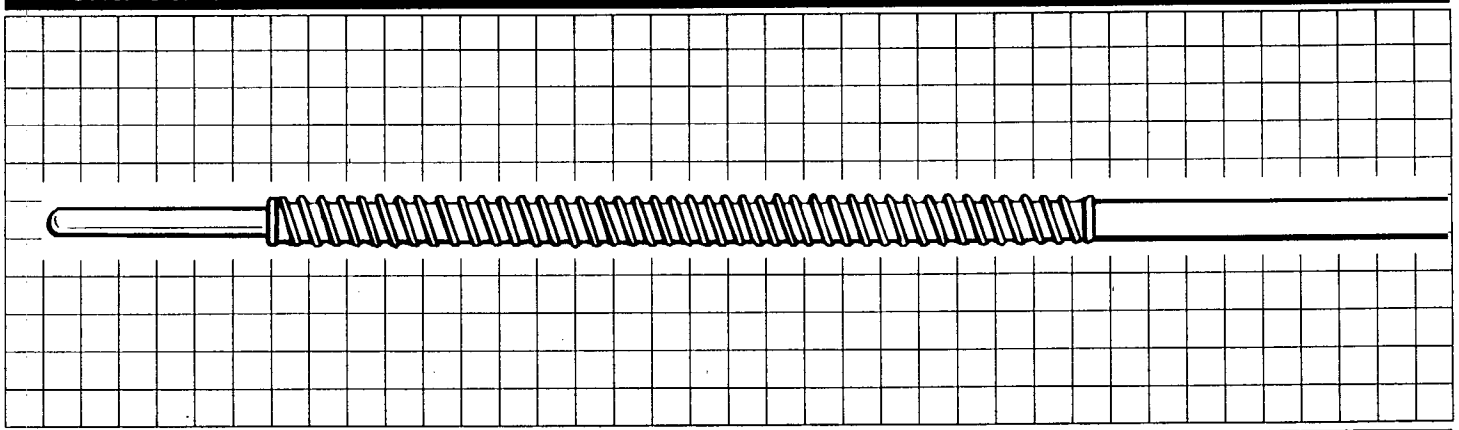
Medtronic

TRANSVENE™ -CS/SVC 6963

Unipolar, Endocardial, Coronary Sinus or Superior
Vena Cava Lead for Cardioversion and Defibrillation



Technical Manual

6963 Cover UC9002088cEN 195421-004/MMC

9

TECHNICAL MANUAL

TRANSVENE™ -CS/SVC UNIPOLAR, ENDOCARDIAL, CORONARY SINUS OR SUPERIOR VENA CAVA LEAD FOR CARDIOVERSION AND DEFIBRILLATION

MODEL 6963

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DESCRIPTION AND INTENDED USE

The Medtronic® TRANSVENE™-SVC Model 6963 Unipolar, Endocardial, Coronary Sinus or Superior Vena Cava Lead is designed for the delivery of cardioversion and defibrillation therapies. It is intended for single long-term use in the coronary sinus or superior vena cava and is designed to be used only with a compatible Medtronic implantable tachyarrhythmia control device along with at least one other Medtronic defibrillation lead.

Silicone insulation surrounds the low resistance conductor coil and the coil electrode is a platinum alloy. The lead also has a 6.5 mm connector.

The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

CONTENTS OF PACKAGE

The leads are supplied sterile. Each package contains:

- 1 TRANSVENE™-SVC lead with two non-radiopaque anchoring sleeves, stylet, and stylet guide
- 1 vein lifter
- Extra stylets
- Product literature

CONTRAINDICATIONS

There are no known contraindications for this lead.

WARNINGS

Do not attempt to use this lead with a non-Medtronic Implantable Cardioverter/Defibrillator device.

Use only battery-powered equipment during lead implantation and testing to protect against fibrillation that may be caused by alternating currents. Line-powered equipment used in the vicinity of the patient must be properly grounded. Lead connector pins must be insulated from any leakage currents that may arise from line-powered equipment.

See also the section titled "General Warning"

PRECAUTIONS

Necessary Hospital Equipment

Defibrillation equipment should be kept nearby for immediate use during the acute lead system testing, implantation procedure, or whenever arrhythmias are possible or intentionally induced during post-implant testing.

Inspecting the Package

Carefully inspect the lead sterile package prior to opening; if the seal or package is damaged, contact your local Medtronic representative.

Handling the Lead

Leads should be handled with great care at all times. **Any severe bending, kinking, stretching, or handling with surgical instruments may cause permanent damage to the lead.**

Lead insulators attract small particles such as lint and dust. Therefore, protect the lead from materials shedding these substances. Handle the lead with sterile surgical gloves that have been rinsed in sterile water or the equivalent.

Do not immerse leads in mineral oil, silicone oil, or any other liquid.

Using an Anchoring Sleeve

Always use an anchoring sleeve with all leads to secure the lead from moving and to protect the lead insulation and conductor coil from damage. A second anchoring sleeve is provided for additional fixation.

Chronic Repositioning

Chronic repositioning or removal of the lead may be difficult because of the fibrotic tissue. **However, if a lead must be removed or repositioned, proceed with extreme caution.** If a lead is abandoned, it should be capped to avoid transmitting electrical signals. Return all removed or unused leads or portions thereof to Medtronic.

See additional cautions in the section titled "Suggested Implantation Procedure."

POTENTIAL COMPLICATIONS

The potential complications related to the use of endocardial leads include, but are not limited to, the following patient-related conditions: fibrillation or other arrhythmias, air embolism, cardiac perforation, heart wall rupture, cardiac tamponade, pericardial rub, infection, myocarditis, constrictive pericarditis, pneumothorax, hemothorax, and tissue necrosis.

Other potential complications related to the lead system, but are not limited to the following: lead dislodgement, lead conductor or electrode fracture, insulation failure, and poor connection which may lead to loss of detection, cardioversion, and defibrillation therapies.

ENSURING PRODUCT INTEGRITY

Carefully inspect the sterile package before opening. It is not recommended that you use the product after its expiration date.

If the integrity of the sterile package has been compromised prior to the product expiration date, place the contents in a gas-permeable bag and resterilize them with ethylene oxide as described below.

CAUTION: Use ethylene oxide only. Do not resterilize more than one time.

The process should not exceed temperatures of 55° C (130° F). Allow proper aeration of ethylene oxide residues prior to implantation. Use some acceptable method to determine sterilizer effectiveness, such as a biological indicator.

Due to the variability between sterilizers, precise sterilization instructions cannot be provided. Contact your sterilizer manufacturer for more information regarding sterilization procedures.

SUGGESTED IMPLANTATION PROCEDURE

General Instructions

The implantation procedure generally includes using a stylet guide, stylets, and a vein lifter; selecting an insertion site; positioning the lead; taking electrical and defibrillation efficacy measurements; anchoring the lead; tunneling the lead; connecting the lead to the pulse generator; and closing the pocket.

Some implantation techniques vary according to physician preference and the patient's anatomy or physical condition.

Opening the Package

Open the package according to the instructions. Inspect the lead. Remove the disc from the distal end of the lead. Verify that two anchoring sleeves are present.

Using the Stylet Guide and Stylets

The lead is packaged with a stylet guide attached and a stylet already inserted. Use of the stylet guide is optional. An attached stylet guide may be removed by gently pulling it off. To attach a stylet guide, gently push it as far as possible onto the connector pin that accepts the stylet (Figure 1).

A stylet provides additional stiffness and controlled flexibility for maneuvering the lead into position. Stylets vary in stiffness for different lead and stylet flexibility. Each stylet knob is etched with the stylet diameter and length.

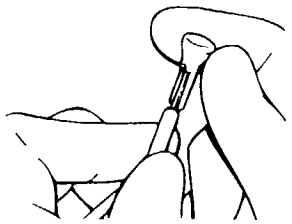


Figure 1. Stylet guide attachment.

If a slight curve is needed for the stylet, refer to instructions in the section titled "Positioning a Lead."

CAUTION: To avoid damage to the lead or body tissue, do not use excessive force or surgical instruments to insert a stylet into the lead. When handling a stylet, avoid overbending, kinking, or blood contact.

CAUTION: Repeated insertions of a stylet increases the chance that blood or other fluids may accumulate on it, which may cause difficulty in passing the stylet through the lead and may cause damage to the lead.

Selecting an Insertion Site

The lead may be inserted by venotomy through several different venous routes, including the right or left cephalic vein or the external or internal jugular vein. In general, a left venous entry site will aid in maneuvering the lead into the coronary sinus orifice.

CAUTION: Given the body diameter of transvenous defibrillation leads, insertion via a subclavian approach should be done as far lateral as possible to avoid clamping the lead body between the clavicle and the first rib (Figure 2). Clamping the lead can eventually cause the conductor to fracture, can cause damage to the insulation, or can cause other damage to the lead. This can result in complications such as loss of detection, loss of pacing therapies, or loss of cardioversion/defibrillation therapy. Certain anatomical abnormalities, such as thoracic outlet syndrome, can also precipitate pinching and subsequent fracture of the lead. If the subclavian approach is required, avoid techniques that can damage the lead. Specifically, do not force the lead if significant resistance is encountered. Do not use techniques such as adjusting the patient's posture (i.e., raising the arm or putting a towel behind the person's back) to facilitate the passage of the lead. If resistance is encountered, it is recommended that an alternate venous entry site be used, e.g., the cephalic vein.

Use fluoroscopy to facilitate accurate lead placement.

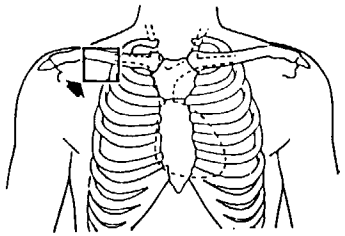


Figure 2. Insertion site.

Using a Vein Lifter

A vein lifter facilitates lead introduction. Insert its tapered end into the incised vein and gently push the lead tip underneath and into the vein (Figure 3). During insertion of the lead into the vein, make sure the anchoring sleeves do not slide off the distal end of the lead.

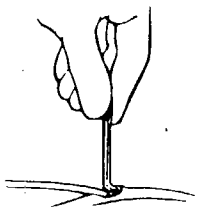


Figure 3. Using the vein lifter.

CAUTION: Avoid placing the lead under extreme tension or angulation to prevent lead dislodgement and possible lead fracture. **Do not grip the lead with surgical instruments.**

Positioning a Lead

For added control in maneuvering the lead tip, the distal end of the lead may be slightly curved by inserting a gently curved stylet as shown in Figure 4. A possible angle of curvature is illustrated in Figures 5 and 6.

CAUTION: To avoid damage to the stylet, do not use a sharp object to impart a curve to the distal end (Figure 4).

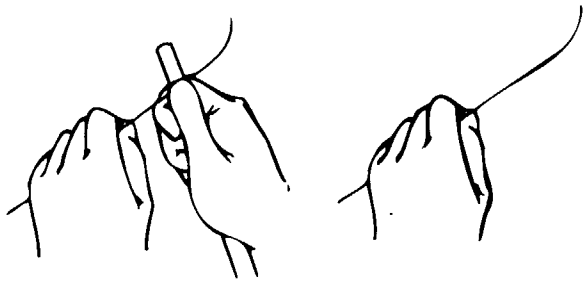


Figure 4. Imparting a curve to the stylet.

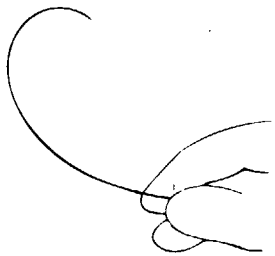


Figure 5. Bend the stylet into a gentle spiral. This gives the lead a gentle curve upward, to the left, and posterior.

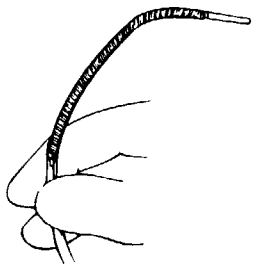


Figure 6. The curve in the stylet is designed to facilitate passage of the lead across the superior surface of the tricuspid valve. The second bend helps to position the lead to the left and posterior toward the coronary sinus ostium.

The electrode may be placed in either the coronary sinus or the superior vena cava.

If placing the electrode in the coronary sinus, advance the lead into the right atrium and rotate the curved stylet to manipulate the tip over the tricuspid valve. Move the tip medially and posteriorly to the coronary sinus ostium and advance the lead into the coronary sinus. Continue advancing the lead through the coronary sinus to the desired position.

If the lead goes through the tricuspid valve opening, retract the lead with a gentle posterior rotation and then advance it toward the coronary sinus ostium.

If the electrode is to be placed in the superior vena cava, advance the tip so that the distal portion of the electrode is approximately 3 to 5 cm proximal to the superior vena cava—right atrial junction.

The electrode for the TRANSVENE™-SVC must be as far as possible from other defibrillation electrodes. Also, the cardiac mass between the electrodes should be as large as possible. Insufficient separation between the electrodes may result in reduced defibrillation efficacy.

Proper positioning of the electrode is essential for defibrillation efficacy. Use fluoroscopy (P-A and lateral position) to ensure that the distal end of the electrode is properly positioned in the superior vena cava or is lodged in the coronary sinus with the proximal end of the electrode advanced beyond the coronary sinus ostium.

Taking Electrical Measurements and Defibrillation Efficacy Measurements

In order to demonstrate reliable defibrillation efficacy, obtain final electrical measurements for the lead system.

Initial electrical measurements may deviate from the recommendations because of acute cellular trauma. If this occurs, wait five to fifteen minutes and repeat the testing procedure. Values may vary depending upon lead type, pulse generator settings, cardiac tissue condition, and drug interactions. If electrical measurements do not stabilize to acceptable levels, it may be necessary to reposition the lead and repeat the testing procedure.

For more information on obtaining electrical measurements, consult the technical manual supplied with the testing device.

Recommended Pacing/Sensing Measurements at Implant
(when using a pacing system analyzer)

Measurements Required	Acute Lead System	Chronic Lead System
Capture threshold		
(at 0.5 ms pulse width)	≤ 1.0 V - endocardial	≤ 3.0 V
Impedance	200 - 800 ohms	200 - 800 ohms
Filtered R-wave amplitude	≤ 5 mV (during sinus rhythm)	≥ 3 mV (during sinus rhythm)
Slew rate	≥ 0.75 V/s	≥ 0.45 V/s

Anchoring the Lead

Do not secure the ligatures so tightly that they damage the vein, lead, or anchoring sleeve. Do not tie a ligature directly to the lead body (Figure 7). During anchoring, take care to avoid dislodging the lead tip.

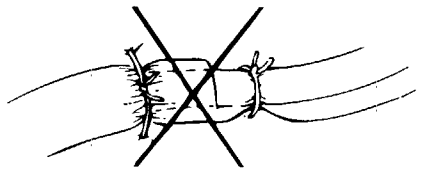


Figure 7. Do NOT secure the sutures too tightly and do NOT tie a suture to the lead body.

Use an anchoring sleeve to secure the lead from moving and to protect the lead insulation and conductor coil from damage caused by tight ligatures. A second anchoring sleeve may be placed in the tunnel entry site or in the pocket area for additional fixation.

Anchor the lead with nonabsorbable sutures.

The TRANSVENE™-SVC uses the triple groove anchoring sleeve illustrated in Figure 8. The triple groove anchoring sleeves are already situated on the lead.

With a triple groove anchoring sleeve, all three grooves should be used with the following procedure (Figure 9).

- Partially insert the distal anchoring sleeve into the vein.
- **Use all three grooves to secure the anchoring sleeve to the lead body.**
- Use the most distal suture groove to secure the anchoring sleeve to the vein.
- Use the middle groove to secure the anchoring sleeve to the fascia and lead. First, create a base by looping a suture through the fascia underneath the middle groove and tying a knot. Continue by firmly wrapping the suture around the middle groove and tying a second knot.

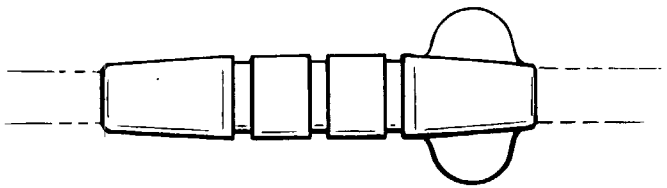


Figure 8. The triple groove anchoring sleeve.

CAUTION: Do not use the anchoring sleeve tabs for suturing.

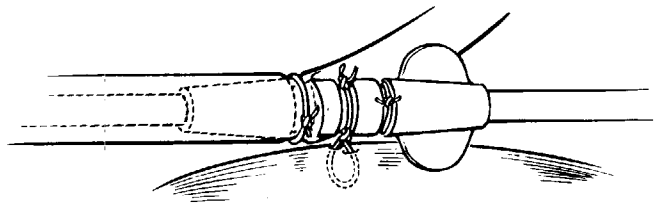


Figure 9. Triple groove anchoring sleeve secured to the lead and fascia using three grooves.

Tunneling the Lead

Before tunneling the lead connector, record each lead's serial number along with the function of the lead. Use of a chest tube is suggested in tunneling the lead connector to the pulse generator to prevent damage to the lead. Tunnel the lead subcutaneously to the pulse generator pocket.

Connecting the Lead to a Tachyarrhythmia Device

Refer to Figures 10a and 10b for instructions and illustrations showing lead connections to the Medtronic® PCD™ Tachyarrhythmia Control Device Model 7217B.

CAUTION: Do not use surgical instruments to grasp the lead or connector pin when tunneling.

Insert the lead connector into the connector block. Refer to the tachyarrhythmia control device technical manual for the use of setscrews and setscrew tools.

Before closing the pocket, verify sensing, pacing, and defibrillation efficacy.

CAUTION: Always remove the stylet before connecting the lead to the pulse generator. Failure to remove the stylet may result in lead failure.

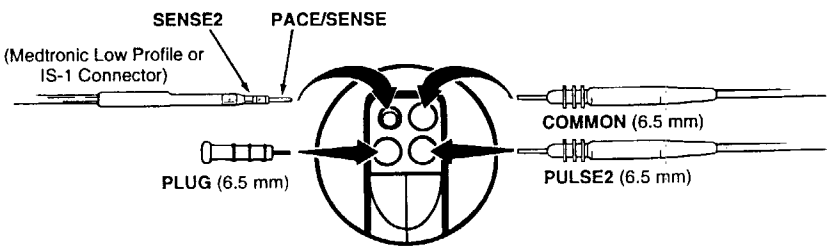
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillation Electrodes	Two-Electrode System Connection Diagram
Medtronic® Model 7217B PCD™ Device	2	**PACE/SENSE, SENSE2** Insert the Pace/Sense lead connector of the TRANSVENE™-RV into the PACE/SENSE, SENSE2 port. **COMMON** Insert the unipolar lead connector of the TRANSVENE™-RV, -SVC, or -SQ into the COMMON port.  **PULSE1** Insert the connector plug packaged with the pulse generator into the PULSE1 port. **PULSE2** Insert the lead connector of the TRANSVENE™-RV, -SVC, or -SQ lead into the PULSE2 port.

Figure 10a. Connections for two-electrode system leads (single pulse) into the Medtronic® PCD™ Tachyarrhythmia Control Device Model 7217B.

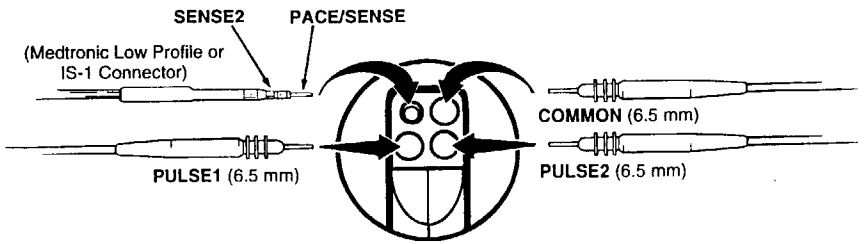
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillation Electrodes	Three-Electrode System Connection Diagram
Medtronic® Model 7217B PCD™ Device	3	**PACE/SENSE, SENSE2** Insert the Pace/Sense lead connector of the TRANSVENE™-RV into the PACE/SENSE, SENSE2 port. **COMMON** Insert the unipolar lead connector of the TRANSVENE™-RV, -SVC, or -SQ into the COMMON port.  **PULSE1** Insert the lead connector of the TRANSVENE™-RV, -SVC, or -SQ lead into the PULSE1 port. **PULSE2** Insert the lead connector of the TRANSVENE™-RV, -SVC, or -SQ lead into the PULSE2 port.

Figure 10b. Connections for three-electrode system leads (simultaneous or sequential pulse) into the Medtronic® PCD™ Tachyarrhythmia Control Device Model 7217B.

Closing the Pocket

To prevent undesirable twisting of the lead body, wrap the excess lead length loosely under the pulse generator and place both into the subcutaneous pocket (Figure 11). Ensure that the leads do not leave the pulse generator at an acute angle. Sharp angles place undue stress on the lead conductor and insulation.

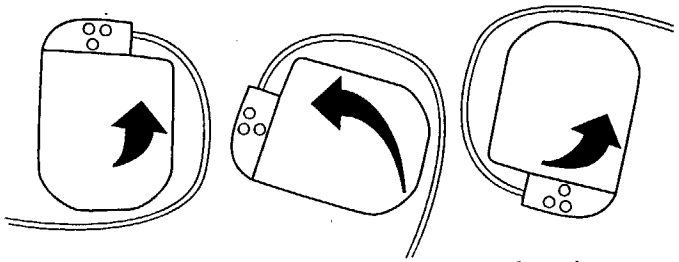


Figure 11. While rotating the pulse generator, loosely wrap the excess lead length and place it under the pulse generator.

To reduce the potential for abrasion on the lead body, it is recommended the PCD be placed in a Parsonnet pouch.

When placing the pulse generator and leads into the subcutaneous pocket:

- Do NOT coil the lead. Coiling the lead can twist the lead body and may result in lead dislodgement (Figure 12).
- Do NOT grip the lead or pulse generator with surgical instruments.

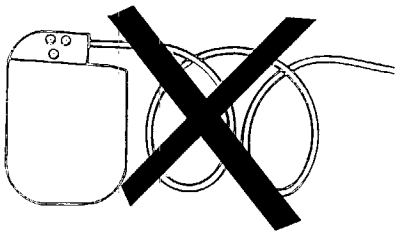


Figure 12. Do not coil or twist the lead body.

After implantation, monitor the patient's electrocardiogram continuously. If a lead dislodges, it usually occurs during the immediate postoperative period.

At the physician's discretion, X-rays may be taken every six months to verify proper lead position and to check for conductor fractures.

SPECIFICATIONS (Nominal)

PARAMETER		MODEL 6963
Type		Unipolar
Position		Coronary Sinus/Superior Vena Cava
Fixation		None. Tip lodges in the Coronary Sinus or is placed in the Superior Vena Cava
Length		20-110 cm
Connector		6.5 mm
Materials	Conductor:	Multifilar MP35N Composite
	Insulator:	Silicone
	Electrode:	Platinum Alloy

PARAMETER		MODEL 6963
Electrode Shadow Area	Coil:	360 mm^2
Electrode Surface Area	Coil:	90 mm^2 (5 cm)
Diameters	Body:	1.7 mm
	Electrode:	2.3 mm
Configuration	Electrode:	Coiled, 48 turns per inch
Unipolar Resistance		3.3 ohms
Lead Introducer (recommended size)		8.0 French

GENERAL WARNING

Medtronic® implantable leads are implanted in the extremely hostile environment of the human body. Leads are necessarily very small in diameter and must still be very flexible, which unavoidably reduces their potential performance or longevity. Leads may fail to function for a variety of causes, including, but not limited to: medical complications, body rejection phenomena, allergic reaction, fibrotic tissue, or failure of leads by breakage or by breach of their insulation covering. In addition, despite the exercise of all due care in design, component selection, manufacture, and testing prior to sale, leads may be easily damaged before, during, or after insertion by improper handling or other intervening acts. Consequently, no representation or warranty is made that failure or cessation of function of leads will not occur or that the body will not react adversely to the implantation of leads or that medical complications (including perforation of the heart) will not follow the implantation of leads or that the lead will, in all cases, restore adequate cardiac function.

For complete warranty information, see the accompanying card enclosed in the package.

SERVICE

Medtronic employs highly trained representatives and engineers located throughout the world to serve you and, upon request, to provide training to qualified hospital personnel in the use of Medtronic products. In addition, Medtronic maintains a professional staff of consultants to provide technical and medical consultation to product users. For supplemental information, contact your local Medtronic representative, or call or write Medtronic at the appropriate address or telephone number listed on the back cover.

Europe

Medtronic Europe
Immeuble Myron
6, avenue E. van Nieuwenhuyse
B-1160, Brussels
Belgium
Telephone: (32) 2-676 08 11

Asia-Pacific

Japan
Medtronic Asia-Pacific
Shuwa Kioi-cho Park Building, 5F
3-6 Kioi-cho, Chiyoda-ku
Tokyo 102
Japan
Telephone: (81) 3-3230-2919

Australia
Medtronic Australasia Pty. Ltd.
22 Clarke Street
Crows Nest, Sydney, N.S.W., 2065
Australia
Telephone: (61) 2 437-6066

Asia
Medtronic International Ltd.
2002 CC Wu Building
308 Hennessey Road, Wanchai
Hong Kong, B.C.C.
Telephone: (852-5) 891-4068

Latin America

Medtronic, Inc.
450 Fairway Drive
Suite 103
Deerfield Beach, FL 33441
U.S.A.
Telephone: (305) 428-8556

North America

Canada
Medtronic of Canada Ltd.
6733 Kitimat Road
Mississauga, Ontario L5N 1W3
Canada
Telephone: (416) 826-6020
Toll-free: 1-800-268-5346
(24-hour consultation service)

United States
Medtronic, Inc.
7000 Central Avenue, NE
Minneapolis, MN 55432
U.S.A.
Telephone: (612) 574-4000
Toll-free: 1-800-328-2518
(24-hour consultation service)

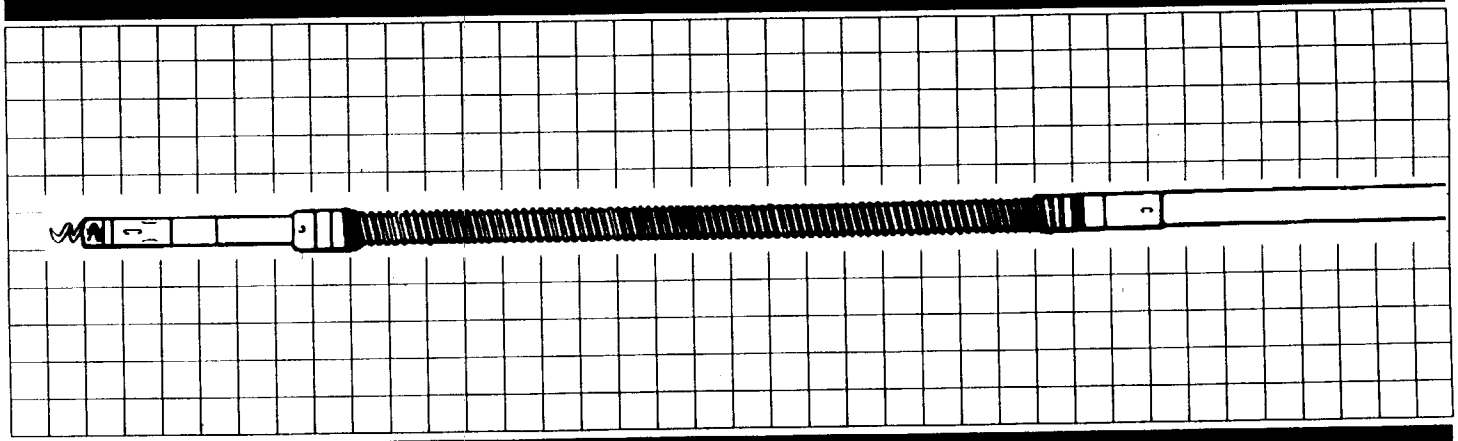
Medtronic

June 1993
UC9002088cEN 195421-004

Medtronic

TRANSVENE™ -RV 6966

Tripolar, Endocardial, Screw-in Ventricular Lead



Technical Manual

6966 Cover UC9002414bEN 195434-003/MMC

TECHNICAL MANUAL

THE TRANSVENE™ -RV TRIPOLAR, ENDOCARDIAL, SCREW-IN LEAD FOR VENTRICULAR PACING, SENSING, CARDIOVERSION AND DEFIBRILLATION

MODEL 6966

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DESCRIPTION AND INTENDED USE

The Medtronic® Model 6966 Tripolar, Endocardial, Screw-In Ventricular Lead is designed for pacing, sensing, and delivering cardioversion and defibrillation therapies. It is intended for single long-term use in the ventricle and is designed to be used only with a compatible Medtronic implantable tachyarrhythmia control device along with at least one other Medtronic defibrillation lead.

The TRANSVENE™-RV lead has a helical electrode made of platinum alloy that can be actively fixed in the endocardium. The helix can be extended or retracted by rotating the lead connector pin with a special fixation tool. Active fixation leads are particularly beneficial for patients who have smooth or hypertrophic hearts where lead dislodgement may be a potential problem.

The three electrodes of this lead are: coil, ring, and helix (Figure 1).

The defibrillating coil electrode is most proximal to the pulse generator and connects electrically to the connector PIN of the UNIPOLAR leg of the bifurcation. This UNIPOLAR leg will not accept a stylet.

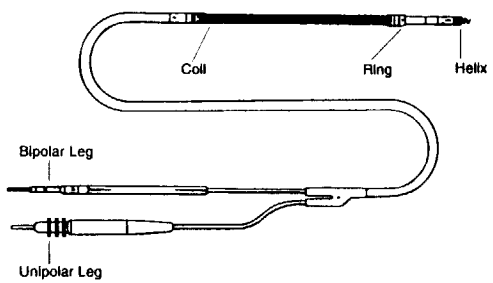


Figure 1. The three electrodes and two connector legs.

The ring electrode is proximal to the helix and connects electrically to the connector RING of the BIPOLAR leg of the bifurcation.

The helix tip electrode is most distal to the pulse generator and provides active fixation in the endocardium. It can be extended or retracted by rotating the lead connector PIN with a special fixation tool. The helix electrode connects electrically to the connector PIN of the BIPOLAR leg of the bifurcation. This BIPOLAR leg is the only one that will accept a stylet.

The coil electrode is intended to be used for delivery of cardioversion and defibrillation pulses. The helix tip electrode and the ring electrode may be used for bipolar

pacing and sensing; however, when used with standard bipolar PCD™ pulse generators, pacing occurs between the helix tip electrode and the coil electrode.

The lead's conductors are in a multifilar configuration and are insulated with polyurethane.

The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

CONTENTS OF PACKAGE

The leads are supplied sterile. Each package contains:

- 1 TRANSVENE™-RV lead with two non-radiopaque anchoring sleeves, stylet, and stylet guide
- 2 fixation tools
- 1 vein lifter
- Extra stylets
- Product literature

CONTRAINDICATIONS

When tricuspid valvular disease or a mechanical heart valve is present, use of a ventricular endocardial lead is contraindicated.

WARNINGS

Do not attempt to use this lead with a non-Medtronic Implantable Cardioverter/Defibrillator device.

Use only battery-powered equipment during lead implantation and testing to protect against fibrillation that may be caused by alternating currents. Line-powered equipment used in the vicinity of the patient must be properly grounded. Lead connector pins must be insulated from any leakage currents that may arise from line-powered equipment.

See also the section titled "General Warning"

PRECAUTIONS

Necessary Hospital Equipment

Defibrillation equipment should be kept nearby for immediate use during the acute lead system testing, implantation procedure, and whenever arrhythmias are possible or intentionally induced during post-implant testing.

Inspecting the Package

Carefully inspect the lead sterile package prior to opening; if the seal or package is damaged, contact your local Medtronic representative.

Handling the Lead

Leads should be handled with great care at all times. **Any severe bending, kinking, stretching, or handling with surgical instruments may cause permanent damage to the lead.**

Lead insulators attract small particles such as lint and dust. Therefore, protect the lead from materials shedding these substances. Handle the lead with sterile surgical gloves that have been rinsed in sterile water or equivalent.

Do not immerse leads in mineral oil, silicone oil, or any other liquid.

The maximum number of revolutions of the electrode fixation tool needed to extend or retract the helix is 20. **Exceeding the maximum revolutions may damage the lead.**

Using an Anchoring Sleeve

Always use an anchoring sleeve with all leads to secure the lead from moving and to protect the lead insulation and conductor coil from damage. A second anchoring sleeve is provided for additional fixation.

Chronic Repositioning

Chronic repositioning or removal of screw-in leads may not be possible because of blood or fibrotic tissue development into the helix mechanism. Removal of the lead could result in avulsion of the endocardium, valve, or vein. In addition, the lead junctions may separate, leaving the lead tip and bare wire in the heart or vein. In most clinical situations, it is preferable to abandon unused leads in place.

However, if a lead must be removed or repositioned, proceed with extreme caution. If a helix does not disengage from the endocardium by rotating the connector pin, rotating the lead body counterclockwise may withdraw the helix and decrease the possibility of damage to the cardiovascular structures during removal.

If a lead is abandoned, it should be capped to avoid transmitting electrical signals from the pin to the heart. Return all removed or unused leads or portions thereof to Medtronic.

See additional cautions in the section "Suggested Implantation Procedure."

POTENTIAL COMPLICATIONS

The potential complications related to the use of endocardial leads include, but are not limited to, the following patient-related conditions: fibrillation or other arrhythmias, air embolism, cardiac perforation, heart wall rupture, cardiac tamponade, pericardial rub, infection, myocarditis, constrictive pericarditis, pneumothorax, hemothorax, and tissue necrosis.

Other potential complications related to the lead system, but are not limited to the following: lead dislodgement, lead conductor or electrode fracture, insulation failure, and poor connection which may lead to loss of detection, cardioversion, defibrillation, or pacing therapies.

ENSURING PRODUCT INTEGRITY

Carefully inspect the sterile package before opening. It is not recommended that you use the product after its expiration date.

If the integrity of the sterile package has been compromised prior to the product expiration date, place the contents in a gas-permeable package and resterilize them with ethylene oxide as described below.

CAUTION: Use ethylene oxide only. Do not resterilize more than one time.

The process should not exceed temperatures of 55° C (130° F). Allow proper aeration of ethylene oxide residues prior to implantation. Use some acceptable method to determine sterilizer effectiveness, such as a biological indicator.

Due to the variability between sterilizers, precise sterilization instructions cannot be provided. Contact your sterilizer manufacturer for more information regarding sterilization procedures.

SUGGESTED IMPLANTATION PROCEDURE

The implantation procedure generally includes checking the mechanical functioning of the lead electrode before it is inserted; using a stylet guide, stylets, and vein lifter; selecting an insertion site; positioning the lead; securing the lead; taking electrical and defibrillation efficacy measurements; anchoring the lead; tunneling the lead; connecting the lead to the pulse generator; and closing the pocket.

Some implantation techniques vary according to physician preference and the patient's anatomy or physical condition.

Opening the Package

Open the package according to the instructions. Inspect the lead. Remove the disc from the distal end of the lead. Verify that two anchoring sleeves are present.

Verifying the Mechanical Functioning of the Helix Electrode

Before implantation, verify the mechanical functioning of the electrode, as described below.

1. Within the sterile field, remove the lead and the accompanying stylets from the sterile packaging. The lead is packaged with a stylet guide attached and a stylet already inserted. The connector pin that accepts the stylet controls the helix mechanism.
2. To attach the fixation tool, first remove the stylet guide. Press both legs of the fixation tool together and place the most distal hole of the fixation tool on the connector pin that accepts the stylet (Figure 2).

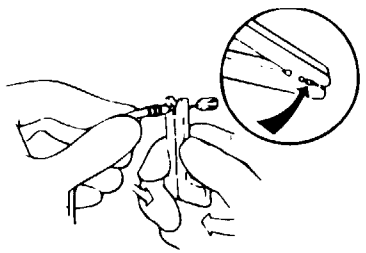


Figure 2. Attachment of the fixation tool to the connector pin.

3. Rotate the tool clockwise until the coiled electrode is completely exposed (Figure 3). Maximum electrode exposure reveals 2 coils.

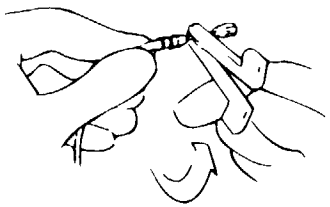


Figure 3. Rotating the fixation tool.

The maximum number of revolutions of the fixation tool needed to extend or retract the helix is 20.

CAUTION: Exceeding the maximum number of revolutions may damage the lead.

4. Disconnect the fixation tool from the connector pin and release the proximal end of the lead body. Allow several seconds for the lead and its conductor coil to unwind.
5. After allowing the lead and its conductor coil to unwind, reattach the fixation tool and turn it counterclockwise until the helix tip is retracted in the sheath.

Using the Stylet Guide and Stylets

The lead is packaged with a stylet guide attached and a stylet already inserted. The connector pin with the stylet in it controls the helix mechanism. Use of the stylet guide is optional. An attached stylet guide may be removed by gently pulling it off. To attach a stylet guide, gently push it as far as possible onto the connector pin that accepts the stylet (Figure 4).

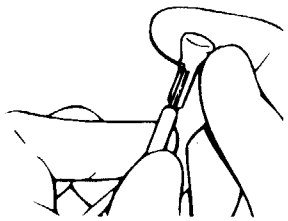


Figure 4. Stylet guide attachment.

A stylet provides additional stiffness and controlled flexibility for maneuvering the lead into position. Stylets vary in stiffness for different lead and stylet flexibility. Each stylet knob is etched with the stylet diameter and length.

If a slight curve is needed for the stylet, refer to instructions in the section titled "Positioning a Lead."

CAUTION: To avoid damage to the lead or body tissue, do not use excessive force or surgical instruments to insert a stylet into the lead. When handling a stylet, avoid overbending, kinking, or blood contact.

CAUTION: Repeated insertions of a stylet increases the chance that blood or other fluids may accumulate on it, which may cause difficulty in passing the stylet through the lead and may cause damage to the lead.

Selecting an Insertion Site

The lead may be inserted by venotomy through several different venous routes, including the right or left cephalic vein or the external or internal jugular vein.

CAUTION: Given the body diameter of transvenous defibrillation leads, insertion via a subclavian approach should be done as far lateral as possible to avoid clamping the lead body between the clavicle and the first rib (Figure 5). Clamping the lead can eventually cause the conductor to fracture, can cause damage to the insulation, or can cause other damage to the lead. This can result in complications such as loss of detection, loss of pacing therapies, or loss of cardioversion/defibrillation therapy. Certain anatomical abnormalities, such as thoracic outlet syndrome, can also precipitate pinching and subsequent fracture of the lead. If the subclavian approach is required, avoid techniques that can damage the lead. Specifically, do not force the lead if significant resistance is encountered. Do not use techniques such as adjusting the patient's posture (i.e., raising the arm or putting a towel behind the person's back) to facilitate the passage of the lead. If resistance is encountered, it is recommended that an alternate venous entry site be used, e.g., the cephalic vein.

Use fluoroscopy to facilitate accurate lead placement.

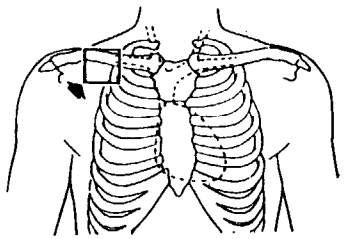


Figure 5. Insertion site.

Using the Vein Lifter

A vein lifter facilitates lead introduction. Insert its tapered end into the incised vein and gently push the lead tip underneath and into the vein (Figure 6).

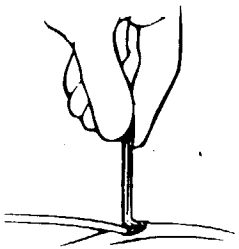


Figure 6. Using the vein lifter.

CAUTION: Avoid placing the lead under extreme tension or angulation to prevent lead dislodgement and possible lead fracture. **Do not grip the lead with surgical instruments.**

Positioning a Lead

Advance the lead into the right atrium. For added control in maneuvering the lead tip through the tricuspid valve, the distal end of the lead may be slightly curved by inserting a gently curved stylet (Figure 7). After the lead tip is passed into the ventricle, the curved stylet may be replaced with a straight stylet. The lead tip may then be advanced to the right ventricular apex while care is taken to avoid perforation of the ventricular wall.

CAUTION: To avoid damage to the stylet, do not use a sharp object to impart a curve to the distal end (Figure 7).

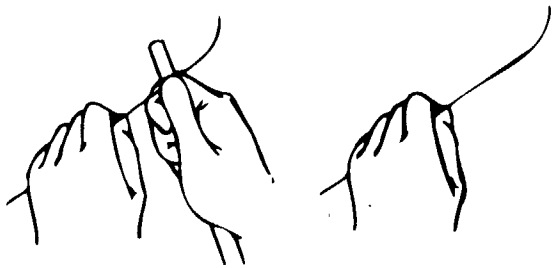


Figure 7. Imparting a curve to the stylet.

Accurate positioning of the electrode is essential for stable endocardial pacing. A satisfactory position is usually

achieved when the lead tip points straight toward the apex, or when the distal end dips or bends slightly.

Use fluoroscopy (lateral position) to ensure that the tip is not in a retrograde position or is not lodged in the coronary sinus.

After the stylet is inserted, gently remove the stylet guide so that it rests alongside the stylet knob.

Securing the Electrode into the Endocardium

The following procedure is recommended for electrode fixation:

1. Press both legs of the fixation tool together and place the most distal hole of the fixation tool on the connector pin that accepts the stylet (Figure 2).
2. Gently press the lead tip against the endocardium by pushing the stylet and the lead at the vein entry site. Then, rotate the tool clockwise until the coiled electrode is completely exposed (Figure 3). Maximum electrode exposure reveals 2 coils.

The maximum number of revolutions of the fixation tool needed to extend or retract the helix is 20.

CAUTION: Exceeding the maximum number of revolutions to extend or retract the helix may damage the lead.

3. Use fluoroscopy to verify helix electrode exposure. Closing of the space between the conductor (A) and the indicator ring (B) implies complete exposure of the helix electrode (Figure 8).

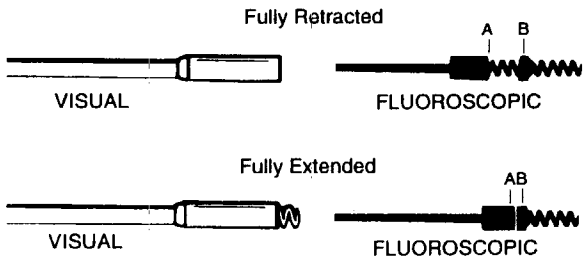


Figure 8. Possible views of the electrode.

4. Disconnect the fixation tool from the connector pin and release the proximal end of the lead body. Allow several seconds for the residual torque in the lead to be relieved.

5. After allowing the residual torque in the lead to be relieved, rotate the whole lead body clockwise approximately one revolution to ensure that the helical electrode is secured to the endocardium.

6. Carefully withdraw the stylet partially.

7. Obtain electrical measurements to verify satisfactory placement and electrode fixation. Refer to the following section, Taking Electrical and Defibrillation Efficacy Measurements, for recommended procedures and values.

8. Verify that the helix is affixed by gently pulling back on the lead and checking for resistance. A properly affixed helix will remain in position. If the helix is not properly affixed, the lead tip may become loose in the right ventricle.

9. If repositioning is required, reattach and rotate the fixation tool counterclockwise until the electrode is withdrawn. Use fluoroscopy to verify withdrawal. Repeat the procedure above.

CAUTION: When retracting the helix, do not rotate the fixation tool more than 20 revolutions. When the electrode is fully retracted, 2 coils of the helix will be visible between the indicator ring and the conductor.

10. Remove the stylet guide and stylet completely. When removing the stylet guide, grip the lead firmly just below the connector pin; this will help prevent possible lead dislodgement.

Taking Electrical Measurements and Defibrillation Efficacy Measurements

In order to demonstrate reliable defibrillation efficacy, obtain final electrical measurements for the lead system.

Initial electrical measurements may deviate from the recommendations because of acute cellular trauma. If this occurs, wait five to fifteen minutes and repeat the testing procedure. Values may vary depending upon lead type, pulse generator settings, cardiac tissue condition, and drug interactions. If electrical measurements do not stabilize to acceptable levels, it may be necessary to reposition the lead and repeat the testing procedure.

For more information on obtaining electrical measurements, consult the technical manual supplied with the testing device.

Recommended Pacing/Sensing Measurements at Implant
(when using a pacing system analyzer)

Measurements Required	Acute Lead System	Chronic Lead System
Capture threshold		
(at 0.5 ms pulse width)	≤ 1.0 V - endocardial	≤ 3.0 V
Impedance	200 - 800 ohms	200 - 800 ohms
Filtered R-wave amplitude	≤ 5 mV (during sinus rhythm)	≥ 3 mV (during sinus rhythm)
Slew rate	≥ 0.75 V/s	≥ 0.45 V/s

Anchoring the Lead

Do not secure the ligatures so tightly that they damage the vein, lead, or anchoring sleeve. Do not tie a ligature directly to the lead body (Figure 9). During anchoring, take care to avoid dislodging the lead tip.

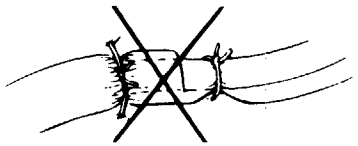


Figure 9. Do NOT secure the sutures too tightly and do NOT tie a suture to the lead body.

Use an anchoring sleeve to secure the lead from moving and to protect the lead insulation and conductor coil from damage caused by tight ligatures. A second anchoring sleeve may be placed in the tunnel entry site or in the pocket area for additional fixation.

Anchor the lead with nonabsorbable sutures.

TRANSVENE™-RV uses a triple groove anchoring sleeve illustrated in Figure 10. The triple groove anchoring sleeves are situated at the connector end of the lead.

Figure 10. The triple groove anchoring sleeve.

With a triple groove anchoring sleeve, all three grooves should be used with the following procedure (Figure 11):

- Partially insert the distal anchoring sleeve into the vein.
- **Use all three grooves to secure the anchoring sleeve to the lead body.**
- Use the most distal suture groove to secure the anchoring sleeve to the vein.

- Use the middle groove to secure the anchoring sleeve to the fascia and lead. First, create a base by looping a suture through the fascia underneath the middle groove and tying a knot. Continue by firmly wrapping the suture around the middle groove and tying a second knot.

CAUTION: Do not use the anchoring sleeve tabs for suturing.

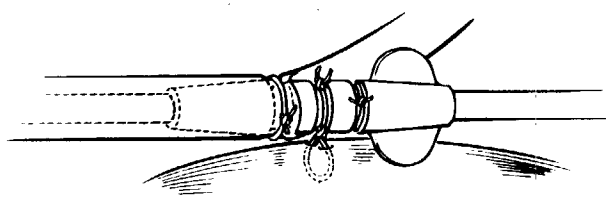


Figure 11. Triple groove anchoring sleeve secured to the lead and fascia using three grooves.

Tunneling the Lead

Before tunneling the lead connector, record each lead's serial number along with the function of the lead. Use of a chest tube is suggested in tunneling the lead connector to the pulse generator to prevent damage to the lead. Tunnel the lead subcutaneously to the pulse generator pocket.

Connecting the Lead to a Tachyarrhythmia Device

Refer to Figures 12a and 12b for instructions and illustrations showing lead connections to the Medtronic® PCD™ Tachyarrhythmia Control Device Model 7217B.

CAUTION: Do not use surgical instruments to grasp the lead or connector pin when tunneling.

Insert the lead connector into the connector block. Refer to the tachyarrhythmia control device technical manual for the use of setscrews and setscrew tools.

Before closing the pocket, verify sensing, pacing, and defibrillation efficacy.

CAUTION: Always remove the stylet before connecting the lead to the pulse generator. Failure to remove the stylet may result in lead failure.

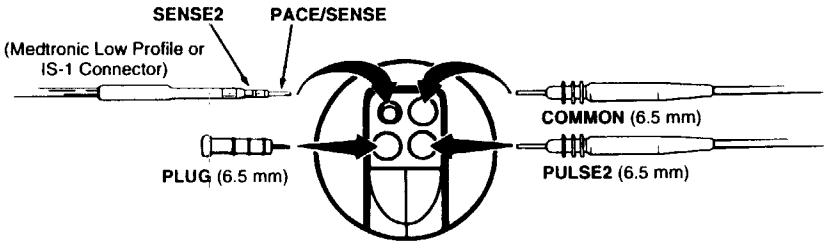
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillation Electrodes	Two-Electrode System Connection Diagram
Medtronic® Model 7217B PCD™ Device	2	**PACE/SENSE, SENSE2** Insert the Pace/Sense lead connector of the TRANSVENE™-RV into the PACE/SENSE, SENSE2 port. **COMMON** Insert the unipolar lead connector of the TRANSVENE™-RV, -SVC, or -SQ into the COMMON port.  **PULSE1** Insert the connector plug packaged with the pulse generator into the PULSE1 port. **PULSE2** Insert the lead connector of the TRANSVENE™-RV, -SVC, or -SQ lead into the PULSE2 port.

Figure 12a. Connections for two-electrode system leads (single pulse) into the Medtronic® PCD™ Tachyarrhythmia Control Device 7217B.

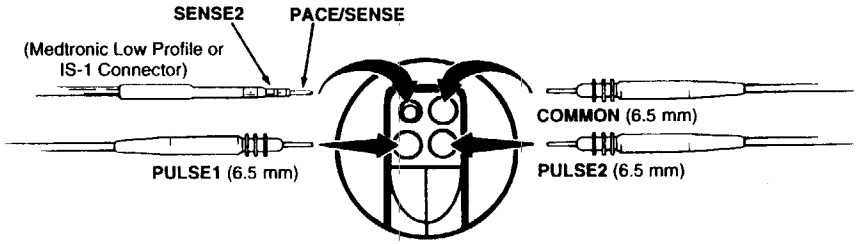
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillation Electrodes	Three-Electrode System Connection Diagram
Medtronic® Model 7217B PCD™ Device	3	**PACE/SENSE, SENSE2** Insert the Pace/Sense lead connector of the TRANSVENE™-RV into the PACE/SENSE, SENSE2 port. **COMMON** Insert the unipolar lead connector of the TRANSVENE™-RV, -SVC, or -SQ into the COMMON port.  **PULSE1** Insert the lead connector of the TRANSVENE™-RV, -SVC, or -SQ lead into the PULSE1 port. **PULSE2** Insert the lead connector of the TRANSVENE™-RV, -SVC, or -SQ lead into the PULSE2 port.

Figure 12b. Connections for three-electrode system leads (simultaneous or sequential pulse) into the Medtronic® PCD™ Tachyarrhythmia Control Device 7217B.

Closing the Pocket

To prevent undesirable twisting of the lead body, wrap the excess lead length loosely under the pulse generator and place both into the subcutaneous pocket (Figure 13). Ensure that the leads do not leave the pulse generator at an acute angle. Sharp angles place undue stress on the lead conductor and insulation.

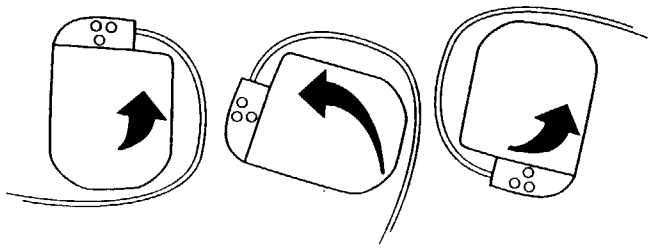


Figure 13. While rotating the pulse generator, loosely wrap the excess lead length and place it under the pulse generator.

To reduce the potential for abrasion on the lead body, it is recommended the PCD be placed in a Parsonnet pouch.

When placing the pulse generator and leads into the subcutaneous pocket:

- Do NOT coil the lead. Coiling the lead can twist the lead body and may result in lead dislodgement (Figure 14).
- Do NOT grip the lead or pulse generator with surgical instruments.

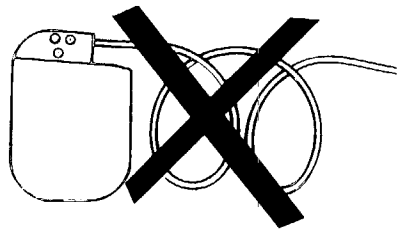


Figure 14. Do not coil or twist the lead body.

After implantation, monitor the patient's electrocardiogram continuously. If a lead dislodges, it usually occurs during the immediate postoperative period.

At the physician's discretion, X-rays may be taken every six months to verify proper lead position and to check for conductor fractures.

SPECIFICATIONS (Nominal)

PARAMETER		MODEL 6966
Type		Tripolar
Position		Ventricle
Fixation		Screw-In
Length		20-110 cm
Connectors	Unipolar:	6.5 mm
	Bipolar:	3.2 mm
Materials	Conductors:	Multifilar MP35N Composite
	Insulator:	Polyurethane
	Electrode:	Platinum Alloy
Electrode Surface Area	Helix:	10 mm^2
	Ring:	37 mm^2
	Coil:	426 mm^2 (5 cm length)
Electrode Shadow Area		448 mm^2

PARAMETER		MODEL 6966
Diameters	Body:	3.3 mm
	Helix:	1.6 mm
	Maximum Head:	3.5 mm
Helix Length (fully extended)		2 mm
Conductor Resistances	Pacing:	45 ohms (unipolar) 190 ohms (bipolar)
	Defibrillation:	3.5 ohms
Lead Introducer (recommended size)		11 French
Maximum Revolutions that can be used to extend or retract the helix when using a straight style		20

GENERAL WARNING

Medtronic® implantable leads are implanted in the extremely hostile environment of the human body. Leads are necessarily very small in diameter and must still be very flexible, which unavoidably reduces their potential performance or longevity. Leads may fail to function for a variety of causes, including, but not limited to: medical complications, body rejection phenomena, allergic reaction, fibrotic tissue, or failure of leads by breakage or by breach of their insulation covering. In addition, despite the exercise of all due care in design, component selection, manufacture, and testing prior to sale, leads may be easily damaged before, during, or after insertion by improper handling or other intervening acts. Consequently, no representation or warranty is made that failure or cessation of function of leads will not occur or that the body will not react adversely to the implantation of leads or that medical complications (including perforation of the heart) will not follow the implantation of leads or that the lead will, in all cases, restore adequate cardiac function.

SERVICE

Medtronic employs highly trained representatives and engineers located throughout the world to serve you and, upon request, to provide training to qualified hospital personnel in the use of Medtronic products. In addition, Medtronic maintains a professional staff of consultants to provide technical and medical consultation to product users. For supplemental information, contact your local Medtronic representative, or call or write Medtronic at the appropriate address or telephone number listed on the back cover.

Europe

Medtronic Europe
Immeuble Myron
6, avenue E. van Nieuwenhuyse
B-1160, Brussels
Belgium
Telephone: (32) 2-676 08 11

Asia-Pacific

Japan
Medtronic Asia-Pacific
Shuwa Kioi-cho Park Building, 5F
3-6 Kioi-cho, Chiyoda-ku
Tokyo 102
Japan
Telephone: (81) 3-3230-2919

Australia
Medtronic Australasia Pty. Ltd.
22 Clarke Street
Crows Nest, Sydney, N.S.W., 2065
Australia
Telephone: (61) 2 437-6066

Asia
Medtronic International Ltd.
2002 CC Wu Building
308 Hennessey Road, Wanchai
Hong Kong, B.C.C.
Telephone: (852-5) 891-4068

Latin America

Medtronic, Inc.
450 Fairway Drive
Suite 103
Deerfield Beach, FL 33441
U.S.A.
Telephone: (305) 428-8556

North America

Canada
Medtronic of Canada Ltd.
6733 Kitimat Road
Mississauga, Ontario L5N 1W3
Canada
Telephone: (416) 826-6020
Toll-free: 1-800-268-5346
(24-hour consultation service)

United States
Medtronic, Inc.
7000 Central Avenue, NE
Minneapolis, MN 55432
U.S.A.
Telephone: (612) 574-4000
Toll-free: 1-800-328-2518
(24-hour consultation service)

Medtronic

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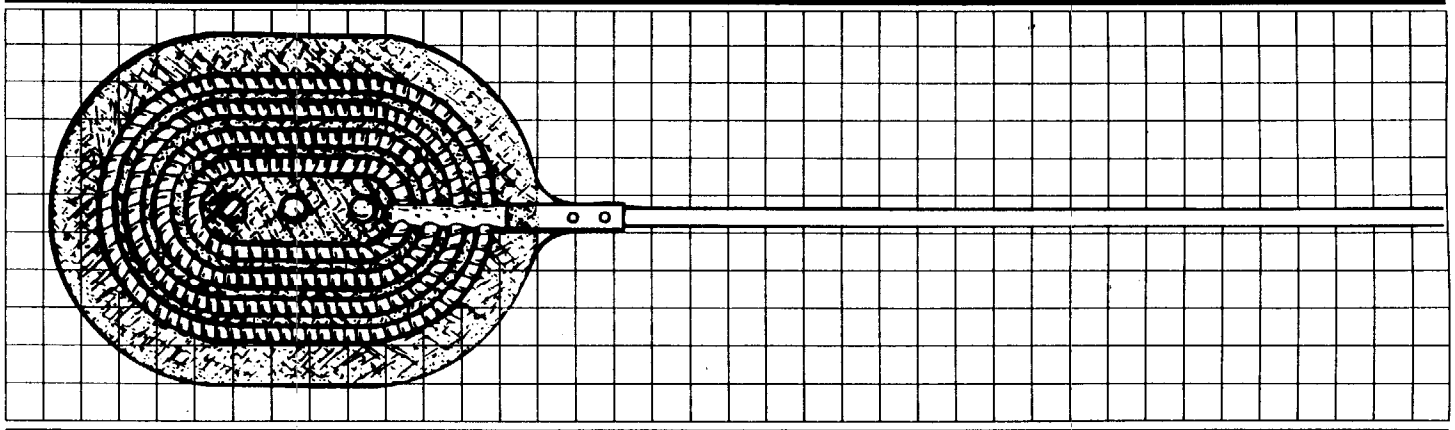
Medtronic

TRANSVENE™ -SQ 6999

Unipolar, Subcutaneous, Oval Patch Lead
for Cardioversion and Defibrillation



Technical Manual

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TECHNICAL MANUAL

TRANSVENE™ -SQ UNIPOLAR, SUBCUTANEOUS, OVAL PATCH LEAD FOR CARDIOVERSION AND DEFIBRILLATION

MODEL 6999

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DESCRIPTION AND INTENDED USE

The Medtronic® TRANSVENE™-SQ Model 6999 Unipolar, Subcutaneous, Oval Patch Lead is designed for the delivery of cardioversion and defibrillation therapies. It is intended for single long-term use only with a compatible Medtronic implantable tachyarrhythmia control device along with at least one other Medtronic defibrillation lead. A third Medtronic defibrillation lead may also be used.

The lead features a low resistance conductor coil and platinum alloy electrode coils for cardioversion and defibrillation therapies. The outer edge of the lead is used for suturing. The lead also has a 6.5 mm unipolar connector.

There are 3 nodes on one side of the patch, and 2 nodes at the junction of the lead body and patch electrode. These nodes are intended to mark the insulated side of the patch electrode.

The lead has application for patients in which implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

CONTENTS OF PACKAGE

The leads are supplied sterile. Each package contains:

- 1 TRANSVENE™-SQ lead
- Product literature

CONTRAINDICATIONS

There are no known contraindications for this lead.

WARNINGS

Do not attempt to use this lead with a non-Medtronic Implantable Cardioverter/Defibrillator device.

Use only battery-powered equipment during lead implantation and testing to protect against fibrillation that may be caused by alternating currents. Line-powered equipment used in the vicinity of the patient must be properly grounded. Lead connector pins must be insulated from any leakage currents that may arise from line-powered equipment.

See also the section titled "General Warning"

PRECAUTIONS

Necessary Hospital Equipment

Defibrillation equipment should be kept nearby for immediate use during the acute lead system testing, implantation procedure, or whenever arrhythmias are possible or intentionally induced during post-implant testing.

Inspecting the Package

Carefully inspect the lead sterile package prior to opening; if the seal or package is damaged, contact your local Medtronic representative.

Handling the Lead

Leads should be handled with great care at all times. **Any severe bending, kinking, stretching, or handling with surgical instruments may cause permanent damage to the lead.**

Lead insulators attract small particles such as lint and dust. Therefore, protect the lead from materials shedding these substances. Handle the lead with sterile surgical gloves that have been rinsed in sterile water or the equivalent.

Do not immerse leads in mineral oil, silicone oil, or any other liquid.

Chronic Repositioning

Chronic repositioning or removal of the lead may be difficult because of the fibrotic tissue. **However, if a lead must be removed or repositioned, proceed with extreme caution.** If a lead is abandoned, it should be capped to avoid transmitting electrical signals. Return all removed or unused leads or portions thereof to Medtronic.

See additional cautions in the section titled "Suggested Implantation Procedure."

POTENTIAL COMPLICATIONS

The potential complications related to the use of subcutaneous patch leads include, but are not limited to, the following patient-related conditions: serous fluid accumulation around the patch; infection; and bleeding after placement, after repositioning, or if sutures tear out.

Other potential complications related to the lead system, but are not limited to the following: lead displacement, lead conductor or electrode fracture, insulation failure, and poor connection which may lead to loss of cardioversion and defibrillation therapies.

ENSURING PRODUCT INTEGRITY

Carefully inspect the sterile package before opening. It is not recommended that you use the product after its expiration date.

If the integrity of the sterile package has been compromised prior to the product expiration date, place the contents in a gas-permeable bag and resterilize them with ethylene oxide as described below.

CAUTION: Use ethylene oxide only. Do not resterilize more than one time.

The process should not exceed temperatures of 55° C (130° F). Allow proper aeration of ethylene oxide residues prior to implantation. Use some acceptable method to determine sterilizer effectiveness, such as a biological indicator.

Due to the variability between sterilizers, precise sterilization instructions cannot be provided. Contact your sterilizer manufacturer for more information regarding sterilization procedures.

SUGGESTED IMPLANTATION PROCEDURE

General Instructions

The implantation procedure generally includes selecting an insertion site; positioning the lead; taking electrical and defibrillation efficacy measurements; tunneling the lead; connecting the lead to the pulse generator; and closing the pocket.

Some implantation techniques vary according to physician preference and the patient's anatomy or physical condition.

Opening the Package

Open the package according to the instructions. Inspect the lead. Remove the disc from the distal end of the lead. Verify that two anchoring sleeves are present.

Positioning a Lead

The recommended starting position for the TRANSVENE™-SQ subcutaneous patch lead is along the left chest near the heart. The patch may be repositioned, if necessary, to meet the implant defibrillation efficacy criteria outlined in the following section. The subcutaneous patch may be placed subcutaneously, submuscularly, or directly on the periosteum of the ribs. The patch may be repositioned on the left lateral chest wall, if necessary, to meet the implant defibrillation efficacy criteria.

Place sutures through the outer edge of the patch electrode. It is recommended that two or more sutures be used for fixation.

CAUTION: **The patch must be placed such that the nodes are facing away from the heart.**

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Taking Electrical Measurements and Defibrillation Efficacy Measurements

In order to demonstrate reliable defibrillation efficacy, obtain final electrical measurements for the lead system.

Initial electrical measurements may deviate from the recommendations because of acute cellular trauma. If this occurs, wait five to fifteen minutes and repeat the testing procedure. Values may vary depending upon lead type, pulse generator settings, cardiac tissue condition, and drug interactions. If electrical measurements do not stabilize to acceptable levels, it may be necessary to reposition the lead and repeat the testing procedure.

For more information on obtaining electrical measurements, consult the technical manual supplied with the testing device.

Recommended Pacing/Sensing Measurements at Implant
(when using a pacing system analyzer)

Measurements Required	Acute Lead System	Chronic Lead System
Capture threshold	≤ 1.5 V Epicardial	≤ 3.0 V
(at 0.5 ms pulse width)	≤ 1.0 V - endocardial	≤ 3.0 V
Impedance	200 - 800 ohms	200 - 800 ohms
Filtered R-wave amplitude	≤ 5 mV (during sinus rhythm)	≥ 3 mV (during sinus rhythm)
Slew rate	≥ 0.75 V/s	≥ 0.45 V/s

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Tunneling the Lead

Before tunneling the lead connector, record each lead's serial number along with the function of the lead. Use of a chest tube is suggested in tunneling the lead connector to the pulse generator to prevent damage to the lead. Tunnel the lead subcutaneously to the pulse generator pocket.

Connecting the Lead to a Tachyarrhythmia Device

Refer to Figures 1a and 1b for instructions and illustrations showing lead connections to the Medtronic® PCD™ Tachyarrhythmia Control Device Model 7217B.

CAUTION: Do not use surgical instruments to grasp the lead or connector pin when tunneling.

Insert the lead connector into the connector block. Refer to the tachyarrhythmia control device technical manual for the use of setscrews and setscrew tools.

Before closing the pocket, verify sensing, pacing, and defibrillation efficacy.

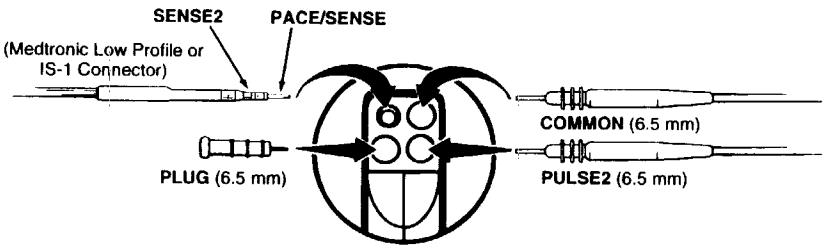
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillation Electrodes	Two-Electrode System Connection Diagram
Medtronic® Model 7217B PCD™ Device	2	**PACE/SENSE, SENSE2** Insert the Pace/Sense lead connector of the TRANSVENE™-RV into the PACE/SENSE, SENSE2 port. **COMMON** Insert the unipolar lead connector of the TRANSVENE™-RV, -SVC, or -SQ into the COMMON port.  **PULSE1** Insert the connector plug packaged with the pulse generator into the PULSE1 port. **PULSE2** Insert the lead connector of the TRANSVENE™-RV, -SVC, or -SQ lead into the PULSE2 port.

Figure 1a. Connections for two-electrode system leads (single pulse) into the Medtronic® PCD™ Tachyarrhythmia Control Device Model 7217B.

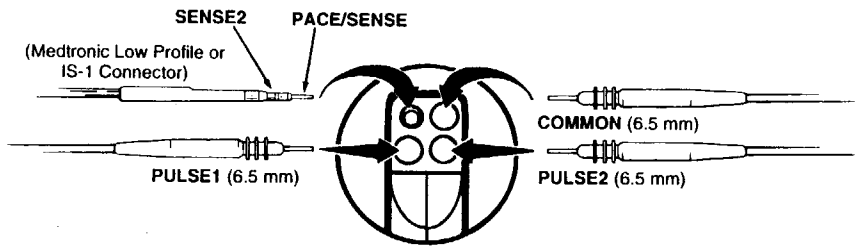
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillation Electrodes	Three-Electrode System Connection Diagram
Medtronic® Model 7217B PCD™ Device	3	**PACE/SENSE, SENSE2** Insert the Pace/Sense lead connector of the TRANSVENE™-RV into the PACE/SENSE, SENSE2 port. **COMMON** Insert the unipolar lead connector of the TRANSVENE™-RV, -SVC, or -SQ into the COMMON port.  **PULSE1** Insert the lead connector of the TRANSVENE™-RV, -SVC, or -SQ lead into the PULSE1 port. **PULSE2** Insert the lead connector of the TRANSVENE™-RV, -SVC, or -SQ lead into the PULSE2 port.

Figure 1b. Connections for three-electrode system leads (simultaneous or sequential pulse) into the Medtronic® PCD™ Tachyarrhythmia Control Device Model 7217B.

Closing the Pocket

To prevent undesirable twisting of the lead body, wrap the excess lead length loosely under the pulse generator and place both into the subcutaneous pocket (Figure 2). Ensure that the leads do not leave the pulse generator at an acute angle. Sharp angles place undue stress on the lead conductor and insulation.

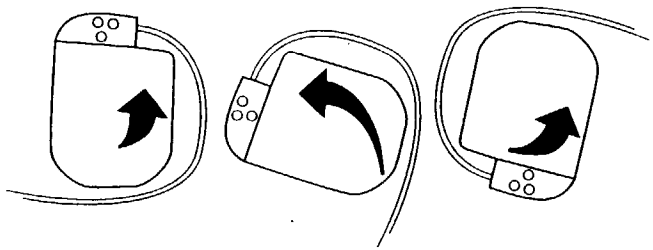


Figure 2. While rotating the pulse generator, loosely wrap the excess lead length and place it under the pulse generator.

To reduce the potential for abrasion on the lead body, it is recommended the PCD be placed in a Parsonnet pouch.

When placing the pulse generator and leads into the subcutaneous pocket:

- Do NOT coil the lead. Coiling the lead can twist the lead body and may result in lead dislodgement (Figure 3).
- Do NOT grip the lead or pulse generator with surgical instruments.

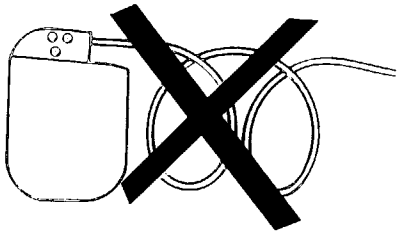


Figure 3. Do not coil or twist the lead body.

After implantation, monitor the patient's electrocardiogram continuously. If a lead dislodges, it usually occurs during the immediate postoperative period.

At the physician's discretion, X-rays may be taken every six months to verify proper lead position and to check for conductor fractures.

SPECIFICATIONS (Nominal)

PARAMETER		MODEL 6999
Type		Unipolar
Position		Subcutaneous chest wall
Fixation		Sutures (may be placed through the outer edge of the patch body)
Length		50 cm
Connector		6.5 mm
Materials	Conductor:	Multifilar MP35N Composite
	Insulator:	Silicone
	Electrode:	Platinum Alloy

PARAMETER		MODEL 6999
Number of Electrode Coils		4
Electrode Shadow Area	Coil:	40 cm^2
Electrode Surface Area	Coil:	660 mm^2
Diameters	Body:	2.5 mm
Patch Dimensions		8.0 cm x 11.0 cm
Silicone Patch Area		50 cm^2
Unipolar Resistance		1.2 ohms

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GENERAL WARNING

Medtronic® implantable leads are implanted in the extremely hostile environment of the human body. Leads are necessarily very small in diameter and must still be very flexible, which unavoidably reduces their potential performance or longevity. Leads may fail to function for a variety of causes, including, but not limited to: medical complications, body rejection phenomena, allergic reaction, fibrotic tissue, or failure of leads by breakage or by breach of their insulation covering. In addition, despite the exercise of all due care in design, component selection, manufacture, and testing prior to sale, leads may be easily damaged before, during, or after insertion by improper handling or other intervening acts. Consequently, no representation or warranty is made that failure or cessation of function of leads will not occur or that the body will not react adversely to the implantation of leads or that medical complications will not follow the implantation of leads or that the lead will, in all cases, restore adequate cardiac function.

For complete warranty information, see the accompanying card enclosed in the package.

SERVICE

Medtronic employs highly trained representatives and engineers located throughout the world to serve you and, upon request, to provide training to qualified hospital personnel in the use of Medtronic products. In addition, Medtronic maintains a professional staff of consultants to provide technical and medical consultation to product users. For supplemental information, contact your local Medtronic representative, or call or write Medtronic at the appropriate address or telephone number listed on the back cover.

Europe

Medtronic Europe
Immeuble Myron
6, avenue E. van Nieuwenhuyse
B-1160, Brussels
Belgium
Telephone: (32) 2-676 08 11

Asia-Pacific

Japan
Medtronic Asia-Pacific
Shuwa Kioi-cho Park Building, 5F
3-6 Kioi-cho, Chiyoda-ku
Tokyo 102
Japan
Telephone: (81) 3-3230-2919

Australia
Medtronic Australasia Pty. Ltd.
22 Clarke Street
Crows Nest, Sydney, N.S.W., 2065
Australia
Telephone: (61) 2 437-6066

Asia
Medtronic International Ltd.
2002 CC Wu Building
308 Hennessey Road, Wanchai
Hong Kong, B.C.C.
Telephone: (852-5) 891-4068

Latin America

Medtronic, Inc.
450 Fairway Drive
Suite 103
Deerfield Beach, FL 33441
U.S.A.
Telephone: (305) 428-8556

North America

Canada
Medtronic of Canada Ltd.
6733 Kitimat Road
Mississauga, Ontario L5N 1W3
Canada
Telephone: (416) 826-6020
Toll-free: 1-800-268-5346
(24-hour consultation service)

United States
Medtronic, Inc.
7000 Central Avenue, NE
Minneapolis, MN 55432
U.S.A.
Telephone: (612) 574-4000
Toll-free: 1-800-328-2518
(24-hour consultation service)

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The Model 7217B PCD Technical Manual has been modified to incorporate the use of Transvene leads.

See section beginning on page 44, Placing Transvene Leads, through page 48.

In addition, the Defibrillation Efficacy Testing section reflects a modified implant criteria consistent with the clinical data, see page 47, Figure 22.

Pages removed for the following reason: Draft Technical Manual

APPENDIX H

EDUCATION OUTLINE:
TRANSVENE PCD IMPLANT

USER EDUCATION PLAN

CONTENT OUTLINE

Medtronic Transvene Lead System

Note: The hours and depth of training will vary based on the experience of the health care professional with the PCD system and transvenous leads.

I. Implant and Expectation Aspects

A. How to access vein

B. Avoiding crush and dislodgements

C. Management of dislodgements

D. Lead Extraction

II. Overview of the Transvene Leads

A. Right Ventricular lead

- Review pacing and sensing measurements
- Lead placement
- Chronic repositioning

B. Superior Vena Cava Lead

- Lead placement options and anchoring

C. Coronary Sinus Lead

- Placement and anchoring

D. Subcutaneous Patch

- Placement options dependent on placement of other leads for optimum defibrillation vectors

III. Implant Procedure

A. Review of Implant steps
- Preprogram PCD in package, set up ETCD and connect to hospital recording/monitoring equipment.
- Place leads and test lead system integrity
- Perform defib efficacy protocol
- Connect PCD and test with lead system

B. Recommended implant criteria for defibrillation efficacy testing.

C. Options if implant criteria is not met
   - Change lead positions
   - Change tilt
   - Change pathways

D. Induction Methods

E. Recommendations for Rescue

F. Hybrid systems
   - Approved/recommended systems
   - When to use

Materials

Workbook with outlines for lecture and discussion
Video demonstrating lead placement options for maximum defib efficacy

Deficiency Responses

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1. **Discuss how the use of a silicone adhesive prevents tissue in-growth in the Model 6963 lead. Where is the adhesive placed? From experience, discuss the use of polyurethane and silicone in leads to prevent tissue in-growth.**

RESPONSE:

The Model 6963 lead has a tight wound electrode coil made of platinum wire. When the lead is constructed, a piece of silicone tubing is fit under the electrode coil. This separates the electrode coil from the conductor coil and prevents fluid penetration from the outside of the lead to the conductor coil, thus permitting free passage of the stylet. The silicone tubing also enhances alignment of the electrode coil. After the electrode coil and silicone tubing are assembled, silicone adhesive is applied between the tight windings of the electrode coil. The silicone adhesive bonds to the silicone tubing and forms a filler between each winding of electrode coil. This filler is intended to minimize the possibility of tissue-growth by filling in some of the space between the electrode coil windings and by eliminating any space between the electrode coil and the silicone tubing underneath.

Medtronic has used both polyurethane and silicone for many years as insulative materials and as fillers for pacing leads. Both polyurethane and silicone perform as well as insulators and as fillers, to discourage tissue in-growth by eliminating gaps. Generally, silicone fillers are used with silicone leads, and urethane fillers are used with urethane leads. This is for ease of manufacturing and is not a requirement, as silicone fillers can be used with urethane leads, and urethane fillers can be used with silicone leads.

One Place Your Text Could Go (See Documentation Section 6)

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FDA/CDRH/ODE/DMC

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2. **Please provide the results of mutagenicity testing for the (b)(4) (anchor sleeve). If the tests have not been done please provide a justification for not doing so.**

RESPONSE:

The Model 6999 unipolar patch lead is intended for use subcutaneously, submuscularly, or directly on the periosteum of the ribs. A (b)(4) (The description of the Model 6999 contained in the "Nonclinical Laboratory Testing" on page 482 (of the PMA) inadvertently stated that the (b)(4) covers the patch; actually, (b)(4) and not directly exposed to body tissue or fluids. Note that the Device Description provided on page 93 of the PMA is correct.)

The (b)(4) was not tested by itself because adequate data exists to demonstrate that it is non-mutagenic. Specifically, Ames Mutagenicity testing was performed on the Model 6921L lead. The Model 6921L is a large epicardial patch lead with (b)(4) embedded in the outer (b)(4) inch perimeter of the silicone patch. This is identical to the (b)(4) in the 6999 lead.

The anchoring sleeve on the Transvene leads is comprised of molded silicone rubber/titanium dioxide. The anchoring sleeve was subjected to mutagenicity testing in conjunction with the transvenous leads. A description of the test and results are as follows.

Ames Mutagenicity

(b)(4)

(b)(4)

The lead Model 6921L and anchoring sleeve were extracted in both (b)(4) and (b)(4) All extracts were tested and results show the materials to be non-mutagenic.

3. **Provide a description of the helix electrode fixation tool and of the tests to verify the torsional force for implanting the helix electrode.**

RESPONSE:

The fixation tool is an injection molded tool made of (b)(4) material. The tool depends on the resiliency of the (b)(4) material to apply a consistent gripping force (hence consistent torque) to the connector pin during rotation. The tool is specified to meet a (b)(4) minimum torque output requirement. The tool was tested and qualified to meet this requirement.

The 6884/6966 lead is specified to fully extend and retract the helix mechanism within (b)(4) connector pin revolutions. Testing completed on the 6884/6966 lead shows that an average of (b)(4) is required to rotate the connector pin of the device (b)(4) revolutions. The labeling (Technical Manual) calls out (b)(4) turns maximum to fully extend the mechanism. The (b)(4) turn specification was qualified (b)(4) (b)(4) Each lead manufactured is tested to this requirement.

Extensive experience with bradycardia pacing leads using the identical helix electrode mechanism shows that the number of rotations required to implant the electrode is virtually identical to the number required to extend the helix in-vitro. Furthermore, testing in canines has shown the number of connector pin rotations to be well within the (b)(4) turns specified.

4. Based on your experience, identify the minimum number of flex cycles that a lead should withstand. Also, give the stress level exerted on the Model 6907 lead (from which the median failure time of (b)(4) cycles was observed), and on the Transvene™ leads.

RESPONSE:

Medtronic developed a test protocol which provides a uniform, accelerated method for evaluating lead bodies in terms of the flexural fatigue life of the conductor. This test is used for evaluation and qualification of new lead designs, inclusive of bradycardia pacing and cardioversion/defibrillation leads.

Test Method/Equipment

(b)(4)

(b)(4)

Sample Size/Configuration

(b)(4)

(b)(4)

Pass/Fail Criteria

(b)(4)

(b)(4)

5

For the purpose of data reporting, Medtronic has historically compared lead flex life to the Model 6907. This is the basis for the (b)(4) cycles flex life design requirement. The Model 6907 is a unipolar, silicone, endocardial lead. The Model 6907 has more than 20 years of field experience. Of approximately (b)(4) sold, only (b)(4) coil fractures have been reported in this time (b)(4) Therefore, any lead with flex life equal to or greater than the Model 6907 is considered safe and effective for its intended use.

Endocardial leads experience flexure, especially where the lead is tied or clamped, at a suture site or where it is held between two bones, i.e., first rib and clavicle. Both pacing and cardioversion/defibrillation endocardial leads experience this flexure, as the insertion site and implant technique are equivalent. Thus, the test that is used to evaluate lead body flex life is applicable to both pacing leads and cardioversion/defibrillation leads.

5. **Since the electrode coil is flexed separately from the insulated conductor, discuss the reliability of the section where the electrode is coaxial to the conductor. Is there friction between the electrode and the conductor when the section is flexed?**

RESPONSE:

Both the insulated lead body (conductor coil(s) and insulation(s)) and the non-insulated defibrillation electrode portion of lead Models 6963, 6966 and 6999 were flexed during the Lead System Life Test.

Per the test protocol, the insulated lead body and the non-insulated defibrillation electrode portion of lead Models 6963, 6966 and 6999 were flexed (b)(4) cycles at each of (b)(4) monitors, for a total of (b)(4) flex cycles. All three lead Models met this requirement and were fully functional at the completion of the (b)(4) long test.

Model 6999 leads were not specifically tested beyond the life test requirement of (b)(4) cycles as this has been completed via similarity to the Model 6921 patch lead. The design of the lead Model 6999 is functionally equivalent to the Model 6921 epicardial lead which has demonstrated an electrode flex life in excess of (b)(4) (b)(4) cycles.

(b)(4) Model 6966 and (b)(4) Model 6963 leads were flexed beyond the test requirement of (b)(4) cycles. (b)(4) Model 6921S/L leads were also flexed following completion of the Lead System Life Test run on epicardial leads. The data for the defibrillation electrode segment of each lead model tested at a (b)(4) inch radius is as follows:

Model 6963	Model 6966	Model 6999 (6921S/L)
(b)(4)		

(b)(4)

A coaxial design is used in lead Models 6963 and 6966. The layer of insulation between the conductor coil and the defibrillation coil does offer support to the design, serving to separate the two coils. Since there is no contact there is no friction between the conductor and electrode coils.

6. **The Model 6999's (b)(4) electrode coil fails at a much lower flex cycle than the (b)(4) electrode coil. Discuss the reliability of the (b)(4) (b)(4) electrode coil, and the effects of its failure on the performance of the lead.**

7. **Please discuss how patient treatment is affected if one or two of the electrode coils of the Model 6999 patch lead becomes damaged.**

RESPONSE:

These deficiencies are addressed together due to similarity.

A flex life specification has not been established for coils used in the Transvene leads (e.g., 6999). However, electrode coils have been tested for comparison to established conductor coil specifications. Since electrode coils experience much less severe flexing than that seen by conductor coils, the electrode coil used in the Model 6999 was flexed (at (b)(4) radius) in order to characterize its flex life performance relative to Medtronic's established standard; the Model 6907.

For the purpose of data reporting, Medtronic has historically compared lead flex life to the Model 6907. The Model 6907 has approximately 20 years of field experience. Of approximately (b)(4) sold, only (b)(4) conductor coil fractures have been reported in this time (b)(4) Therefore, ANY lead with a flex life equal to or greater than the Model 6907 is considered safe and effective for its intended use. This is the basis for the design requirement of a median failure time of (b)(4) cycles, or greater, at a bend radius of (b)(4) inches. Therefore, since the median flex lives of the non-insulated electrode coil of the Model 6999 lead exceeds the (b)(4) cycle requirement at (b)(4) inches, the coil is considered acceptable.

The median failure time of the Model 6999 non-insulated (b)(4) (b)(4) cycles) and (b)(4) (b)(4) cycles) electrode coils both exceed (b)(4) cycles and are therefore considered acceptable and reliable for their intended use relative to flex life.

Note that in addition to the aforementioned flex testing of just the electrode coils of the Model 6999 patch lead, the composite patch electrode was subjected to (b)(4) month life test. This composite design effectively enhances the flex life of the electrode coils by virtue of having the silicone core and surrounding silicone patch body dampening and supporting the electrode coils.

The difference in flex life of these coils can be attributed to the coil design. Several factors are considered in the design of all electrode coils. These factors determine characteristics of the coil such as flex fatigue resistance. Because the design parameters are unique to the individual coil design and differ from other coil designs, direct comparison cannot be made between the coils of different leads.

The flex life of a coil is dependent on the outer diameter of the coil, the diameter of the wire and the spacing of the wire. The outer diameter of (b)(4) and (b)(4) coils are identical, however, the diameter of the wires, (b)(4) inch and (b)(4) inch respectively, giving the (b)(4) coil reduced flex fatigue resistance. However, the spacing of the (b)(4) coil is twice that of the (b)(4) (b)(4) coil. Increases in spacing contribute to a reduction in flex fatigue resistance. Therefore, the reduced spacing gives the (b)(4) coil greater resistance to flex failure.

The flex test protocol provides a uniform, accelerated method for evaluating electrode coils in terms of the flexural fatigue life. The test fixture induces three types of forces on the test samples, (b)(4) and (b)(4) The failure mechanism seen in the flex test performed on the Model 6999 lead was that of (b)(4) (b)(4) occurs when a point on the coil(s) is(are) held (b)(4) while the remaining coil is (b)(4) The (b)(4) forces eventually fatigue the metal and the (b)(4)

The redundant design of the Model 6999 lead was intended to eliminate the effect of an electrode coil failure from completely removing the coil from the electrical circuit. A failure would need to occur in two locations on the same coil loop before any portion of the electrode coil would be removed from the electrical circuit. The (b)(4) coil carries approximately (b)(4) of the total current of the patch.

Damage to one or two of the electrode coils of the Model 6999 lead can range from (b)(4) of the electrode coil with no loss of electrical continuity, to (b)(4) of the electrode coil loop. Any damage to the electrode coils that does not affect electrical continuity would not affect patient treatment.

However, (b)(4) of an electrode coil would not affect patient treatment due to the (b)(4) design of the lead. A (b)(4) in any (b)(4) of the design would not remove any portion of the electrode coil from the electrical circuit. This holds true for (b)(4) with discontinuities in the electrode coil, i.e., the electrode coils would still remain in the circuit.

Animal studies simulating the loss of certain of the coil (b)(4) in subcutaneous patch electrodes have been conducted. Impedance data was gathered from (b)(4) (b)(4) implanted with (b)(4) patch configuration at (b)(4) A special subcutaneous patch electrode which had separate electrical connections for each coil was used. This allowed for selective removal of (b)(4) from the circuit and a measurement of the effect on impedance.

The data in Table 1 demonstrate that impedance increases if coils are removed from the circuit and the increase will be associated with a change in electric field distribution. A small effect on DFT would be expected if both innermost coils failed. If one or both of the outer coils failed the increase in DFT would be somewhat larger, however, in neither case would it represent a serious threat to treatment of the patient. Also, it is important to bear in mind that this experiment simulated complete removal of (b)(4) or (b)(4) from the circuit, a condition which has not been observed in either the bench testing or the clinical study.

Table 1

Coils in circuit	Total Average Impedance (ohms)
(b)(4) (b)(4)	
(b)(4)	
(b)(4)	

8. **Please specify the section of each lead assembly that was flexed during life testing. Does this section include the electrode coil? The results of the tests should be included.**

RESPONSE:

Both the insulated lead body (conductor coil(s) and insulation(s)) and the non-insulated defibrillation electrode portion of lead Models 6963, 6966 and 6999 were flexed during the Lead System Life Test. The test method as described on page 505 of the PMA inadvertently states that only the Model 6999 defibrillation electrode (patch) was flexed. In fact, the insulated lead body and the non-insulated defibrillation electrode were flexed on all leads. An updated version of the test method is attached that clarifies these items.

The defibrillation electrode section of lead Model 6963 which was flexed included the (b)(4) long defibrillation coil. A schematic is shown below:

(b)(4)

(b)(4)

The defibrillation electrode section of lead Model 6966 also included the (b)(4) long defibrillation coil. A schematic is shown below:

(b)(4)

(b)(4)

The defibrillation electrode section of lead Model 6999 includes the entire molded patch assembly. A (b)(4) was developed to flex the assemblies. A schematic of the lead and test fixture are shown below:

(b)(4)

(b)(4)

Test (b)(4) for Flex Test of Patch Body

Per the test protocol, the insulated lead body and the non-insulated defibrillation electrode portion of lead Models 6963, 6966 and 6999 were flexed (b)(4) cycles at each of (b)(4) monitors, for a total of (b)(4) flex cycles. All three lead Models met this requirement and were fully functional at the completion of the (b)(4) long test. The (b)(4) Model 6966 and (b)(4) Model 6963 leads have been placed onto the flex tester and are being further flexed to (b)(4) cycles. The Model 6999 leads were not specifically tested beyond the life test requirement of (b)(4) cycles as this has been completed via similarity to the Model 6921 patch lead. The design of the lead Model 6999 is functionally equivalent to the Model 6921 epicardial lead which has demonstrated a flex life in excess of (b)(4) cycles (reference PMA P900061, Amendment submitted October 31, 1991).

Lead System (Life) Testing

High-Voltage Testing

a) Test Method

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

b) **Rationale**

(b)(4)

(b)(4)

c) **Test Equipment**

(b)(4)

(b)(4)

9. Provide an update of the (b)(4) month life test.

RESPONSE:

Transvene Lead System (Life) Testing: Update June 1992

High-Voltage Testing

a) Test Method

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

b) Rationale

(b)(4)

(b)(4)

c) Test Equipment

(b)(4)

(b)(4)

d) Samples Tested

(b)(4)

(b)(4)

e) Results

(b)(4)

(b)(4)

Model 6963 D.C. Resistance Specification

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Model 6966 D.C. Resistance Specification

(b)(4)

(b)(4)

Model 6968 D.C. Resistance Specification

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Model 6999 D.S. Resistance Specification

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Model 6963 Model 6966 Model 6999 (6921S/L)

(b)(4)

(b)(4)

10. The data indicate that a new lead is used for each (temperature tolerance, crush load, or life) test. Correlate the results from those tests to the worst case condition where the same lead has to face temperature differences, crushing, and flexing. Why was sequential testing not performed?

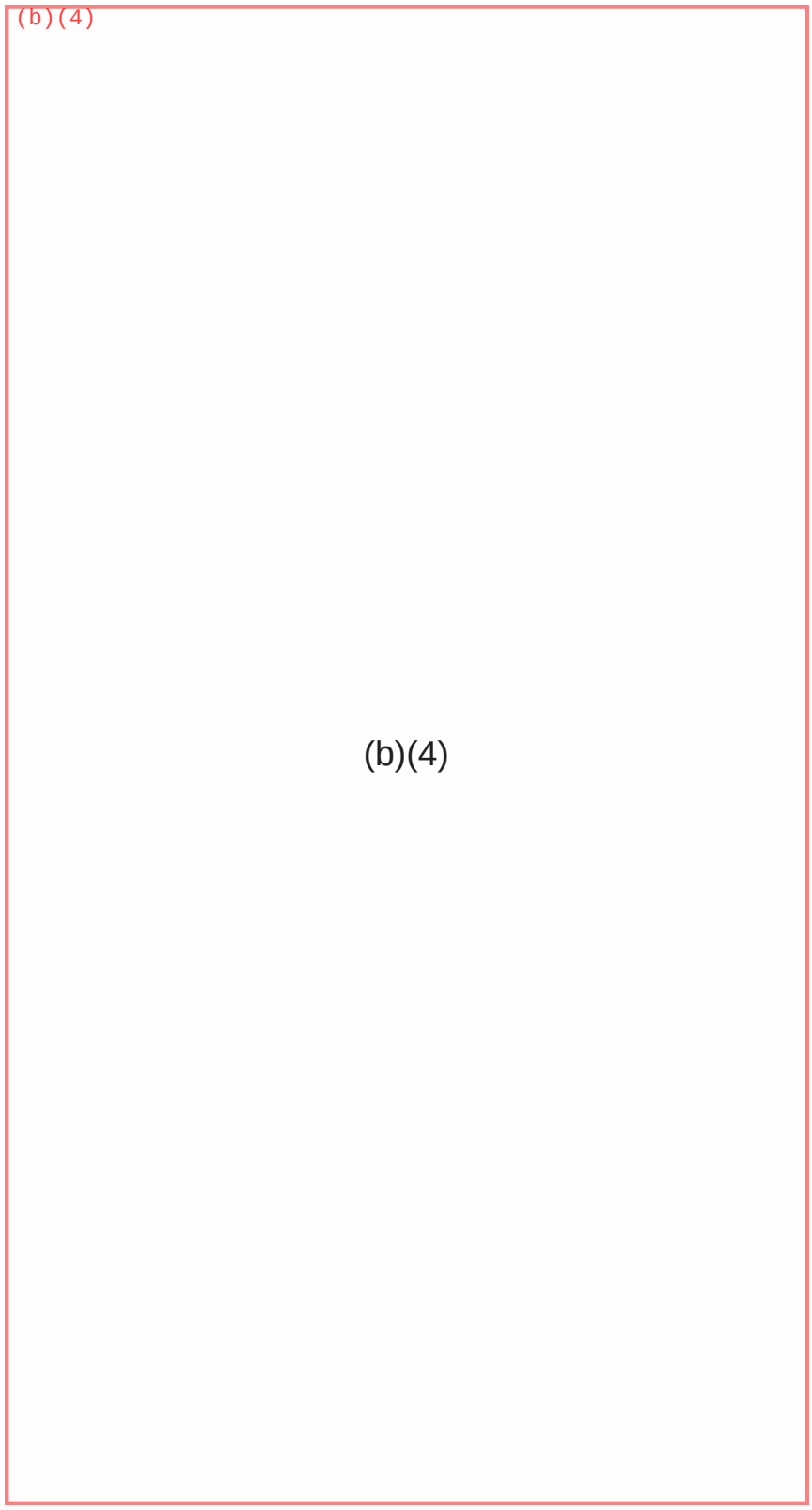
RESPONSE:

A separate lead is required for those tests which are considered destructive by the nature of the test. This includes lead joint tensile strength testing, crimp/weld pull strength testing, flex testing, anchoring sleeve testing and life testing. Therefore, it is not possible to get meaningful results from sequential testing of these tests.

Sequential testing, however, of non-destructive tests are performed throughout the qualification process, wherever possible. This includes thermal shock, resistance and stiffness testing. See the bench testing flow diagram on the following page. These data were presented in the non-clinical bench testing section of this PMA.

(b)(4)

Bench Testing Flow Diagram



11. Discuss the differences in battery life or energy requirements between the epi-lead system and the Transvene™ system.

RESPONSE:

The longevity of the Model 7217B device depends upon several factors including programmed bradycardia pacing parameters, the percentage of paced to sensed events, the frequency of high voltage capacitor charging, and on the pacing load. The first three parameters depend on the specific patient needs and are not related to the implanted lead system. The pacing load, or the pacing impedance of the system, is different for the two lead systems (Epicardial and Transvene).

The epicardial lead system impedance measured clinically ranges from (b)(4) (b)(4) ohms acutely. The mean is (b)(4) ohms. The Transvene lead system impedance measured clinically ranges from (b)(4) ohms acutely. The mean is (b)(4) ohms. The greater the system impedance, the less energy required for both bradycardia and anti-tachy pacing. The greatest battery drain occurs when bradycardia pacing is required 100% of the time. The anti-tachy portion is relatively insignificant.

To summarize, the battery life of the Model 7217B PCD device depends upon several factors, the most significant of which is the need for 100% (fulltime) pacing for bradycardia. The lead system impedance has an influence on the energy required to pace. The Transvene lead system is slightly more efficient as verified by the impedance values measured clinically.

12. An update of the chronic animal studies should be provided.

RESPONSE:

Two chronic animal studies are updated in response to this deficiency. These include Study Nos. 2 and 4, as presented in the March 31, 1992 PMA application.

Study No. 1 was acute; an update is not relevant. Study No. 2 was essentially completed at the time the March 31, 1992 PMA application was submitted. However, a pathology status report, post-study, is presented in this response for completeness. Study No. 3 was also completed at the time of the March 31, 1992 PMA application; therefore, an update is not relevant. Study No. 4 was presented in the March 31, 1992 PMA and included data through (b)(4) weeks. An update is included through approximately (b)(4) weeks.

Study No. 2

Pathology Status

(b)(4)

(b)(4)

Pathology Observation: (b)(4)

Submitted to FDA as an IDE Supplement (G870102) on July 31, 1992.

History

(b)(4)

(b)(4)

Pathology Summary, Canine 4832

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Reference Information

(b)(4)

(b)(4)

Background: Mastocytoma (Mast Cell Tumor) in the (b)(4)

(b)(4)

(b)(4)

Conclusion

(b)(4)

(b)(4)

References:

1. J. E. Moulton, Tumors in Domestic Animals, 3rd Ed., University of California Press, Berkeley & Los Angeles, 1990.
2. Veterinary Cancer Medicine, 2nd Ed., Gordon Thulien and Bruce R. Wadewell, 1987, pp 310-315.
3. D.E. Bostock, The prognosis following surgical removal of mastocytoma in dogs, Journal Small Animal Practice 14: 27-40, 1973.
4. C. R. Dorn, Journal National Cancer Institute 40: 307-318, 1968.
5. W. N. Priester & F. W. McKay, The occurrence of tumors in domestic animals, National Cancer Institute Monograph 54, Washington D.C., 1980.

Study No. 4

Update

Abstract

Study Objectives

(b)(4)

(b)(4)

Materials and Methods

Defibrillation Electrodes

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Study Results

(b)(4)

(b)(4)

Study Relevance/Significance

(b)(4)

(b)(4)

Study No. 4

Model 6963/6966/6999 Chronic Lead Defibrillation Study

Introduction

(b)(4)

(b)(4)

Materials and Methods

Lead Description

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Lead Implants

(b)(4)

(b)(4)

The lead configuration/pulse pathways are summarized in Table VI-B-9.

Table VI-B-9. Summary of lead configurations and pulse pathways. The CS Lead dislodged at Week (b)(4) in (b)(4) and was repositioned in the SVC. Superscript designations used in chart are explained below.

Canine No.	Pulse Pathway	RV Lead	CS Lead	SVC Lead	SQ Patch
(b)(4)					

(b)(4)

(b)(4)

(b)(4)

Mechanical Evaluation

(b)(4)

(b)(4)

(b)(4)

(b)(4)

- (b)(4)
- (b)(4)
- (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Termination

(b)(4)

(b)(4)

Study Results

Overview

(b)(4)

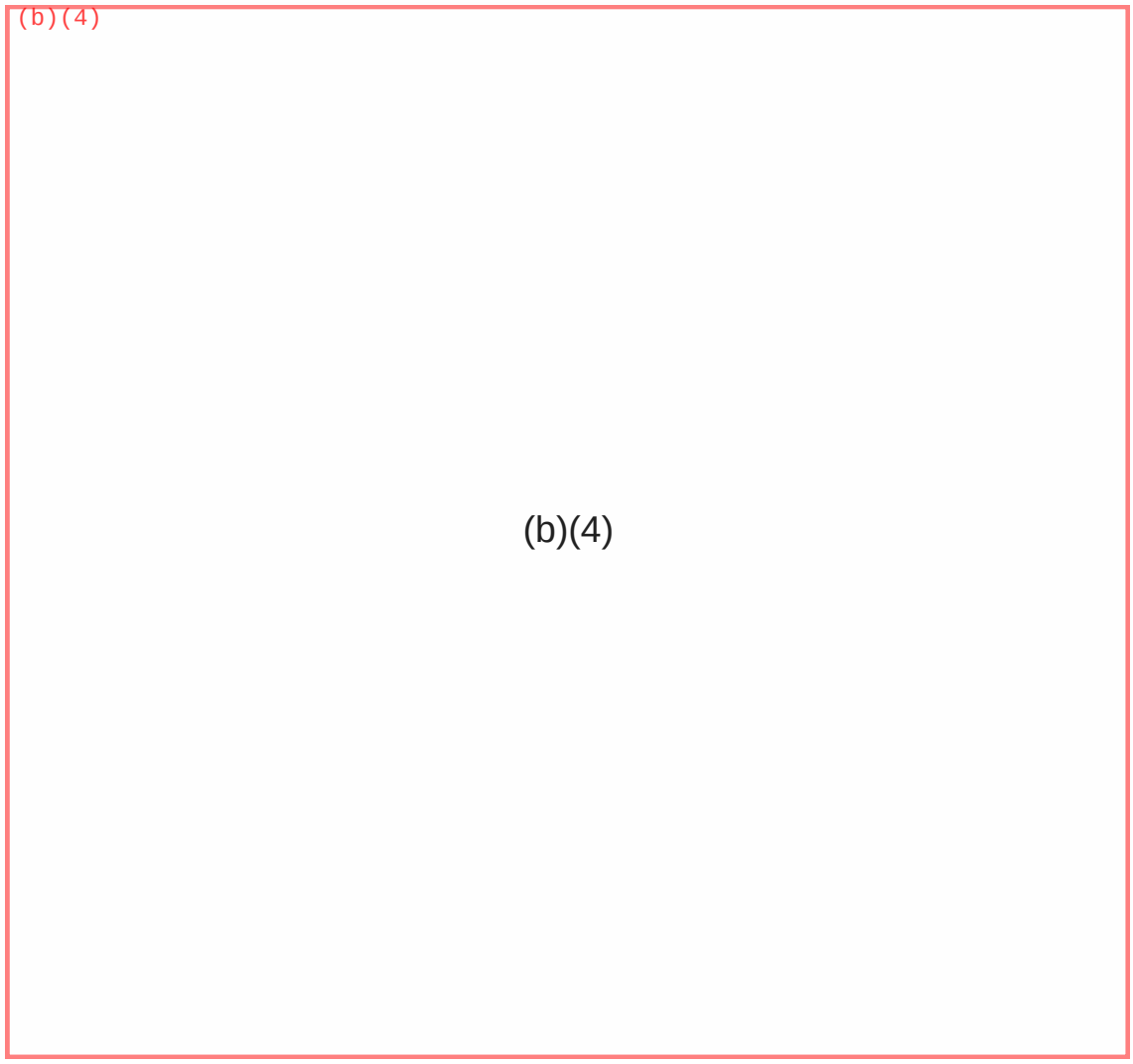
(b)(4)

Mechanical Evaluation

(b)(4)

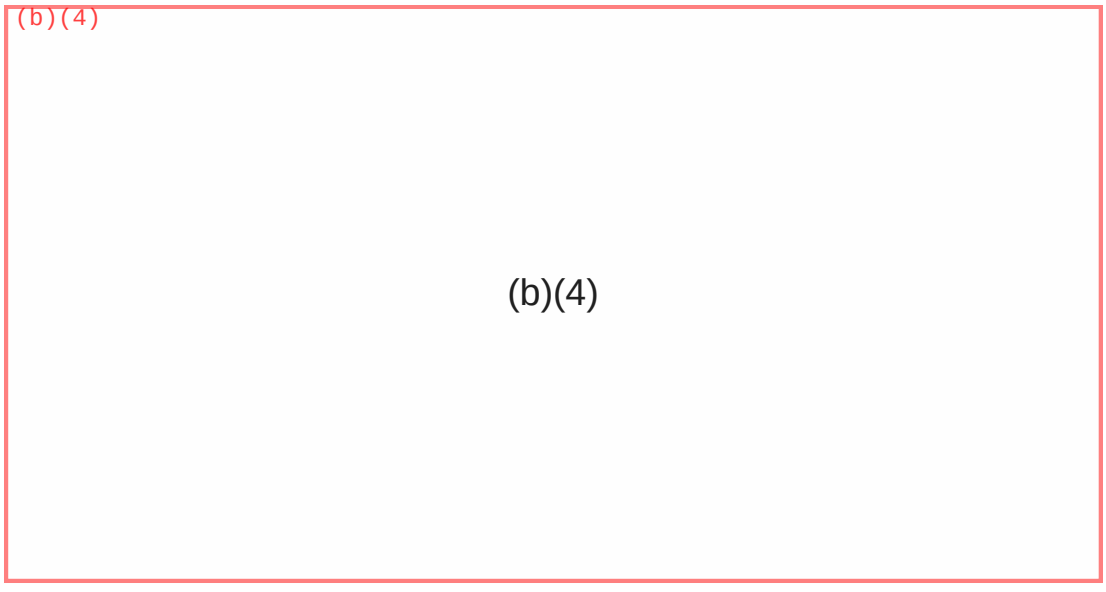
(b)(4)

(b)(4)



Defibrillation Thresholds

(b)(4)



(b)(4)

(b)(4)

Canine No.	Configuration*	Pulse Path	Duration (Weeks)	Implant DFT (Joules)	Range (all monitors)	Cumulative Energy Delivered (Joules)
(b)(4)						

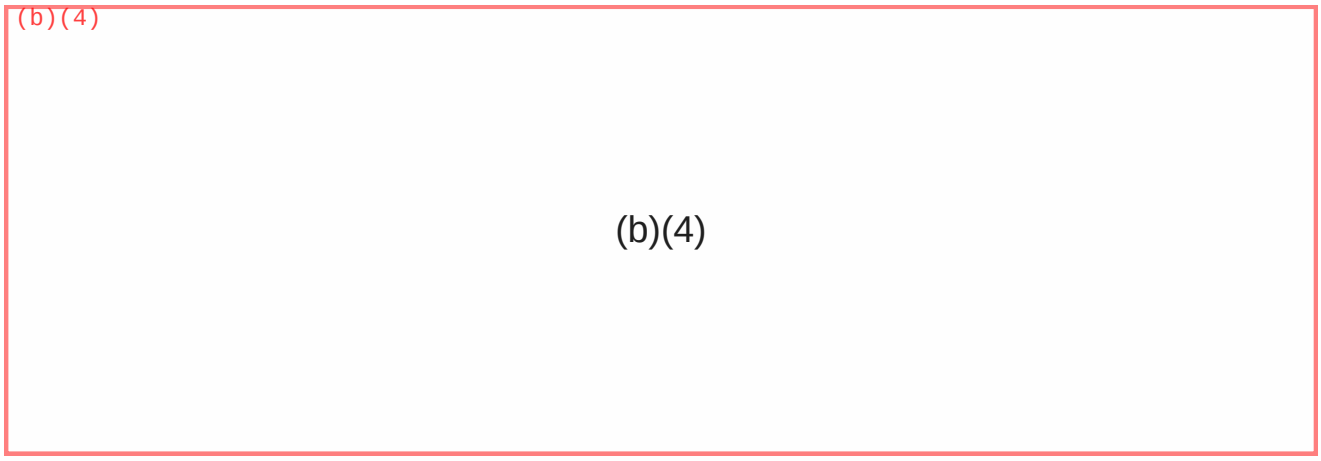
(b)(4)

(b)(4)

* Bold indicates common electrode.

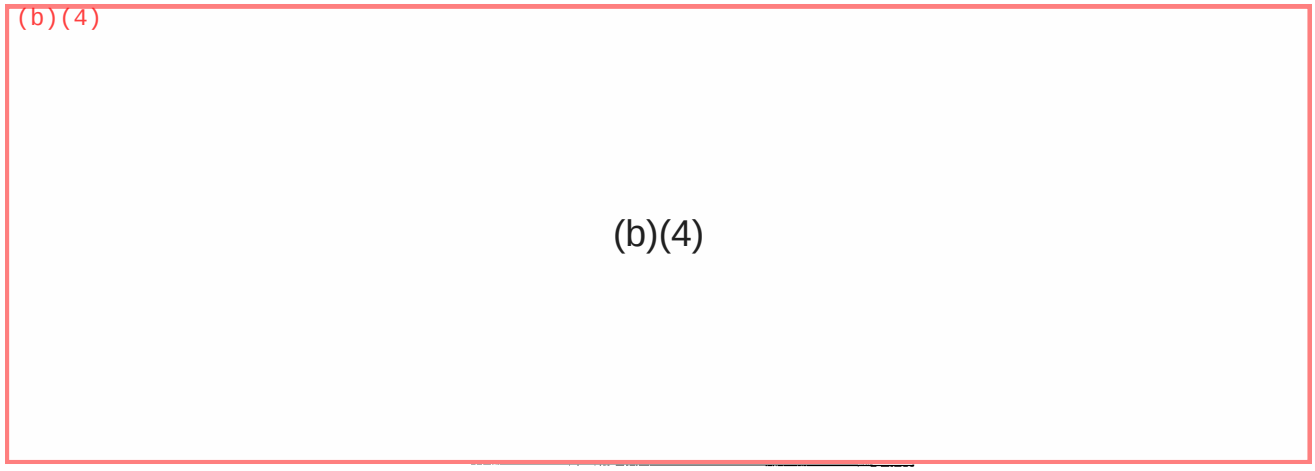
Chronic Defibrillation Thresholds in (b)(4)

(b)(4)



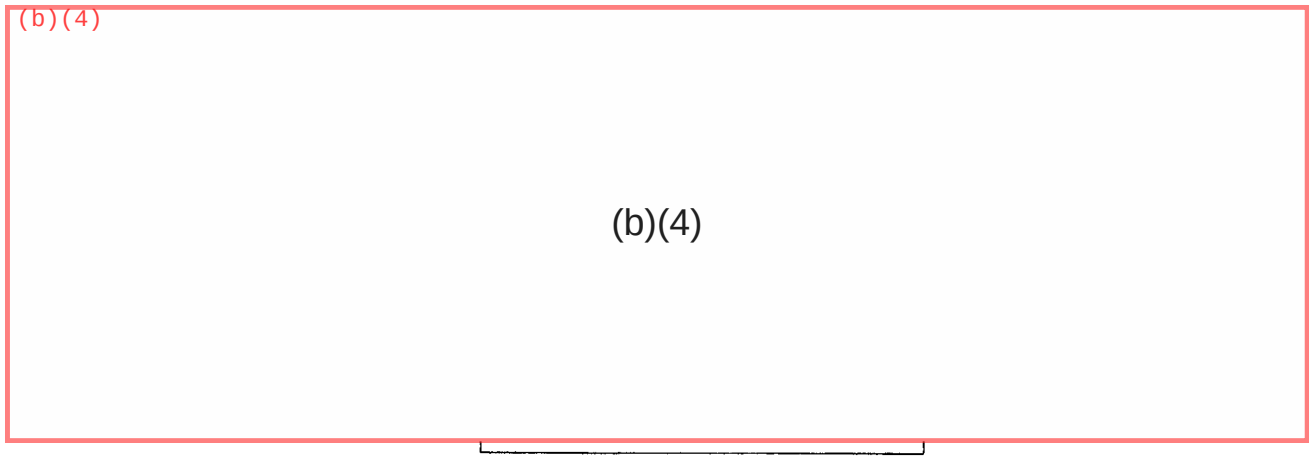
Chronic Defibrillation Thresholds in (b)(4)

(b)(4)



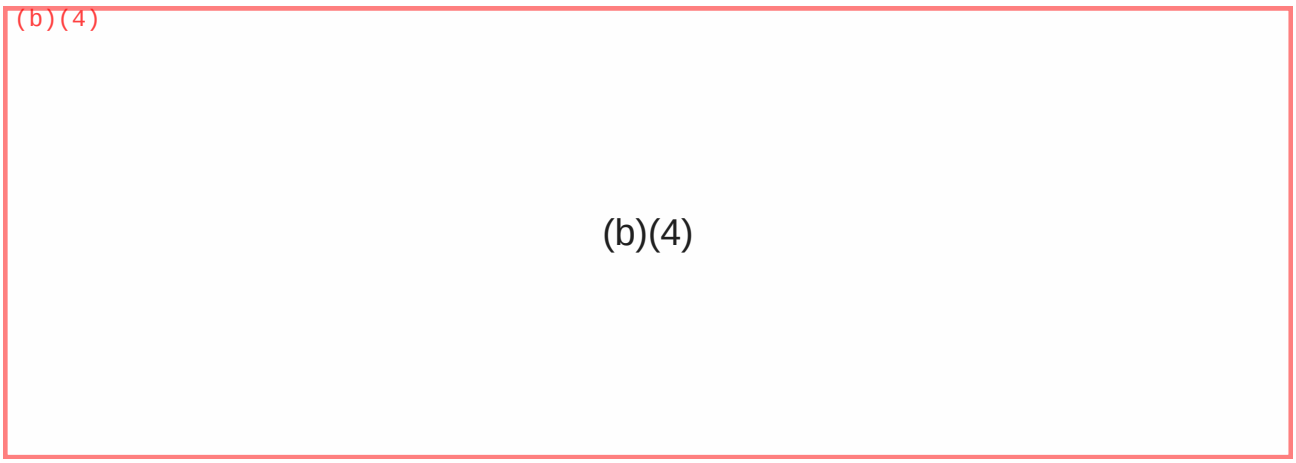
Chronic Defibrillation Thresholds in (b)(4)

(b)(4)



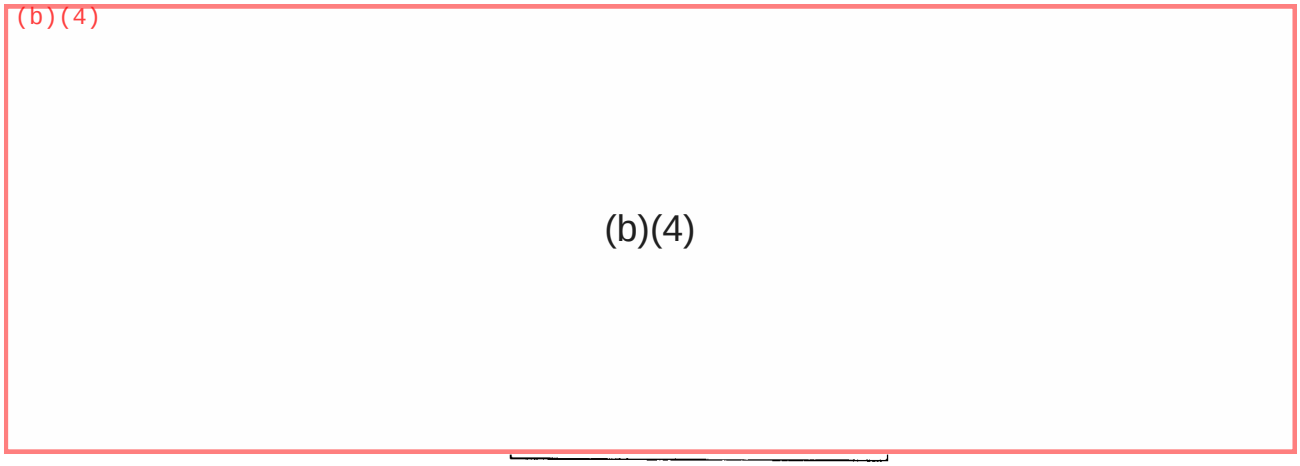
Chronic Defibrillation Thresholds in (b)(4)

(b)(4)



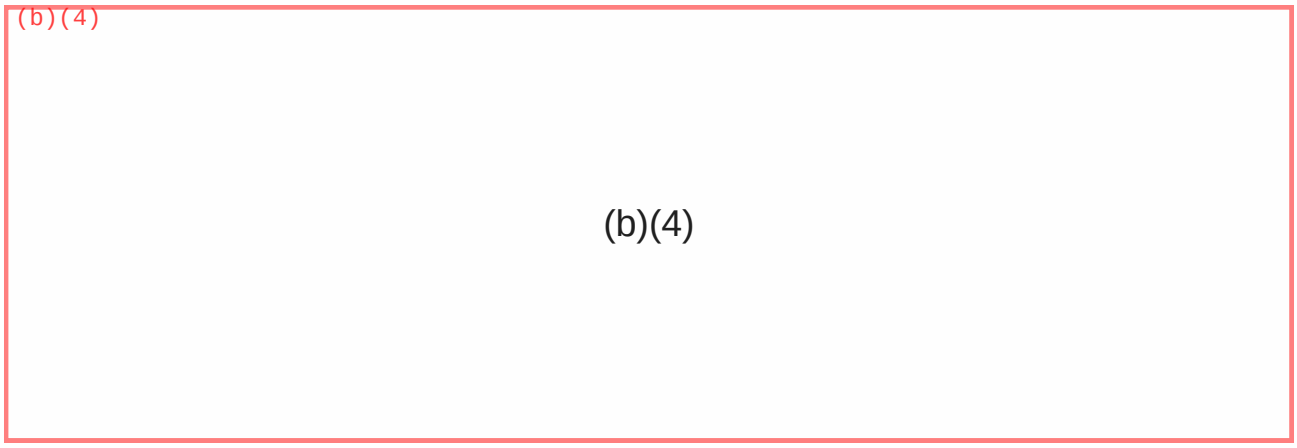
Chronic Defibrillation Thresholds in (b)(4)

(b)(4)



Chronic Defibrillation Thresholds in (b)(4)

(b)(4)



Chronic Defibrillation Thresholds in (b)(4)

(b)(4)

(b)(4)

Chronic Defibrillation Thresholds in (b)(4)

(b)(4)

(b)(4)

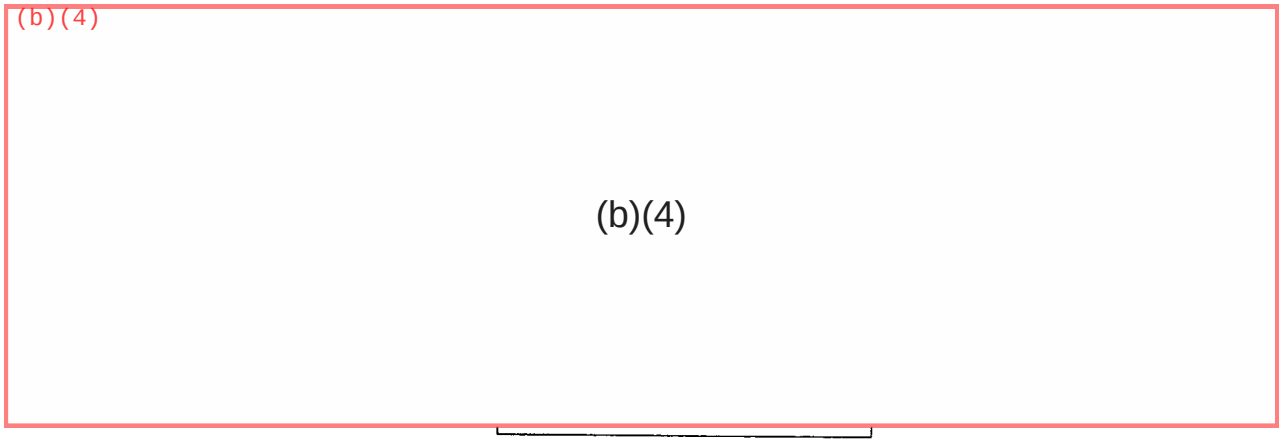
Chronic Defibrillation Thresholds in (b)(4)

(b)(4)

(b)(4)

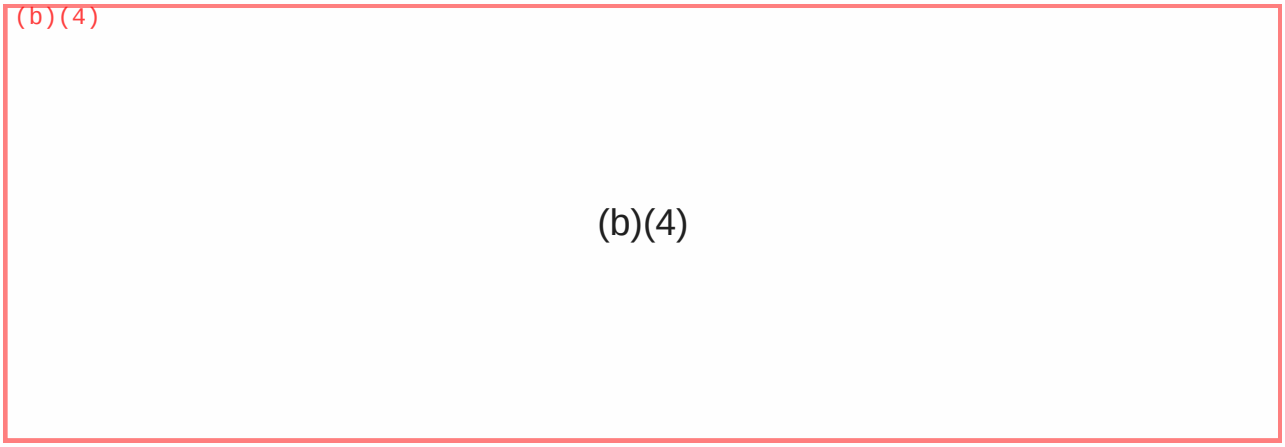
Chronic Defibrillation Thresholds in (b)(4)

(b)(4)



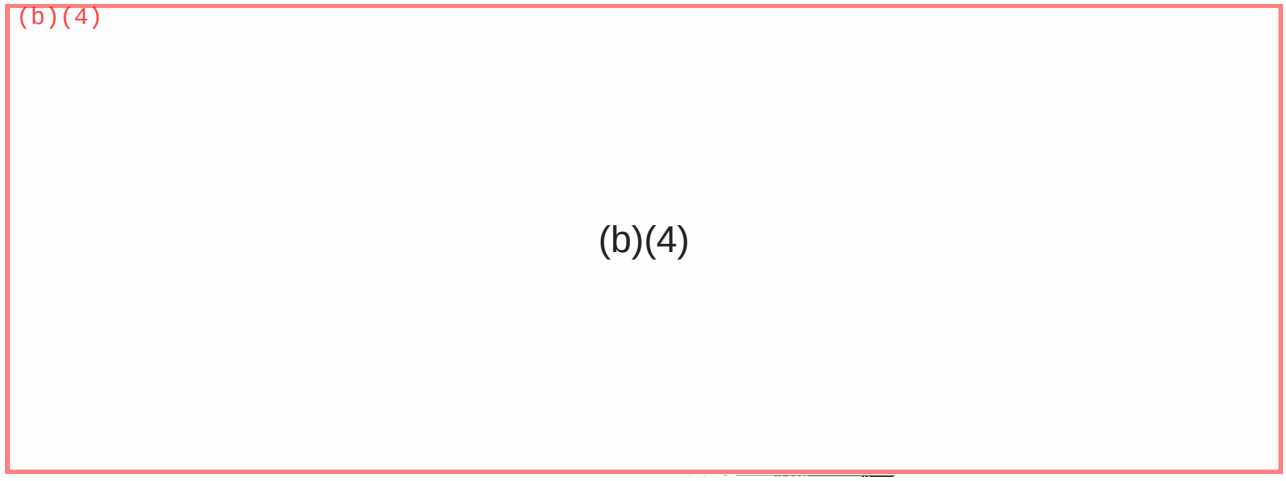
Chronic Defibrillation Thresholds in (b)(4)

(b)(4)



Chronic Defibrillation Thresholds in (b)(4)

(b)(4)



Pacing and Sensing Measurements

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Table VI-B-11. Summary of pacing thresholds from Chronic NTL Lead Study. The data was collected using the Model 6966 RV lead in an integrated bipolar configuration. The common defibrillation electrode (pacing anode) is designated in bold print.

			Measured Pacing Thresholds			
Canine No.	Lead System	Duration (Weeks)	Implant (volts)	Mean (volts)	Standard Deviation	Peak (volts)
(b)(4)						

(b)(4)

Pacing Thresholds for Model 6966 RV Lead

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Table VI-B-12. Summary of sensing data from Chronic NTL Lead Study. The data was collected using the Model 6966 RV Lead in a standard bipolar sensing configuration. Data designated as (b)(4) were greater than the sensing capabilities of the Model 5311 Pacing System Analyzer. Note: Data points at weeks (b)(4) and (b)(4) for (b)(4) are missing due to standard pace/sense disconnection from externalized skin button.

Canine No.	Lead System	Measured Sensing Amplitudes		
		Implant (mVolts)	Mean (mVolts)	Range (mVolts)
(b)(4)				

(b)(4)

Sensing Amplitude for Model 6966 RV Leads

(b)(4)

(b)(4)

Gross Pathology and Histopathology

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Discussion

(b)(4)

(b)(4)

(b)(4)

(b)(4)

13. **An update of the clinical experience of the Transvene™ Lead System should be provided. The update should include all additional patients and the clinical experience to date. The data should be presented as done in your original PMA application, and should include, e.g., implant and follow-up data, lead orientations including patch location, spontaneous episode experience, analyses by different groups, complications/observations, and survival analysis. All remaining deficiencies listed below which pertain to your patient population should be addressed using the updated patient group.**

RESPONSE:

An updated clinical experience report is provided in Volume 2 of this PMA Amendment. The data is presented as it was in our original (March 31, 1992) Transvene PMA application.

The updated experience is inclusive of 757 patients followed for an average of six months.

14. Please discuss your clinical data which support the claim which states that the Transvene™ Lead System improves both perioperative and long term patient morbidity.

RESPONSE:

In order to evaluate the impact of the PCD Transvene System on perioperative and long term patient morbidity, patient hospital stay post implant and the incidence of complications in patients with implant durations greater than six months was evaluated.

Hospital stay is an indicator for improved patient morbidity since it represents the amount of time required for patient recovery. Patients undergoing thoracotomy procedures generally require additional time for recovery due to the invasiveness of the procedure and related pulmonary complications.

In the case of the PCD Transvene System, the mean time for hospital stay post implant of the system was 7.2 days. This compared with a mean post implant hospital stay for the PCD Epicardial System of 10.3 days. This difference in hospital stay was statistically (b)(4) (b)(4) A shorter hospital stay for the patients who received a PCD Transvene System indicated that these patients were able to recuperate more quickly from the implant procedure due to the fact that a thoracotomy was not required. Those patients who require a thoracotomy have the added perioperative risk of complications associated with a thoracotomy such as pulmonary complications.

In the case of long term patient morbidity, Medtronic is not claiming that the PCD Transvene System improves long term patient morbidity. Instead, the long term patient morbidity should be similar to that reported with the PCD Epicardial System.

Analysis was performed to determine the types of complications which occurred in patients with implant durations of equal to or greater than six months. It is not expected that the PCD Transvene System would improve long term patient morbidity but rather should not increase the patient risk over long implant durations.

There were (b)(4) patients who received a PCD Transvene System in whom the implant duration was equal to or greater than six months. Of these patients (b)(4) (18.9%) experienced a medical event which was classified as a complication. It should be noted that these complications may have

occurred at any time during the implant duration and not necessarily after six months of implant duration.

As a comparison in the PCD Epicardial System, a total of (b)(4) patients have implant durations equal to or greater than six months. In this patient group, (b)(4) patients (14.1%) have experienced a medical event which was classified as a complication.

Thus based on this clinical data, the use of the PCD Transvene System results in a shorter hospital stay post implant and does improve perioperative morbidity. In addition, the use of the PCD Transvene System does not place the patient at increased long term morbidity.

15. Based on your experience and on the data as reported in the literature, what is the percentage of patients who have been found unable to withstand a thoracotomy?

RESPONSE:

Patients who are generally considered for implantation of an ICD System have a history of moderate to severe cardiovascular dysfunction. These patients have a history of coronary artery disease, cardiomyopathy, congestive heart failure as well as depressed left ventricular function. The multiple concomitant cardiovascular disease processes place these patients at increased perioperative mortality after a thoracotomy procedure.

There is a class of patients who cannot tolerate the thoracotomy required for the placement of the epicardial patch lead system and who are at high risk of sudden cardiac death. Because of the surgical risks and postsurgical complications associated with epicardial lead system, implantation in the following patient groups may not be possible:

(1) patients in whom there is no indication for concomitant cardiovascular surgery at the time of ICD implant;

(2) patients with severe pulmonary disease who cannot tolerate prolonged anesthesia or an open chest procedure;

(3) patients with severe congestive heart failure (ejection fraction < 40%) who are at increased risk for perioperative mortality after a thoracotomy procedure;

(4) patients who may eventually require open chest procedures for treatment of their coronary artery disease or cardiac transplant.

For these patients, the PCD Transvene System is the only therapy available. The PCD Transvene System simplifies and greatly reduces the risk associated with lead introduction, making therapy available to these patient groups. Because there is no need to open the chest of these patients, options for future therapy remain available; e.g. CABG is associated with decreased morbidity and mortality if there has been no prior open chest surgery.

In the case of the PCD Epicardial System, 35 patients expired in the perioperative period with a perioperative mortality of 4.7%. These patients, again due to there underlying cardiovascular disease, could not tolerate a thoracotomy. Lehman, et al [Lehman, et al. Implantable Cardioverter Defibrillators in Cardiovascular Practice: Report of the Policy

Conference of the North American Society of Pacing and Electrophysiology. PACE. 1991;12:969-79.] reports a perioperative mortality of 2.5% - 5.4% in a multicenter experience with an AICD Epicardial System. These patients again represent a group which could not tolerate a thoracotomy for implantation of an ICD System.

In the case of the PCD Transvene System, (b)(4) patients were initially screened for a PCD Transvene System. Of this group, 757 received a PCD Transvene System with **28.3%** of the patients (214/757) receiving the system despite not meeting the recommended implant criteria. The physician felt that in these cases the potential morbidity and mortality associated with the thoracotomy required for an epicardial defibrillation lead system outweighed the risk of not meeting the Medtronic recommended defibrillation requirement. It should be noted that the majority of these patients (97.3%) who received a PCD Transvene System, had at least a 10 Joule safety margin between the lowest successful defibrillation energy and the maximum output of the PCD Device (34J).

The use of an ICD System that requires a thoracotomy for implantation of the defibrillation lead system has been a mainstay in the treatment of ventricular tachyarrhythmias for over ten years. The system has performed remarkably as witnessed by its positive effect on sudden cardiac death mortality.

However, with the use of the ICD System in sicker patients, the need for an implantation procedure that decreases perioperative risk has arisen and lead to the development of a nonthoracotomy defibrillation lead system. But, there will continue to be patients, such as those undergoing concomitant cardiovascular surgery or patients who do not the meet recommended defibrillation implant criteria with the PCD Transvene System, who will receive an ICD System with an epicardial defibrillation lead system.

16. Data such as treatment efficacy, complications and survival analysis on the patients followed for 6 months should be provided.

RESPONSE:

A summary table of this data and relevant discussion is provided below.

PCD™ Transvene™ System Data Summary		
	All Patients (3 Electrode Systems)	Patients with 6 months of Follow-up
Number of Patients	(b)(4)	
Device Months Follow-up		
Mean Follow-up Time		
Maximum Follow-up Time		
Number, % Male Number, % Female		
Mean Age		
Primary Indication: SCD VT SCD/VT		
Coronary Artery Disease		
Mean Ejection Fraction		
Lead Orientation: RV-CS-SQ RV-SQ-SVC RV-CS-SVC		
Mean LED		
Mean DFT		
Spontaneous VT: Number of Patients Number of Episodes % Success		
Spontaneous VF: Number of Patients Number of Episodes % Success		
One Year Overall Survival One Year SCD Survival		
Patients with complications		

(b)(4)

The patient population (b)(4) with six months of follow-up are predominantly male (80.2%) with a mean age of 58.0 years. In the majority of patients the primary indication for implant was recurrent, sustained ventricular tachycardia without an episode of sudden cardiac death. The treatment efficacy for this patient population was 99.0% for spontaneous VT episodes, and 98.7% for spontaneous VF episodes, which is equivalent to the total patient population 98.7% and 99.1% respectively. Overall survival at one year for these patients is 99.4% and sudden cardiac death survival at one year was 100.0%. (b)(4) (18.3%) of the patients followed for six months had a complication.

Based on the data above, the PCD™ has performed safely and reliably for patients followed for 6 months or greater.

17. Please discuss your clinical experience (treatment efficacy, lead orientation, complications and survival rates) of the patients who have been followed for 1 year and more.

RESPONSE:

A summary table of this experience and relevant discussion is provided below.

PCD™ Transvene™ System Data Summary		
	All Patients (3 Electrode Systems)	Patients with 12 months of Follow-up
Number of Patients	757	115
Device Months Follow-up	4246.4 mo	1835.5 mo
Mean Follow-up Time	5.6 mo	15.7 mo
Maximum Follow-up Time	28.6 mo	28.6 mo
Number, % Male **Number, % Female**	610 80.6% 147 19.4%	91 79.1% 24 20.9%
Mean Age	59.4 yrs	57.0 yrs
Primary Indication: **SCD** **VT** **SCD/VT**	 281 37.1% 377 49.8% 99 13.1%	 45 39.1% 56 48.7% 14 12.2%
Coronary Artery Disease	561 74.1%	85 73.9%
Mean Ejection Fraction	35.6% (n=688)	40.5% (n=104)
Lead Orientation: **RV-CS-SQ** **RV-SQ-SVC** **RV-CS-SVC**	 222 29.3% 496 65.5% 39 5.2%	 33 28.7% 73 63.5% 9 7.8%
Mean LED	16.0 (n=702)	15.2 (n=105)
Mean DFT	14.8 (n=316)	13.8 (n=62)
Spontaneous VT: **Number of Patients** **Number of Episodes** **% Success**	 226 5430 98.7%	 60 1770 98.9%
Spontaneous VF: **Number of Patients** **Number of Episodes** **% Success**	 198 973 99.1%	 37 248 98.8%
One Year Overall Survival **One Year SCD Survival**	95.3% 99.8%	100.0% 100.0%
Patients with complications	138 18.2%	24 20.9%

The patients population (b)(4) with 12 months or more of follow-up is predominantly male (79.1%) with a mean age of 57.0 years. In the majority of patients (48.7%), the primary indication for implant was recurrent, sustained ventricular tachycardia without an episode of sudden cardiac death. The treatment efficacy for this patient population was 98.9% for spontaneous VT episodes, and 98.8% for VF episodes, which is equivalent to the overall patient population with 98.7% and 99.1% respectively. Overall and sudden cardiac death one year survival for this patient population is 100.0% since all patients have been followed for one year or greater. In the patients followed for 12 months or more there has been one death which is classified as non-sudden cardiac. This death occurred 684 days (22.5 months) post implant. (b)(4) (20.9%) of the patients followed for 12 months had a complication.

Based on the data above, the PCD™ has performed safely and reliably for patients followed for 12 months or greater.

18. **Provide a detailed discussion of the clinical experience (implant duration, lead orientations, spontaneous episodes, treatment efficacy, survival analysis, complications, etc.) of the patients who did not meet the implant criteria and were implanted with the Transvene™ System. Also discuss the experience of the patients who were implanted without the 10 Joule safety margin.**

RESPONSE:

For purposes of the PCD Transvene System, the recommended implant criteria was defined as successful VF termination at least 3 times in 4 attempts with the final lead configuration with an output energy of 18 Joules or less. The determination of a defibrillation threshold was not necessary.

Of the 757 patients who received a PCD Transvene System, 214 patients (28.3%) received the system despite not meeting the recommended implant criteria.

Table 1 summarizes the physician justification for implanting the PCD Transvene System despite not meeting the recommended defibrillation implant criteria.

PCD Transvene System Patients Not Meeting Implant Criteria Physician Justification 6/24/92	
Reason	**Number of Patients**
LED < 24 Joules	170 (79.4%)
Difficult to Induce VF	24 (11.2%)
Patient Condition	20 (9.4%)
TOTAL	214

Table 1: Physician Justification for Patients Not Meeting Implant Criteria - 6/24/92

It should be noted, however, that 90.7% (194/214) of these patients had at least a 10 Joule defibrillation safety margin between the lowest successful defibrillation energy and the maximum output of the PCD Device (34J). Table 2 provides clinical data on this group of patients who received a PCD Transvene System.

PCD Transvene System Patients Not Meeting Implant Criteria Clinical Experience 6/24/92	
Patient Characteristics	
Number of Patients	214
Mean Follow-Up	4.0 months
Indication for Implant **SCD** **VT** **SCD/VT**	 72 (33.6%) 99 (46.3%) 43 (20.1%)
Cardiovascular History **CAD** **Cardiomyopathy**	 165 (77.1%) 65 (30.4%)
Mean EF	33.7%
Implant Data	
Mean DFT	18.8J
Mean LED	19.5J
Implanted Lead System **RV-SVC-SQ** **RV-CS-SQ** **RV-CS-SVC**	 145 (67.8%) 63 (29.4%) 6 (2.8%)
Spontaneous VT/VF Episode Efficacy	
Spontaneous VT Episode Efficacy	98.4%
Spontaneous VF Episode Efficacy	99.2%
One Year Survival Analysis	
Sudden Cardiac	99.3%
Non-Sudden Cardiac	98.6%
All Cardiac	97.9%
Noncardiac	100%
Overall	97.4%

Table 2: Patients Not Meeting Implant Criteria Clinical Experience - 6/24/92

There were 20 patients in whom the implant procedure was terminated due to poor patient condition. These patients received a PCD Transvene System without at least a 10 Joule defibrillation safety margin. The implant circumstances of these patients is summarized as follows:

- At least one successful defibrillation was obtained at an energy level greater than 24 Joules but less than 34 Joules (**N=11 patients**);
- Multiple inductions of VT were performed and successfully reverted with an energy level of 18 Joules or less. However, induced VF was not successfully reverted by an energy level of less than or equal to 34 Joules (**N=6 patients**); and
- Physician elected to terminate the procedure due to the patient's condition before inductions with the final implanted lead configuration were performed (**N=3 patients**).

The mean ejection fraction of this group was 26.9%, indicating more severe underlying cardiovascular disease, and may have contributed to the physicians decision to terminate the implant procedure prior to meeting implant criteria. This group had a mean of 6.8 VF inductions, 2.2 lead configurations evaluated and a mean duration of VT/VF for the implant procedure of 220 seconds. The circumstances of the implant procedures, mainly the duration of induced ventricular tachyarrhythmia and associated hemodynamic compromise, limited the number of inductions that could be performed and whether the recommended implant criteria could be met.

Of these twenty patients, ventricular fibrillation has been induced at a chronic follow-up visit in 15 patients (75%) and in all cases successful defibrillation with the implanted PCD Transvene System was documented.

The overall spontaneous VF episode efficacy for this patient group was 92.6%, however, further review indicated that one patient experienced atrial fibrillation that was detected as VF and in whom all four programmed VF therapies were ineffective. This patient's antiarrhythmic drug therapy was modified and there were no further reports of ineffective therapies.

Thus there have been no patients who have experienced an actual spontaneous VF episode where all four programmed VF therapies failed to terminate the episode.

There has been one reported patient death, (Patient (b)(6) which was classified as non-sudden cardiac secondary to end stage heart failure. The one year sudden cardiac death survival in this patient population is 100% while the overall one year survival was 93.8%. This lower overall one year survival may be due to the lower mean ejection fraction of this patient group.

The clinical outcome in these twenty patients was not adversely affected by not meeting implant criteria since there was no reports of failure to terminate a spontaneous VF episode and the overall one year sudden cardiac death survival was 100%.

The recommended implant criteria for the PCD Transvene System is defined as successful VF termination at least 3 times in 4 attempts with the final lead configuration with an output energy of 18 Joules or less. However, in some cases, the investigators felt that the patient's medical condition precluded a PCD Epicardial System implant with a thoracotomy approach and its associated morbidity and mortality. This clinical experience indicates that the PCD Transvene System performed safely and effectively in this patient population.

19. A breakdown of the different lead orientations within the patient population, and the treatment efficacy reported for each configuration should be included.

RESPONSE:

The following table shows the clinical data by type of lead system for the three lead systems presented in the Transvene™ PMA clinical report. the majority of patients (718 or 94.8%) received used a subcutaneous patch as part of their defibrillation lead system. The majority of patients (65.5%) received a lead in the Superior vena cava; 29.3% received a lead in the Coronary Sinus. Only 39 patients or 5.2% received a totally transvenous three lead system.

The performance of these three lead systems in terminating episodes of spontaneous ventricular tachycardia and ventricular fibrillation was very good. All systems had at least a 98.5% success rate in treating spontaneous episodes of ventricular tachycardia and at least a 98.8% success rate in treating spontaneous episodes of ventricular fibrillation. The RV/SVC/SQ and RV/CS/SVC lead systems had a 1 year actuarial survival of 100.0%. The RV/CS/SQ lead system had a 1 year actuarial survival of 99.4%. All of these lead systems have performed safely and effectively.

PCD™ Transvene System Lead Systems				
	RV/SVC/SQ	**RV/CS/SQ**	**RV/CS/SVC**	**All Patients**
# of Patients	496	222	39	757
Mean LED	16.7J (N=456)	14.6J (N=210)	15.2J (N=37)	16.0J (N=703)
Mean DFT	15.8J (N=187)	12.8J (N=110)	16.0J (N=19)	14.8J (N=316)
Spontaneous VT:				
# of Patients	126	84	16	226
# of Episodes	3093	1804	533	5430
% Success	98.5%	98.9%	99.4%	98.7%
Spontaneous VF:				
# of Patients	124	59	15	198
# of Episodes	645	277	52	973
% Success	98.8%	99.6%	100.0%	99.1%
1 Year Survival:				
Sudden Cardiac	100.0%	99.4%	100.0%	99.8%
Non-Sudden Cardiac	97.1%	99.4%	85.3%	96.8%
All Cardiac	97.1%	98.9%	85.3%	96.6%
Non-Cardiac	99.4%	100.0%	96.5%	99.4%
Overall	95.8%	97.9%	82.3%	95.3%
Number of Deaths	14	4	4	22

Table DEF19: Data Summary: Implanted Lead System

20. Based upon your clinical experience, the Physician's Manual should recommend the sequence of testing with the different lead orientations during implant.

RESPONSE:

Proposed changes to the Model 7217B PCD technical manual are provided in the attachment following this response, see section from technical manual, "Implanting the PCD Device - Implantation Procedure." Specific areas relative to the sequence of testing with different lead orientations during implant are highlighted for reference.

Implantation Procedure

Overview

Patients should undergo the following procedures before implant of the PCD device to help determine if they are appropriate candidates for a PCD system:

- Electrophysiologic evaluation to determine the patient's ventricular arrhythmia and how it responds to different therapies,
- Exercise stress test to determine the patient's maximum sinus rate, and
- Cardiac catheterization to determine if there is a need for concomitant surgery.

Clinical studies indicate that patients who fail a transvenous lead implant and immediately receive an epicardial lead system may be at higher risk than those patients who received the epicardial leads more than one day later. If patients do not meet the implant criteria for a transvenous lead system, physicians should consider the patients' number and duration of induced VF episodes before proceeding to an epicardial lead implant.

Implanting the PCD device and corresponding lead system involves seven main steps:

- Operative Set-Up
- Lead System Implantation and Evaluation
- Defibrillation Efficacy Testing
- Connecting the Leads to the PCD Device
- Placing the PCD Device
- PCD System Evaluation
- Closing

During implantation, the PCD system requires an appropriate Medtronic programmer and MemoryMod cartridge and the Medtronic External Tachyarrhythmia Control Device (ETCD) to evaluate and monitor the implanted lead system and therapy efficacy.

Each of the above steps is explained in the following sections. At the end of this chapter, instructions for replacing a PCD device and implanting a PCD device with a chronically implanted lead system are also given.

Operative Set-Up

The preparation and procedures before implanting the lead system are grouped into four main steps: assembling the necessary equipment, setting up the equipment, pre-programming and testing the PCD device, and pre-programming and testing the ETCD and auxiliary equipment.

Necessary Equipment

The equipment listed below should be available for each implant. Duplicates of sterile items should also be on hand.

- Model 7217B PCD device
- External Tachyarrhythmia Control Device (ETCD)
- Appropriate Medtronic programmer and printer
- Appropriate MemoryMod software cartridge
- Cardioversion/defibrillation and pacing/sensing leads
- Appropriate adaptors
- External defibrillator
- Pacing system analyzer (PSA)
- Patient cable for connecting lead system to the ETCD
- EGM cable to connect the programmer to the ETCD
- Cable (and connector pins if necessary) to connect a pacing system analyzer to the ETCD or a surgical cable to connect the PSA directly to the leads
- Test load for discharging high-voltage shocks from the ETCD
- Cables for connecting the EGM output of the ETCD and Marker Channel output of the programmer to a hospital monitor/recorder
- Appropriate batteries for the pacing system analyzer and ETCD
- Extra printer paper for the pacing system analyzer and programmer/printer
- Sterile bag to place over programming head and cable
- Implant documentation forms

Some optional equipment includes an external fibrillation source or stimulator, tape or multi-channel recorder, dual-channel oscilloscope, and appropriate cables.

Equipment Set-Up

Set up the ETCD/programmer with the appropriate MemoryMod cartridge, an external defibrillator, and auxiliary equipment such as monitors, recorders, a fibrillator, and their related cabling. Also, connect the test load to the ETCD.

Pre-Programming and Testing the PCD Device

Prepare the PCD device for implant by doing the following:

1. Interrogate the device while it is still in its sterile package and print out a full report.

2. Review the battery status. Devices with an initial battery voltage less than 6.1 volts before charging should not be implanted. If the device is charged without obtaining the initial voltage, it should be implanted only if the battery voltage reaches 6.1 volts or more within thirty minutes after charging.

3. Test the charge circuit by charging the capacitors to the maximum output. The charge time must meet the following requirements:
   - If the charge time is less than or equal to 10 seconds, implant the device. If it is greater than 10 seconds, wait 5 minutes, discharge (dump) the capacitors, and then perform a second charge.
   - If the second charge time is less than or equal to 10 seconds, implant the device. If it is greater than 10 seconds, do not implant the device.

4. While still in the sterile package set the device parameters for implant as appropriate for the patient.

5. Ensure that VT and VF Detection are programmed OFF.

Pre-Programming and Testing the ETCD & Auxiliary Equipment

To prepare for lead system evaluation and defibrillation efficacy testing, do the following:

1. Verify that the ETCD's battery status is acceptable.

2. While recording the ETCD's output signals and the Marker Channel output from the printer, calibrate the hospital's monitoring/recording equipment.

3. Test the ETCD's high-energy output capability using the test load.

Lead System Implantation and Evaluation

The PCD lead system uses electrodes designed to carry high current for cardioversion or defibrillation. The cardioversion/defibrillation electrodes (PULSE1, PULSE2, and COMMON) must be specifically suited for this purpose and have a large electrode surface area to reduce cardioversion/defibrillation thresholds and minimize tissue damage possibly caused by the high cardioversion/defibrillation currents.

While the PCD is connected to the leads, no metal portion of any electrode should contact the metal of any other electrode. If the electrodes are in contact during a cardioversion or defibrillation therapy, the current will bypass the heart and may also damage the PCD device.

Pacing occurs between a pacing/sensing lead and one of the cardioversion/defibrillation leads (COMMON). Sensing is accomplished through two pacing/sensing electrodes. Either epicardial or endocardial leads may be used. To reduce the effects of electromagnetic interference (EMI), the PACE/SENSE and SENSE2 electrodes should be positioned adjacent to each other, and where separate leads are used, the lead wires should be routed together with several loose twists.

Depending on what kind of operative approach is used to implant the leads, the PCD Device can use two different kinds of lead systems: an epicardial lead system or a Transvene™ lead system. Each system is described briefly below. See the appropriate Lead Technical Manual for more details.

The physician chooses the lead system that best meets the patient's needs. Patient factors that affect the decision include the following:

- Overall size of the patient's heart,
- Size and location of previous infarcts, aneurysms, or bypass grafts, and
- Surgical approach.

The epicardial lead system uses two or three epicardial patch leads for cardioversion/defibrillation.

Three patch sizes allow the physician the flexibility to meet the varying patient conditions. Clinical experience has shown that approximately half of all patients receive a three-patch system; the other half receives two patches. Three patches may be required initially if the physician expects difficulty in meeting defibrillation implant criteria. Adding a third patch to a two-patch system may be required if the implant criteria cannot be met with the two-patch system.

The Transvene™ non-thoracotomy lead system can use two or three leads in four different areas:

- A tripolar lead in the right ventricle (RV).
- A unipolar lead in the coronary sinus (CS) and/or superior vena cava (SVC).
- A subcutaneous (SQ) patch lead.

Cardioversion/defibrillation occurs between the COMMON electrode (cathode) and one or two anodes. These electrodes can be any of the following: the CS lead, the SVC lead, the RV coil, or the SQ patch. Sensing occurs between the tip and ring of the tripolar RV lead. Pacing occurs between the tip of the RV lead and the COMMON electrode.

Lead system implantation and evaluation consists of placing the lead system, connecting the leads for pacing and sensing measurements, performing pacing and sensing measurements, and verifying lead connections. Each step is explained in the following sections. See the appropriate lead technical manual for more details.

Placing the Lead Systems

Placing the Epicardial Lead System

Depending on the physician's preference, a variety of surgical approaches can be used to implant the lead system, such as a limited thoracotomy or median sternotomy.

Placing Pacing/Sensing Leads:
The pacing/sensing leads should be placed close to the ventricular apex to avoid sensing P-waves. Approximately 1 cm should separate the electrodes from each other.

Placing Epicardial Patch Leads:
Suture two or three patch leads to the epicardium or pericardium in locations that produce optimal defibrillation, pacing, and sensing. In all locations, place the leads so that they encompasses the maximum amount of cardiac mass and they have approximately equal amounts of mass between them.

For a two-patch system, a typical approach is to use an anterior right ventricular patch as COMMON and a posterolateral left ventricular patch as PULSE2. For a three-patch system, a typical approach is to use a posterior ventricular septal patch as COMMON, an anterior right ventricular patch as PULSE1, and an anterolateral left ventricular patch as PULSE2. The PULSE1 and PULSE2 patches should be the same size.

Placing Transvene™ Leads

CAUTION: If insertion is done via a subclavian approach, the lead should be positioned far laterally to avoid clamping the lead body between the clavicle and the first rib. Clamping the lead may eventually cause the conductor to fracture, may cause damage to the insulation, or may cause other damage to the lead. This may result in complications such as loss of detection, loss of pacing therapies, or loss of cardioversion/defibrillation therapy. Certain anatomical abnormalities, such as thoracic outlet syndrome, may also precipitate pinching and subsequent fracture of the lead. If significant resistance is encountered during a subclavian stick implant procedure, do not force the lead by adjusting patient's posture (i.e., raising the arm or putting a towel behind the person's back) to facilitate the passage of the lead. In such cases it is recommended that an alternate venous entry site be used.

There are several possible lead systems that can be evaluated depending on the desired pathway and physician placement preference.

Three Lead System:

- Right ventricle, superior vena cava, and subcutaneous patch.
- Right ventricle, coronary sinus, and subcutaneous patch.
- Right ventricle, coronary sinus, and superior vena cava.

Two Lead System

- Right ventricle, coronary sinus.

- Right ventricle, subcutaneous patch.
- Right ventricle, superior vena cava.

For recommendations on the order of lead system evaluation refer to "Defibrillation Efficacy Testing" (the next section of this manual).

The RV, CS, and SVC lead should be implanted using standard transvenous implant techniques. Follow the general guidelines below for initial positioning of the Transvene™ lead system (the final positions will be determined by defibrillation threshold tests):

- Position the RV lead tip in the right ventricular apex.
- Advance the CS lead tip to just under the left atrial appendage, if possible.
- Place the SVC lead tip approximately 5 cm proximal to the right atrium and SVC junction.
- Place the SQ patch lead along the left midaxillary with the center over the fourth-to-fifth intercostal space.

Other positioning recommendations to consider:

- The CS lead position should be considered unacceptable if the proximal end of the CS defibrillation coil is at or outside the CS ostium.
- A cutaneous patch electrode may also be used during acute testing to minimize invasive procedures. Once defibrillation efficacy has been demonstrated, a permanent subcutaneous can be implanted.
- The subcutaneous patch may be placed subcutaneously, submuscularly, or directly on the periosteum of the ribs. The patch may be repositioned, if necessary, to meet the implant defibrillation efficacy criteria.
- If the Transvene™ lead system implant criteria cannot be met, an epicardial lead system may be evaluated, as described in this section.
- If the CS lead is proving difficult to position, a temporary pacing catheter can be positioned in the coronary sinus ostium. This can be used as a guide to cannulate the coronary sinus with the permanent lead.

Connecting the Leads for Pacing and Sensing Measurements

Depending on the physician's preference, two approaches can be used to connect a pacing system analyzer (PSA) to the implanted leads: passing through the ETCD or by direct connection. See the appropriate ETCD or PSA technical manual for connecting instructions.

Performing Pacing and Sensing Measurements

For a Transvene™ lead system, the pacing connections should be the RV tip electrode as cathode (-) and the defibrillation COMMON electrode as anode (+). Sensing measurements should be made between the RV tip and RV ring electrodes.

For an epicardial lead system, the PACE/SENSE electrode serves as the cathode (-) for pacing and the COMMON patch electrode serves as the anode (+). Measure between this patch electrode and each pacing/sensing electrode to obtain the best pacing threshold. Designate the best pacing/sensing electrode as PACE/SENSE. The other electrode should be SENSE2.

Listed below are the acceptable PCD system implant values for acute and chronically implanted lead systems.

	Acceptable Implant Values	
Measurements Required	**Acute Lead System**	**Chronic Lead System**
Capture threshold	≤ 1.5 V - epicardial	≤ 3.0 V - epicardial
(at 0.5 ms pulse width)	≤ 1.0 - endocardial	≤ 3.0 V - endocardial
Impedance	200 - 800 ohms	200 - 800 ohms
Filtered R-wave amplitude	≥ 5 mV (during sinus rhythm)	≥ 3 mV (during sinus rhythm)
Slew rate	≥ 0.75 V/s	≥ 0.45 V/s

Also, check that P- and T-wave oversensing are not occurring by pacing at the maximum output (5.4 V, 1.59 ms) and sensing at the maximum sensitivity (0.3 mV).

Defibrillation Efficacy Testing

Verifying Lead Connections

After connecting all of the leads to the ETCD, confirm that the sensing leads are connected properly by observing sensed events on the Marker Channel telemetry. Verify the cardioversion/defibrillation lead connections to the ETCD by delivering a low-energy shock (0.6 joules) synchronously into sinus rhythm.

Listed below are the expected values for the voltage, current, impedance, and energy.

	Approximate Expected Values	
Parameter	**Epicardial**	**Transvene™**
Stored Joules (Energy):	0.6	0.6
Applied Joules (Energy):	Depends on impedance and pulse width	Depends on impedance and pulse width
PULSE1		
Peak Volts:	100	100
Peak Amps:	1-5	0.7-2.5
Path Ohms:	20-100	40-150
PULSE2		
Peak Volts:	100	100
Peak Amps:	1-5	0.7-2.5
Path Ohms:	20-100	40-150

If the path resistance measurements (ohms) do not fall within these ranges, check the lead connections and lead placements and tighten or reposition if necessary.

CAUTION: Implanting the PCD device when the path resistance is less than 20 ohms may damage the device.

Performing Defibrillation Efficacy Testing

After checking the lead connections, test defibrillation efficacy to show the ability to properly treat ventricular fibrillation. Before testing defibrillation efficacy, ensure an external defibrillator is charged for a rescue shock. Use the ETCD to perform the following:

1. Program the ETCD to properly detect VF with an adequate safety margin (sensitivity = 1.2 mV, VF NID = 18, FDI = 320 ms).
2. Program the VF therapy parameters (energy, pathway, and pulse width) to the desired settings. See Table 5 in "General Device Information" for information on choosing optimal pulse widths.
3. Induce VF using AC stimulation or the fibrillation induction feature present in the ETCD. See the appropriate programmer manual for specific instructions on inducing VF with the ETCD.
4. Convert the arrhythmia using the ETCD and lead system.

To demonstrate reliable defibrillation efficacy with acute or chronic leads, it is recommended that VF be initiated and terminated three out of four times at a stored output energy of 18 joules or less. The protocol shown in Figures 22 and 23 are suggested. If more than one of the four VF inductions are not terminated by the ETCD and lead system, the decision to implant the PCD device should be re-evaluated.

At their option, physicians may also test for ventricular tachycardia therapy efficacy after testing for defibrillation efficacy.

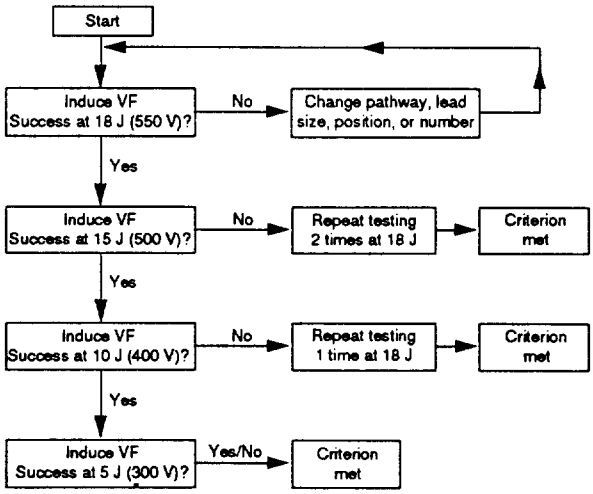


Figure 22. Defibrillation Efficacy Protocol Flowchart

Evaluating VF Sensing

While testing for defibrillation efficacy, evaluate VF sensing by reviewing the Marker Channel symbols and electrograms and checking for post-shock T-wave sensing. If VF sensing is not appropriate, it may be necessary to reposition the leads and repeat the VF inductions.

665

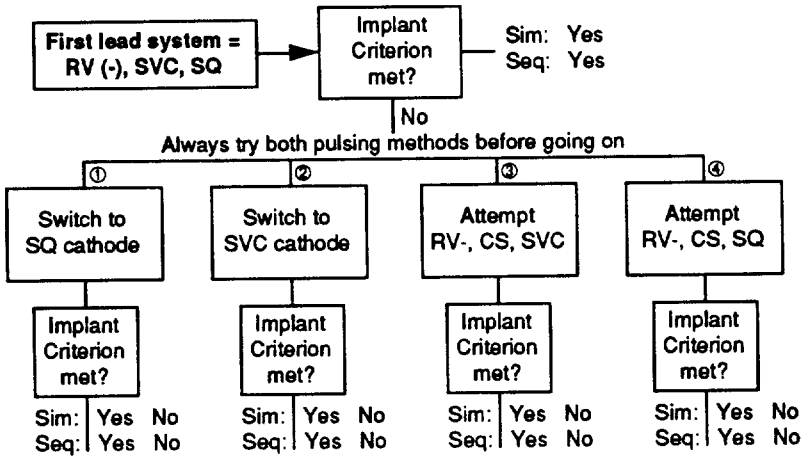


Figure 23. Transvene™ Lead System Evaluation Protocol Flowchart

Connecting the Leads to the PCD Device

The Model 7217B PCD device is connected to a lead system consisting of either two or three cardioversion/defibrillation electrodes. Figures 24 and 25 illustrate these two connection configurations. Both the PULSE2 and COMMON electrodes are used in either configuration. The PULSE1 electrode is required in a lead system that uses the sequential or simultaneous therapy current pathway, but it is not required when the single pulse therapy is used. When the PULSE1 electrode is not used, the 6.5 mm plug provided with the PCD device must be positioned in the lower left port of the connector block.

The COMMON, PULSE2 and PULSE1 lead connectors must be of the 6.5 mm style. If the lead connector is not the correct size, an adaptor designed for use in a 6.5 mm port must be positioned on the lead connector.

In either configuration shown in Figures 24 and 25, both a PACE/SENSE and a SENSE2 electrode are required. The PACE/SENSE and SENSE2 lead connector must be either the Medtronic low-profile bipolar or the IS-1[1] bipolar style. The PACE/SENSE electrode must be on the pin of the lead connector and the SENSE2 electrode must be on the ring of the lead connector. If two unipolar myocardial leads are used for pacing and sensing, insert their connectors into an appropriate adaptor that will fit into the PCD device's bipolar pacing/sensing port. See the appropriate lead technical manual for more details.

CAUTION: For questions about lead—pulse generator compatibility, consult your Medtronic representative or call Medtronic Technical Services at our 24-hour toll-free number, 1-800-328-2518.

1. IS-1 refers to a draft International Connector Standard (ISO/DIS 5841-3; 1989) whereby generators and leads so designated are assured of a basic mechanical fit.

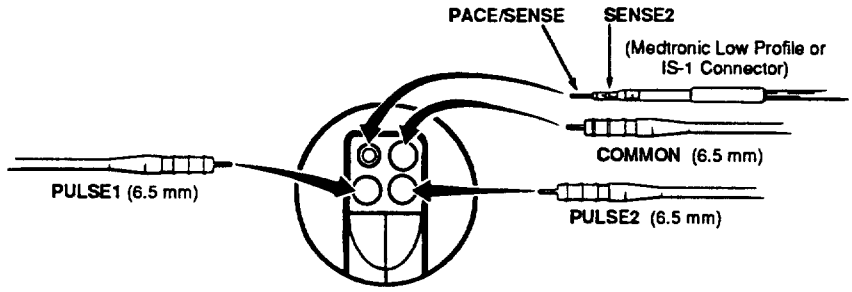


Figure 24. The Three Cardioversion/Defibrillation Electrode System

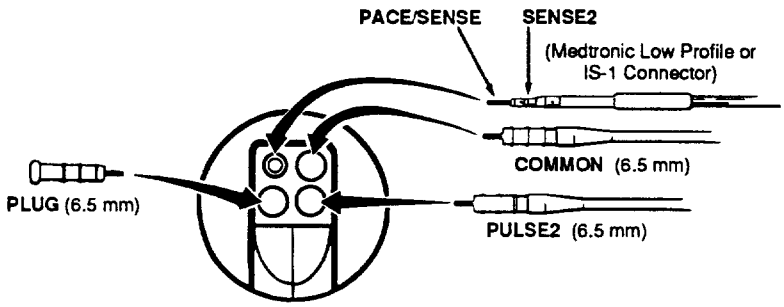


Figure 25. The Two Cardioversion/Defibrillation Electrode System

It should be noted that the insertion depth of an IS-1 lead pin is less than the insertion depth of a low-profile lead pin. The insertion mark for the IS-1 lead connector on the connector module (Figure 26) indicates that the IS-1 lead pin may not be inserted any further than the bar. Since the pin cavity is longer than the IS-1 requirement, the front part of the pin cavity will be empty when using an IS-1 lead.

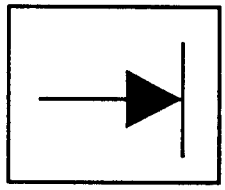


Figure 26

To connect each of the leads and plug, if required, to the PCD device:

1. Place a lead or plug into the appropriate port as shown in Figure 24 or 25.
2. Ensure full insertion of the connector pin by observing it protrude into the pin viewing area (i.e., beyond the metal block of the connector).
3. Pass the hex wrench through the associated grommet and tighten the setscrew securely by turning clockwise until tight. For the PACE/SENSE and SENSE2 connector, tighten both setscrews.

If there is difficulty with lead insertion due to the setscrew obstructing the port, turn the setscrew counterclockwise—but only until the port becomes clear.

> **CAUTION:** Counterclockwise rotation beyond this point may disengage the setscrew from the connector block.

The setscrews must be tightened securely using the hex wrenches provided with the PCD device. The hex wrenches are designed to yield at the handle when overtorqued, thus preventing damage to the socket of the setscrew. **Do not use Medtronic blue handled, right angle, or allen-type wrenches** since they possess torque capabilities far greater than intended for this device.

PCD System Evaluation

After connecting the leads to the PCD device, test the defibrillation efficacy of the PCD system. Before testing defibrillation efficacy, ensure an external defibrillator is charged for a rescue shock. Perform the following:

1. Program the PCD device to appropriately detect and treat the VF episode.
2. If using external fibrillation equipment, place the PCD device in magnet mode (VT and VF Detection are suspended).
3. Induce VF using external fibrillation equipment or the fibrillation feature present in the PCD device. If using external fibrillation equipment, apply the signal between the PACE/SENSE terminal of the PCD and an indifferent electrode attached to body tissue. The SENSE2 terminal may be used instead of the PACE/SENSE terminal with an indifferent electrode. See the appropriate programmer manual for specific instructions on inducing VF with the PCD device.

   > **CAUTION:** When using external fibrillation equipment, make only one connection to the PCD lead system. This connection should be disconnected immediately after VF is induced.

   > **CAUTION:** DO NOT MOVE THE PROGRAMMING HEAD from the beginning of detection through delivery of the shock. If the head is moved, remove it from the PCD device to allow the device to operate automatically. Replacing the head during the sequence may suspend VF Detection or abort the therapy.

4. After verifying sustained VF, press the CANCEL MAGNET key and then the PROGRAM key to allow automatic VF detection and therapy delivery to convert the arrhythmia.[1]
5. Observe the ECG signal and Marker Channel symbols for proper detection and therapy. Proper sensing following therapy delivery must be observed. Wait ten seconds after VF has been terminated before interrogating the device and printing a partial summary report of the data.
6. Program VT and VF Detection OFF before closing.

1. When using the fibrillation feature present in the PCD device, pressing the CANCEL MAGNET key and then the PROGRAM key prior to induction of VF will cause VF Detection to be enabled immediately after the end of the fibrillation sequence.

Placing the PCD Device

To ensure telemetry and programming function post-implant, the Model 7217B PCD device must be placed within 5 cm of the skin and with the engraved side facing toward the skin.

The Model 7217B PCD device has two suture holes located in the connector assembly. Use of these suture holes may help secure the device in the subcutaneous pocket, thus minimizing rotation and/or migration of the device post-implant. Penetration of the holes can be achieved with normally available surgical needles.

Closing

At closing perform or verify the following:

- All leads are sutured or positioned for chronic implant.
- All leads are fully inserted into the PCD device connector and all setscrews are tight.
- Place the PCD device in the pocket within 5 cm of the skin and with the **engraved side toward the skin.**
- Ensure that there are no kinks in the leads. If using separate PACE/SENSE and SENSE2 leads, lightly intertwine them with several twists.
- Close the pocket.
- Program VF Detection and Therapies ON.
- Interrogate the device and print a full summary to document the post-operative programmed status of the PCD device.

Replacing a PCD Device

To replace a Model 7217B PCD device:

1. Program VT and VF Detection OFF.
2. Carefully dissect the leads and the PCD device free from the surrounding tissues in the pocket. Be especially careful not to nick or breach the lead insulation inadvertently during the process of exposing the PCD system.
3. Insert the proper hex wrench through the slits in the rubber grommet and loosen the setscrew by turning counterclockwise.
4. Gently retract the lead connectors from the connector ports.
5. If any lead pin shows signs of pitting or corrosion, the entire lead should be evaluated and tested to assure the integrity of the system.
6. Take pacing, sensing, and defibrillation efficacy measurements.
7. Connect the leads to the replacement device.
8. Evaluate the defibrillation efficacy of the PCD system.
9. Place the PCD device and close.
10. Return the explanted device after cleaning/gas sterilizing to your Medtronic representative for device evaluation.

Implanting a PCD Device With a Chronic Lead System

When implanting a PCD device that connects to a chronically implanted lead system, evaluate the following to ensure the device will detect and treat ventricular arrhythmias appropriately:

1. Integrity of the chronic patch leads. Evaluate by chest X Ray, inspection, or test shock.
2. Chronic pacing and sensing measurements (see "Performing Pacing and Sensing Measurements" in "Implantation Procedure"). Repositioning the chronic leads or implanting new pacing/sensing or patch leads may be necessary.
3. Defibrillation efficacy (see "Defibrillation Efficacy Testing" in "Implantation Procedure"). Repositioning the chronic leads or positioning a third patch lead may be necessary to meet the defibrillation efficacy protocol (Figure 22).
4. VF sensing (see "Evaluating VF Sensing" in "Defibrillation Efficacy Testing"). Repositioning the chronic leads or implanting new pacing and sensing leads may be required.
5. Fit of the connectors in the PCD device (see "Connecting the Leads to the PCD Device" in "Implantation Procedure"). The leads must be properly inserted into the connector block for the device to function properly.

21. Please provide the P-values as listed in Table IV-B and IV-C of the original PMA application for the new patient population.

RESPONSE:

Comparison of Model 7216A and Model 7217B

Table IV-B summarizes the results of statistical analysis comparing the Model 7216A to Model 7217B. No parameters were found to be statistically significant between the two PCD™ models at a 0.05 significance level.

PCD™ Transvene™ System
7216A and 7217B
Summary of Variables Tested

CATEGORY	7216A	7217B	(b)(4)
Mean Age	62.4	59.4	
Number, % Male Number, % Female	15 83.3% 3 16.7	595 80.5% 144 19.5%	
Mean Ejection Fraction	37.8%	35.5%	
Primary Indication: SCD VT SCD & VT	 5 27.8% 8 44.4% 5 27.8%	 276 37.4% 369 49.9% 94 12.7%	
NYHA Classification: I/II III/IV	 15 83.3% 3 16.7%	 594 82.7% 124 17.3%	(b)(4)
Coronary Artery Disease	83.3%	73.9%	
Myocardial Infarction	83.3%	67.8%	
Congestive Heart Failure	16.7%	33.4%	
Cardiomyopathy	11.1%	31.9%	

Table IV-B: Summary of Variables Tested for Pooling 7216A AND 7217B -6/24/92

Lead Configurations

Table IV-C shows comparisons of patient variables for the three lead systems. This was done to document that there were no significant differences in patient characteristics between the implanted lead configurations.

PCD™ Transvene™ System
RV/SVC/SQ vs RV/CS/SQ vs RV/CS/SVC

CATEGORY	RV/SVC/SQ	RV/CS/SQ	RV/CS/SVC	(b)(4)
Mean Age	59.2	60.3	57.0	
Number, % Male Number, % Female	403 82.0% 93 18.0%	182 81.3% 40 18.7%	25 64.1% 14 35.9%	
Mean Ejection Fraction	36.2%	34.0%	35.8%	
Primary Indication: SCD VT SCD & VT	 187 36.05% 114 51.4% 28 12.6%	 80 37.7% 114 49.0% 28 13.3%	 14 35.9% 20 51.3% 5 12.8%	
NYHA Classification: I/II III/IV	 396 81.7% 89 18.3%	 180 84.9% 32 15.1%	 33 84.6% 6 15.4%	
Coronary Artery Disease	75.0%	73.0%	69.2%	
Myocardial Infarction	68.0%	68.8%	61.5%	
Congestive Heart Failure	35.1%	32.3%	30.8%	
Cardiomyopathy	140 28.2%	88 39.6%	10 25.6%	

Table IV-C: Summary of Variables Tested on Lead Configurations - 6/24/92

Of the variables analyzed in tables IV-C sex and cardiomyopathy showed a statistically significant difference between the three lead configurations at a 0.05 significance level. The difference in sex and percentage of patients with cardiomyopathy becomes insignificant when adjusting for multiple inference using the Hochberg procedure (Dunnett and Tamhane, "A Step-Up Multiple Test Procedure," Journal of the American Statistical Association, March 1992, 87:162-170).

22. **Please discuss the reasons why some patients dropped out of the study, either withdrawn alive or lost to follow-up. There were 224 patients at 1 month and only 154 patients at 3 months. Please explain the difference of 70 patients during this 2 month period.**

RESPONSE:

To be consistent with the rest of these deficiency responses, Medtronic has elected to answer this deficiency with the updated clinical data base. The clinical report presented as the response to deficiency #13 has 631 patients with a 1 month follow-up and 496 patients with a 3 month follow-up. This is a difference of 135 patients. Twelve of these patients died during this follow-up period and 5 were explanted because of device infection. Fifteen (15) patients missed their 3 month follow-up time window and were included in the 6 month window. The remaining patients were not lost to follow-up but had not yet reached the 3 month follow-up window.

23. For the comparison of complications/observations rates for the PCD™ versus the AICD™, please provide the following:

a. the number of complications and patients for the PCD™ and AICD™ populations;

b. the clinical success/failure criteria used for "Failure to Cardiovert/Defibrillate and Inappropriate Problematic VT/VF Therapy Delivery"; and

c. a discussion of the pocket infection rate of the PCD™ and the AICD™ and the lead related complications of the PCD™ Transvene™ System versus the PCD™ Epicardial System.

RESPONSE:

For the purposes of comparison of reported complications/ observations between the PCD Transvene System and the AICD Epicardial System, the AICD System patient population was that described in Winkle, et al, Long Term Outcome with Automatic Implantable Cardioverter-Defibrillator; JACC, May 1989; 13(6); 135-161. This article only discussed specific reported complications and not all reported complications. Thus, the total number of complications and patients cannot be provided. In the case of the PCD Transvene System, as of June 24, 1992, there have been 138 complications reported in 138 patients. For purposes of this PMA, complications were defined as a symptomatic or asymptomatic clinical event with potential adverse effects, which CANNOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

Failure to cardiovert/defibrillate was defined as the continuation of an **induced** ventricular tachyarrhythmia despite all cardioversion/defibrillation therapies having been delivered. This was due to increased cardioversion or defibrillation energy requirements caused by a change in the patient status or loss of integrity of the implanted defibrillation lead system.

Inappropriate or problematic VT/VF therapy delivery was defined as the delivery of VT and/or VF therapy in response to a rhythm other than VT or VF, such as atrial fibrillation with a rapid ventricular response, sinus tachycardia or device issues such as a loose set screw. In all cases, the PCD Device performed appropriately based

on the programmed VT/VF detection criteria however the delivery of therapy was not for an episode of sustained VT or VF.

In the Winkle, et al experience, information was only provided on the patients in whom pocket infection resulted in explant of the AICD System. The incidence of pocket infection that required explant of the AICD system was 2.2% In the PCD Transvene System, the incidence of pocket infection that resulted in explant of the implanted system was 2.0%. As a further reference, the incidence of pocket infection that resulted in the explant of the implanted system in the PCD Epicardial System was 1.9%. Thus the reported incidence of pocket infection was similar in all three patient groups.

For purposes of the PCD Transvene and Epicardial Systems, "Lead Related " complications includes lead dislodgement, lead fracture and perforation. Table 1 provides a comparison of the reported lead related complications in the two patient populations.

PCD Transvene System versus PCD Epicardial System Lead Related Complications 6/24/92		
Category	**PCD Transvene System (N=757)**	**PCD Epicardial System (N=742)**
Right Ventricle Perforation	5 (0.7%)	-
Subclavian Vein Thrombosis	1 (0.1%)	-
Patch Crinkling	7 (0.9%)	1 (0.1%)
Pace/Sense Lead System Fracture	-	7 (0.9%)
Lead Body Fracture	4 (0.5%)	4 (0.5%)
Lead Body Silicone Wear	-	2 (0.3%)
Lead Body Abrasive Wear	-	2 (0.3%)
Cardiac Vessel Abrasion	-	6 (0.8%)
Dislodgement	33 (4.4%)	7 (0.9%)
TOTAL	**50 (6.6%)**	**28 (3.8%)**

Table 1: PCD Transvene System versus PCD Epicardial System Reported Lead Related Complications - 6/24/92

Each system has specific lead complications related only to that system, however the incidence of lead dislodgement in the two patient groups was clinically different. In both systems, the clinical impact of a lead dislodgement is the potential for inappropriate therapy delivery, nondetection of VT/VF or ineffective VT/VF therapy for an episode of VT/VF. Also in both systems, reoperation is usually required to reestablish a lead system that provides adequate defibrillation efficacy. The incidence of lead dislodgement in the PCD Epicardial System was 0.9% while in the PCD Transvene System the incidence of lead dislodgement was 4.4%. This difference was not unexpected since in the PCD Epicardial System, the patch leads are usually physically sutured either to the epicardium or pericardium resulting in marked decrease in potential for dislodgement.

In the case of the PCD Transvene System, there were typically two or perhaps three transvenous leads implanted. Though the leads are secured by suturing the anchoring sleeve at the venous entry site,

they are more suspectable to dislodgement due to patient activity, particularly movement of the upper extremities.

Lead dislodgements are not specific to the PCD Transvene System and have been reported with dual chamber pacemakers and the current market released implantable cardioverter defibrillator (ICD) system. The early history of dual chamber pacemakers demonstrated a high lead dislodgement rate of at least 20%. (Smyth PND, et al. Permanent pervenous atrial sensing and pacing with a new J-shaped lead. J Thoracic Cardiovascular Surgery 1976;72:565-570.) Winkle, et al reported that the incidence of dislodgement of the superior vena cava spring leads used with the current market release ICD System to be 6.3% (Winkle, et al. Automatic Implantable Cardioverter-Defibrillator: Efficacy, Complications and Survival in Patients with Malignant Ventricular Arrhythmias. JACC Vol.11. No.6 June 1988: 1278-86).

In 47 patients (53%) the lead dislodgement was identified prior to the patient's discharge from the hospital. Therefore more than half of the dislodgements were identified prior to the patient being in an outpatient setting where the risks of a lead dislodgement are greater. None experienced an episode of spontaneous VT/VF prior to the identification of the lead dislodgement.

In the remaining 40 patients, 21 patients experienced spontaneous VT episodes and 24 experienced spontaneous VF episodes prior to diagnosis of the lead dislodgement. The spontaneous VT episode efficacy was 97.9% and the spontaneous VF episode efficacy was 99.3% None of these episodes required Therapy #4 for successful termination. None of patients experienced episodes of VT/VF where the PCD Transvene System was ineffective in terminating the episode due to the lead dislodgement.

Though the incidence of dislodgement was higher in the PCD Transvene System, the clinical outcome was identical in the two patient groups - there have been no reported patient deaths secondary to a lead dislodgement in either patient group.

24. **Some Transvene™ patients were also evaluated with the Model 10388 hollow can electrode. Please compare the infection rate of these patients to those who did not undergo the hollow can evaluation.**

RESPONSE:

Pocket infection was reported in 23 of the 757 patients (3.1%) who received a PCD Transvene System patients. In 15 of the cases (2.0%), all of which were classified as complications, the pocket infection resulted in explant of the entire implanted PCD Transvene System. Four of the patients subsequently had a new PCD Transvene System implanted while the remaining patients still have not had a new system implanted. In 8 cases classified as an observation, the infection was successfully treated with antibiotic therapy. **As of the date of this report, none of the thirty patients who were evaluated with the Model 10388 hollow can electrode developed a pocket infection.** These patients will continue to be monitored and the incidence of pocket infection will continued to be reported to the agency in subsequent submissions.

25. Please discuss and/or provide the following regarding the 1 year actuarial survival comparison of mortality between the PCD™ and the AICD™:

a. the statistical test that was used to compare survival; and

b. the two survival or life tables by year of follow-up.

RESPONSE:

For purposes of comparison, the Ventak-P Epicardial System patient population described in the Summary of Safety and Effectiveness Data (PMA Application Number P890061) dated May 2, 1991 was used. A copy of this summary was obtained through the Freedom of Information Act.

In order to compare the PCD Transvene System one year sudden cardiac death and overall survival to the Ventak-P Epicardial System, a confidence interval analysis was performed which indicated there was a statistical difference in the reported overall mortality. [PCD Transvene System = 95.6%; Ventak-P Epicardial System = 90.8%]

The Ventak-P Epicardial System summary only provided one year sudden cardiac death and overall survival. Information was not provided on when the patient deaths occurred or individual implant duration for patients who received a Ventak-P Epicardial System. Therefore, we are unable to provide survival or life tables by year of follow-up for the Ventak-P Epicardial System.

26. Please discuss the statistical techniques used to derive the P-values in Table XI G-2, page 862, Vol. 5 and Table J-2, page 54, Vol. 1.

RESPONSE:

The information contained in Tables J-2 (page 54) and XI G-2 (page 862) from volume 1, provide the survival probability at one year for the various categories and conditions presented in each table. The unique feature of survival analysis is that it permits the estimation and comparison of groups survival experience during the follow-up (in this case one-year) and may be used for the analysis of any dichotomous response variable such as a nonfatal or an adverse effect. In this situation the probabilities represent the percentage of patients in the specified category who are alive at one-year.

The survival probabilities in these two tables were estimated using the Cutler-Ederer or otherwise referred to as the actuarial method. The Cutler-Ederer procedure is a widely accepted method which estimates survival probabilities uniformly across time. The P-values were calculated using the Wilcoxon survival test which compares the overall survival experience between groups. If a P-value was 0.05 or less the comparison was classified as being statistically different. All calculations were conducted using the statistical software SAS.

References:

Friedman, L.M., Furberg, C.D., DeMets, D.L. (1985). Fundamentals of Clinical Trials. Littleton, MA: PSG Publishing Company, Inc., pg. 191-211.

Lee, E.T. (1980). Statistical Methods for Survival Data Analysis. Belmont, CA: Lifetime Learning Publications, pg. 88-96, 123-127.

Woolson, R.F. (1987). Statistical Methods for The Analysis of Biomedical Data. Wiley, New York, pg. 442-464.

ADDITIONAL DEFICIENCIES

1. **Discuss the properties of polyurethane which make it the ideal insulation material for the 6966 lead. Why was silicone not chosen?**

RESPONSE:

The Model 6966 is a tripolar lead intended for transvenous implantation into the right ventricle. For this purpose design characteristics which are conducive to small diameter leads are important. Polyurethane offers unique combinations of physical properties needed for implantable devices such as cardiovascular leads. Among these are, elasticity and strength. Polyurethane has distinct advantages with regards to these characteristics over silicone for a tripolar lead design. These are discussed below.

1) The modulus of elasticity of polyurethane is greater than silicone. This means that the insulation material absorbs more of the force that the lead is subjected to in situ, and less of the force is transferred to the coil and other components of the lead.

2) The strength of a given cross-sectional area of polyurethane is greater than that of an equivalent cross-sectional area of silicone. This allows the use of thinner tubing when using polyurethane as the insulation material which translates into smaller diameter leads. In addition, the greater strength of polyurethane facilitates the torque transfer from connector pin to helix. This is necessary for extension/retraction of helix electrode leads such as the Model 6966.

In addition, both (b)(4) and (b)(4) polyurethanes used in the Model 6966 lead have been used for other, Medtronic, commercially available, implantable, cardiovascular leads. Polyurethanes have been shown to be biocompatible, and enhancements in processing have significantly reduced the potential for metal induced oxidation (MIO) and environmental stress cracking. Furthermore, polyurethanes offer other material properties such as, elongation, flexibility and low thrombogenicity which makes them suitable for cardiovascular leads.

2. **Discuss the biostability tests (stress cracking, metal induced oxidation, etc.) performed on the (b)(4) polyurethane. Why was a different polyurethane chosen for the inner coil?**

RESPONSE:

Biostability testing performed on the two types of polyurethane is discussed in detail in Appendices 1 and 2. This includes testing on polyurethane (b)(4) and (b)(4) Extensive testing has been performed and results have demonstrated the biostability of both (b)(4) and (b)(4)

Polyurethane (b)(4) was chosen for the inner coil of the 6966 lead because its design was based on another lead with an extendable/retractable helix electrode, specifically the Model 4058M lead. The Model 4058M is comprised of (b)(4) for the inner insulation and (b)(4) for the outer insulation. This combination of insulation materials allows for a small diameter, flexible, screw-in lead with acceptable torsional (torque transfer) characteristics comparable to a unipolar screw-in polyurethane lead.

Specifically, the stiffness imparted to the inner coil due to the use of (b)(4) as the inner insulation, facilitates torque transfer. However, if the entire lead was comprised of (b)(4) it would be too stiff. Therefore, (b)(4) insulation was chosen to maintain flexibility of the lead.

Additional information on biostability testing is presented below.

Background

Medtronic performs in-depth reliability assurance testing on all cardiac pacing leads. The nature of the testing is such that an overall assessment of lead safety or integrity can be determined from it. Since one of the Transvene leads, Model 6966, is a pace/sense lead in addition to being a cardioversion/defibrillation lead, it was evaluated in a manner similar to other pacing leads in addition to specific testing designed to assess effects of cardioversion/defibrillation (as were the other Transvene leads, Models 6963 and 6999).

Testing consisted of electrical and mechanical evaluation, flexing of coils and insulated lead bodies, tensile strength testing, stiffness evaluation, leak testing, biocompatibility and biostability testing. This is consistent with all bradycardia (brady) pace/sense leads. Regarding cardioversion/ defibrillation capabilities, the Model 6966/6884 was also subjected to a

series of accelerated, in-vitro tests specifically designed to simulate severe, potential, implant conditions. This included high voltage multiple pulse discharge testing and high voltage crush testing. Data demonstrated that the Model 6966/6884 lead satisfies device design requirements for cardioversion/defibrillation, in addition to pacing/sensing, and is therefore acceptable for its intended application.

A specific test was performed to evaluate the polyurethane insulation of the Model 6966/6884 lead. This was the standard, (b)(4) day, (b)(4) test modified to include high voltage shocking.

The rationale for performing (b)(4) testing via a modified process to include high voltage shocking is as follows. The standard, Medtronic (b)(4) protocol was modified to include high voltage (b)(4) shocking in order to evaluate the effects (if any) voltages in excess of typical brady pacing voltage (e.g., (b)(4) would have on the polyurethane insulation while it was subjected to the accelerated bench testing. (b)(4) shocks was selected because it is approximately (b)(4) times the estimated life of present-generation, implantable, cardioversion/defibrillation devices.

Metal Induced Oxidation

The (b)(4) day (b)(4) test was developed as an accelerated, in-vitro (bench) test to evaluate metal-induced oxidation (MIO) in polyurethane leads. Significant data related to polyurethane degradation mechanism and how to prevent (minimize) it has been provided to FDA over the years. A detailed, chronological discussion which describes polyurethane lead history and research regarding MIO as a degradation mechanism is provided in Appendix 1.

The (b)(4) test method includes visual and microscopic examination and electrical impedance measurements every (b)(4) days throughout the (b)(4) day test period in order to assess the lead integrity.

The lead integrity requirements relative to (b)(4) testing for defibrillation leads are identical to those for brady leads. That is, no visible sign(s) of MIO after (b)(4) days in (b)(4) In addition, there must be greater than (b)(4) impedance as measured between conductors.

(b)(4) testing of the Model 6966/6884 has shown no degradation (cracking or breaching) after (b)(4) days in (b)(4) (standard testing time). These results are similar to other leads with (b)(4) conductor coils.

Additional (b)(4) information is provided below.

(b)(4) History/Test Development

In the early 1980s, when Medtronic became aware of the problem with the Model 6972 leads, preliminary conclusions indicated that (b)(4) were a potential cause of polyurethane degradation. Subsequent research over the years has demonstrated that certain metal ions, such as the those found in (b)(4) conductor coils, in contact with polyurethane can cause degradation. More recently, research has shown that an effective method for preventing metal ion-polyurethane contact (and therefore degradation) is through the use of a barrier coating between the conductor coil and insulation. An effective barrier coating is platinum. It is precisely for this reason that Medtronic has been designing new polyurethane leads, including the Model 6966/6884, with platinum sputtered (barrier coated) conductor coils.

(b)(4) has very stringent test requirements. Specifically, lead samples evaluated in (b)(4) are required to show no signs of MIO, in order to satisfy design requirements. Samples must be free of any sign(s) of MIO as examined visually (b)(4) after (b)(4) days in (b)(4) That is, there must be no evidence of MIO after (b)(4) days in (b)(4) Therefore, there is not a statistical confidence level associated with the results. Over the years, (b)(4) sample sizes have varied from (b)(4) test units.

It should be noted that over the past (b)(4) years (approximately) Medtronic has been designing cardiovascular leads with barrier coated (platinum sputtered) conductor coils. Since then, design assurance testing for new leads has included (b)(4) testing. Some of the recently designed leads subjected to (b)(4) testing and FDA approved or judged substantially equivalent are:

Models 4004/4504, P830061/S6, Feb. 10, 1989
Models 4082/4582, K896313, March 6, 1990
Model 4023/4523, P830061/S10, August 7, 1991
Model 4024/4524, P830061/S12, August 19, 1991

All of these leads (totaled in excess of (b)(4) samples) showed no failures (insulation breaches) or visual evidence (cracks) of MIO degradation after (b)(4) days in (b)(4) All of these leads were still functional after (b)(4) days in (b)(4) The sum total of barrier coated polyurethane leads evaluated in (b)(4) over the past (b)(4) years is significantly more than (b)(4) samples; all of them have demonstrated that a barrier coating, such as a

platinum sputter coating, effectively eliminates, or at least minimizes, MIO by simply preventing the (b)(4) conductor coil from direct contact with the polyurethane insulation.

In setting up the (b)(4) test of the Model 6966/6884 leads it was apparent that the lead design, from a materials perspective (e.g., the conductor coil, insulation, etc.), was very similar to the previously tested leads (Models 4004/4504, etc). Therefore, it was reasonable to expect similar (b)(4) test results. Nonetheless, (b)(4) Model 6966/6884 lead samples were subjected to testing according to design assurance requirements. Given the relatively high confidence established over the past (b)(4) years that platinum sputtered conductor coils will remain functional and free of MIO after (b)(4) days in (b)(4) (b)(4) Model 6966/6884 samples were considered sufficient for testing.

After (b)(4) days in (b)(4) the (b)(4) Model 6966/6884 leads did not have any visual evidence (cracks) of MIO degradation. All leads were still functional after (b)(4) days in (b)(4) These results were in keeping with all other platinum sputtered, barrier coated leads previously tested in (b)(4)

Environmental Stress Cracking

Additional testing applicable to the biostability of the Transvene leads consists of environmental stress cracking (ESC) evaluation. Significant testing of transvenous, polyurethane leads and prototype leads (comprised of (b)(4) and (b)(4) as the 6966 lead is) has demonstrated that leads that incorporate state-of-the-art processing enhancements, i.e., barrier coating and thermal annealing in an inert environment, exhibit minimal ESC and MIO. ESC testing, as well as additional MIO testing, is discussed in detail in Appendix 2.

Conclusions

With respect to biostability of the Model 6966/6884 lead, barrier coated (platinum sputtered) (b)(4) (b)(4) coils have been shown to be effective in preventing direct contact between polyurethane insulation and (b)(4) coils, and therefore, MIO degradation in the Model 6966/6884 cardioversion/defibrillation lead. Additionally, thermal annealing polyurethane leads in an inert environment (as the Model 6966/6884 lead is) has been shown to significantly minimize ESC.

3. Based on the results of the life test, what is the life expectancy of the leads? Please include your assumptions.

RESPONSE:

The purpose of this life test, also referred to as "Lead System Testing," was/is to simulate extreme conditions for a relative measure of the effect of the combination of flexing and high-energy pulsing on the electrical and mechanical performance of the lead. It was/is not intended to correlate to lead life expectancy.

However, during the development of the investigational protocol for the NTL leads, we were encouraged by the FDA to develop a test model whereby the transvenous lead system was evaluated under extreme conditions. Subsequently, the life test as presented in this PMA (and several Medtronic NTL IDE supplement submissions) was developed.

Results of the multiple-pulse, high voltage pulsing in conjunction with flex testing, and crush testing demonstrated that electrical shock, mechanical flexing and crushing yield acceptable lead performance.

The system testing, is consistent with the flex testing presented in the non-clinical bench testing section of the Transvene PMA. Additionally, the system testing is consistent with the long-term field experience for the Model 6907, which is the basis for the flex life test requirement of (b)(4) cycles. Note that the Model 6907 has more than twenty years field experience. Of approximately (b)(4) sold, only (b)(4) coil fractures have been reported in this time (b)(4) Therefore, any lead with flex life equal to or greater than the Model 6907 is considered safe and effective for its intended use.

4. Provide a side-by-side comparison between the Model 6999 and the epicardial patch lead.

RESPONSE:

A side-by-side comparison is presented below of the Model 6999 and the medium epicardial patch, Model 6921M. The Model 6999 has (b)(4) embedded throughout the silicone to provide a sightly stiffer backing for the subcutaneous placement of the lead. The Model 6921 has an embedded (b)(4) around the outer electrode coil loop, and slightly thinner silicone adhesive for a more flexible patch to facilitate placement either extra or intra pericardially.

Model 6999 - Model 6921 Comparison

	Model 6999	Model 6921M
Polarity:	(b)(4)	
Placement:		
Fixation:		
Length:		
Materials: • Conductor Coil • Insulator • Electrode Coil		
Electrode Area:		
Lead Body Diameter:		
Patch Thickness:		
Connector:		
Wire Characteristics: • Conductor • Electrode		

5. Discuss the possible interactions between implanted pacemaker leads and the Transvene™ leads. Also, discuss the effects of the leads on the tricuspid valve and the host vein.

RESPONSE:

In the PCD Transvene System patient population of 757 patients, (b)(4) (b)(4) patients who had previously implanted bradycardia pacemakers retained these devices post implant of the PCD Transvene System. (b)(4) patients the device was a DDD pacemaker, (b)(4) patients a DDD-R pacemaker, in (b)(4) patient a VVI-R pacemaker and in the final patient a AAI pacemaker.

Clinical experience with (b)(4) patients indicates that bradycardia pacemakers, including dual chamber devices, can be safely implanted in conjunction with a PCD Transvene System

The PCD device technical manual recommends that if the patient meets the PCD device implant criteria the physician should explant a previously implanted pacemaker and remove or cap the leads. However if the pacemaker must be retained due to conduction disease or for hemodynamic reasons the following recommendations are provided:

- If a unipolar pacemaker is implanted, it must be explanted.
- If a previously implanted pacemaker has a switchable polarity option, it must be programmed to the bipolar configuration.
- If a previously implanted pacemaker with a switchable polarity option has the potential to be reset to the unipolar configuration by defibrillation shocks, it should be explanted.

If the bradycardia pacemaker is to remain implanted, evaluations are performed to ensure that there are no deleterious interactions between the devices. In particular, it should be demonstrated that the PCD device does not sense pacemaker output pulses when the pacemaker is programmed to its maximum output amplitude and pulse width and when the PCD device is programmed to a sensitivity of 0.3 mV for testing.

To avoid inappropriate interaction between the two devices, the bradycardia pacemaker should be programmed to the minimum selectable rate, pulse width, amplitude and least sensitive setting clinically possible.

Finally, the bradycardia pacemaker lead system should be carefully monitored to ensure that defibrillation shocks do not result in loss of output or capture from the pacemaker.

Possible interactions between implanted pacemaker leads and the PCD Transvene Lead System are as follows:

Physical Interaction

Possible insulation wear from the contact and movement between the leads could occur. This had not occurred,however, in the PCD Transvene System Study among the 16 patients who have a concomitant bradycardia pacemaker.

There is a potential risk of subclavian vein thrombus. There were 4 patients who developed a subclavian vein thrombus in this study. These patients, however, did not have a concomitant bradycardia pacemaker.

Electrical Interaction

Possible damage to pacemaker leads from defibrillation shocks could occur. There have been no reported incidents of this occurring in this subgroup of patients. The bradycardia pacemaker lead system should be carefully monitored to ensure that the defibrillation shocks do not result in loss of output or capture from the pacemaker.

If the bradycardia pacemaker is to remain implanted, evaluations are performed to ensure that there are no deleterious interactions between the devices. In particular, it should be demonstrated that the PCD device does not sense pacemaker output pulses when the pacemaker is programmed to its maximum output amplitude and pulse width and when the PCD device is programmed to a sensitivity of 0.3 mV for testing.

There have been no reports of inappropriate interaction between the PCD and bradycardia device in the 16 patients in whom the bradycardia device was retained after the PCD Transvene System was implanted.

Possible Effects on Tricuspid Valve and Host Vein

Possible effects of the leads on the tricuspid valve include injury, rupture, dissection, or damage to the valve. There have been no reported Complications or Observations involving the tricuspid valve in this study, acutely or chronically, nor have there been reported problems related to the tricuspid valve as of 6/24/92.

Possible effects of the leads on the host vein include injury to the vessel, perforation, claudication, and clot formation. There have been 4 patients who developed a subclavian vein thrombus. One patient required explant of the leads and the other 3 patients received thrombolytic therapy with resolution.

6. **The Transvene™ leads seem to tolerate crush testing better than the pacing leads. Please discuss the properties of the Transvene™ leads which support this capability.**

RESPONSE:

There is no data available that allows for a comparison of the crush resistance of the Transvene leads to other commercially available leads. Medtronic makes no claims relative to crush testing/resistance of the leads.

6. **The Transvene™ leads seem to tolerate crush testing better than the pacing leads. Please discuss the properties of the Transvene™ leads which support this capability.**

RESPONSE:

There is no data available that allows for a comparison of the crush resistance of the Transvene leads to other commercially available leads. Medtronic makes no claims relative to crush testing/resistance of the leads.

7. Are there patients currently implanted with the Model 6895 and 10317 patch leads? If so, please provide a breakdown of the clinical data, e.g., complications, survival, etc. for each lead.

RESPONSE:

Of the 757 patients who received a PCD Transvene System, 718 patients have an implanted lead system which incorporates a subcutaneous patch electrode. Of these patients, 5 patients (0.7%) have a Model 10317 subcutaneous patch electrode, 249 patients (34.7%) have a Model 6895 subcutaneous patch electrode and 464 patients (64.6%) have a Model 6999 subcutaneous patch electrode.

The incidence of potentially patch related complications and observations in this patient group was evaluated. The overall incidence of seroma at the subcutaneous patch site was 1.1%, the overall incidence of hematoma at the subcutaneous patch site was 1.4% and the overall incidence of subcutaneous patch crinkling was 1.7%. Table 1 provides the incidence of these complications and observations by implanted subcutaneous patch lead model. There was no difference in the incidence of reported complications and observations based on the lead model implanted.

PCD Transvene System Patch Related Complications and Observations						
Category	**Model 10317 (N=5)**		**Model 6895 (N=249)**		**Model 6999 (N=464)**	
	Complication	**Observation**	**Complication**	**Observation**	**Complication**	**Observation**
Seroma	(b)(4)					
Hematoma						
Patch Crinkling						
TOTAL						

(b)(4)

Table 1: PCD Transvene System - Patch Related Complications and Observations - 6/24/92

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8. Please list the reasons for not performing pre-hospital discharge testing.

RESPONSE:

The Pre-Hospital discharge evaluation is performed to assure the implanted PCD™ Transvene™ system is performing properly. This is usually the first time ventricular tachycardia detection and therapies are evaluated and is also an appropriate time to assure ventricular fibrillation detection and therapy parameters are programmed appropriately. Evaluating these programmable parameters involves induction of ventricular tachyarrhythmias and titration of programmed parameters.

There are a total of 753 Pre-Hospital Discharge forms included in this clinical report representing 719 patients. Patients have multiple Pre-Hospital Discharge forms if they were readmitted for system modification after the initial implant procedure. Thirty-eight patients did not have a Pre-Hospital discharge form. Sixteen of these 38 patients had a subsequent follow-up form, because their hospital stay was long enough to be in the 1 month follow-up window. The remaining patient's Pre-Hospital Discharge form was not entered into the PCD™ data base before the data cutoff for this analysis. All patients are evaluated by the investigator before hospital discharge to determine if the patient's condition and the device operation are appropriate for hospital discharge.

Six-hundred (600) or 79.7% of these 753 Pre-Discharge evaluations had either ventricular tachycardia or ventricular fibrillation induced and the corresponding therapies evaluated.

The reasons for not performing inductions include:

- Adequate Implant Testing: If the patient is a primary ventricular fibrillation patient and the implant defibrillation therapy efficacy was within acceptable limits, the investigator often elects not to subject the patient to additional episodes of ventricular fibrillation.

- Previous implant: If a patient was receiving a device after having a previous device explanted and had demonstrated therapeutic efficacy with previous programming, the investigator could elect not to subject the patient to additional tachyarrhythmic episodes.

- Patient request: Some patients do not want additional inductions beyond the absolute minimum to assure efficacy. If implant defibrillation efficacy was known and the patient had extensive preimplant electrophysiologic testing, the investigator may agree with this patient request.

- Postponement: If the patients underlying medical condition is such that induction of tachyarrhythmias would pose a significant health risk, the investigator may elect to postpone additional inductions until the patient's condition improves.

The PCD™ study protocol asks that patients be induced at the pre-hospital discharge evaluation, and the majority do (79.7%), the primary responsibility for patient care rests with the physician investigator. The very high 1 year sudden cardiac death survival rate of 99.8% indicates that the PCD™ Transvene™ is being evaluated and followed to an appropriate level. The PCD™ Transvene™ system and the implant and follow-up procedures used in this clinical study have been demonstrated to provide safe and effective treatment for serious life threatening ventricular tachycardias.

9. The number of spontaneous episodes of the patients followed for 6 months and beyond should be provided.

RESPONSE:

A total of 329 patients with the PCD™ Transvene™ System have been followed for a minimum of 6 months or beyond. There has been a total of 3752 spontaneous episodes of VT in 130 patients (39.5% - 130/329) with an overall efficacy rate of 99.0% and 667 spontaneous episodes of VF in 120 patients (36.5% - 120/329) with an overall efficacy rate of 98.7%.

Table 9-1 presents the total number of VT episodes that were treated with a specific therapy type (Ramp, Burst, or Cardioversion) and how effective that therapy type was in terminating the episode. Also included in this table is the number of episodes (# success) successfully treated by all four therapies.

PCD™ Transvene™ System Spontaneous VT Episodes Therapeutic Efficacy			
	# Success	**# Episodes**	**% Success**
Ramp	2046	2244	91.2%
Burst	1432	1558	91.9%
Cardioversion	235	276	85.1%
	# Success	**Cumulative #**	**Cumulative %**
VT Therapy #1	3474	3474/3752	92.6%
VT Therapy #2	158	3632/3752	96.8%
VT Therapy #3	59	3691/3752	98.4%
VT Therapy #4	22	3713/3752	99.0%

Table 9-1: PCD™ Transvene™ System - Spontaneous VT Episodes Therapeutic Efficacy

Table 9-2 presents the total number of VF episodes (# success) successfully treated by all four therapies.

PCD™ Transvene™ System Spontaneous VF Episodes Therapeutic Efficacy			
	# Success	Cumulative #	Cumulative %
VF Therapy #1	563	563/667	84.4%
VF Therapy #2	72	635/667	95.2%
VF Therapy #3	19	654/667	98.1%
VF Therapy #4	4	658/667	98.7%

Table 9-2: PCD™ Transvene™ System - Spontaneous VF Episodes Therapeutic Efficacy

10. A copy of the Summary of Safety and Effectiveness with the updated clinical data should be submitted.

RESPONSE:

An updated Summary is provided, see Volume 1 of this Amendment. This includes updated clinical data, bench test and canine data.

None clinical

Append,

(b)(4) and (b)(4) Biostability

(P830061/S6)

Reference Document Control Number P830061/S6,
FDA approved on February 10, 1989.

(b)(4)

(b)(4)

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e. Biostability

Introduction

The objective of this section is to present information relative to the biostability of Medtronic polyurethane cardiac pacing leads.

First, a history of polyurethane cardiac pacing leads will be presented. This includes discussion of Medtronic's first polyurethane lead products and relevant field performance. An overview of Medtronic's field performance data base is also included. The primary polyurethane failure mechanisms will be discussed in general, and then specifically, as they relate to individual lead models. This will be followed by a detailed discussion of the unipolar and bipolar (atrial and ventricular) polyurethane lead products comparing configuration, materials and processes as they have changed, i.e., been improved over time. Lead characteristics will also be related to field performance.

Following configuration, materials and processing features and field data, will be a discussion of lead failure mechanisms and accelerated test procedures for their evaluation. This includes recent polyurethane lead research and results, both in-vitro and in-vivo testing methods and rationale. Models 4004/4504 biostability data are then presented.

Finally, conclusions relative to the Models 4004/4504 and the supporting biostability data will be clearly established.

The intent of the discussion is to put into perspective the implementation of lead improvements as they were validated over time. That is, Models 4003/4503 utilized the state-of-the-art in configuration, materials and processes, and now, approximately three years later, Models 4004/4504 are incorporating more recent state-of-the-art lead technology.

Summary: History of Polyurethane Pacing Leads

Polyurethane elastomers have been extensively studied and evaluated for use in implantable devices. Polyester polyurethanes were of major interest in the artificial heart program in the 1960s but lacked the necessary hydrolytic stability. Polyether polyurethanes (e.g., (b)(4) (b)(4) were introduced in the early 1970s. These polymers are hydrolytically stable under implant conditions and offer unique combinations of physical properties needed for implantable devices such as pacing leads. These properties include high tear strength, tensile strength, elongation, modulus of elasticity, flexibility and low thrombogenicity, etc.

The first human implant of a permanent polyurethane insulated lead occurred in 1975. This was a neurologic device insulated with (b)(4) (b)(4) The first cardiac pacing leads (b)(4) (b)(4) were implanted in humans in 1977. Four models (Medtronic Models 6971, 6972, 6991U and 6990U) were released to the U.S. market in April-June, 1980. The "market release" of these devices was based on human clinical and canine studies as well as extensive biocompatibility and biostability tests of the materials per se.

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The performance of these early polyurethane insulated leads appeared to be excellent. On May 15, 1981, Medtronic received their first explanted lead (a Model 6991U) exhibiting signs of what now is known to be an environmental stress cracking phenomenon, (ESC), previously unknown in this type of polymer. ESC is defined as the generation of cracking or crazing of lead insulation in-vivo in the presence of excess stress. As of today, leads made by improved processes are known to have dramatically reduced ESC failures. Several Model 6972 leads were returned in late 1981 that had ESC failure at the site of fixating ligatures. An anchoring sleeve was placed on the lead (instead of separately placed in the package) as of February, 1982 to protect the lead from ligature induced ESC.

In late 1982-early 1983 it was discovered that some other additional mechanism (not ESC) was causing degradation of the polyurethane inside Model 6972 leads. This mechanism was subsequently identified as metal induced oxidation (MIO), generally associated with leakage of body fluids into the lead lumen and with the presence of metal ions and/or metal ion complexes such as the conductor coil and polyurethane tubing. MIO results in oxidative degradation of the polyurethane insulation

material. This mechanism was also previously unknown in polyurethanes. Meanwhile, as demonstrated by acceptable human clinical performance, the biostability of other (b)(4) (b)(4) insulated leads (including the Model 6971, the unipolar version of the Model 6972) continued to be excellent. Figure IV in the Medtronic Product Performance Report, June 1988, see Appendix A, presents unipolar and bipolar ventricular lead survival probabilities. Note that all leads except Models 6972 and 4002 (a variation of the 6972) have demonstrated survival probabilities comparable to the silicone lead Models 6961/6962.

Differences in insulation failures and ultimately lead failure rates between unipolar and bipolar leads can be attributed to configuration differences. A bipolar lead is more complex than a unipolar lead. Bipolar leads have two conductor coils and therefore two insulators (inner and outer), and more joints. Therefore, they are more susceptible to fluid leakage and/or compromised bond joints. Note the following configuration differences between Medtronic bipolar (Model 6972) and unipolar (Model 6971) pacing leads.

Model 6972 insulation minimum wall thickness was (b)(4) for both outer and inner tubings, whereas the Model 6971 minimum wall thickness was (b)(4) In other words, the Model 6971 was (b)(4) that of the inner or outer insulations of the Model 6972. Thicker insulations are known to be more resistant to tubing failure mechanisms.

In addition to polyurethane failure mechanisms, the thinner insulations of the Model 6972 were more susceptible to stylet perforation as well as scalpel cuts, nicks, etc., encountered at implant, and also suture damage if anchoring sleeves were not used. In all of the above circumstances, the Model 6971 was more resistant to failure due to its thicker insulation.

The potential for interference fit, that is tubing with an inner diameter smaller than the coil outer diameter, was more constrictive (smaller) for the 6972 than the 6971. Outer coil to outer tubing minimum clearance was (b)(4) and inner coil to inner tubing minimum clearance was (b)(4) for the 6972. For the 6971, the minimum clearance was (b)(4)

Sale of the Models 6971/6972 were discontinued in 1985/1984, respectively. Even though the

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Model 6971 continued to perform well, sales were discontinued due to the introduction of the Target Tip® family of pacing leads, Models 4011, 4012 (ventricular) and 4511, 4512 (atrial). The Target Tip family continues to demonstrate excellent performance. Reference Figures IV and V, Medtronic Product Performance Report, Appendix A.

Appendix B contains additional information on the performance of Medtronic pacing leads.

Monitoring Lead Field Performance

Medtronic monitors the human field performance of implantable pacing leads through three different sources: 1) Returned Product Analysis (RPA), 2) Medtronic CardioCare telephone monitoring service, and 3) a multi-center (eleven) U.S. clinical study of lead performance referred to as the Chronic Lead Study (CLS). Thorough descriptions of these sources are presented in Medtronic's Product Performance Report (Appendix A).

Relevant data from the CLS and RPA are presented in this biostability section as they relate to long-term lead performance. The CLS uses

clinically derived actuarial data to track and monitor real-time lead performance. In some cases the quantity of leads sold is relatively small and the minimum number of implants for statistically significant data are not yet available (Models 4003/4503, 4016, 4016A) and, therefore significant survival probabilities are not available. The RPA data base examines electrical and visual characteristics of leads, primarily to identify failure mechanisms. However, since leads are commonly not removed, RPA data cannot be used for monitoring the survival probabilities of leads.

Models 4003, 4503 As State-of-the-Art

Data from the Product Performance Report demonstrate the excellent performance of Medtronic's polyurethane pacing leads. With the exception of Models 6972, 4002 and 6991U, all bipolar and unipolar leads perform well. Complications with these models are related primarily to the insulation and have since been corrected. Several configuration, material and process conditions were subsequently modified after Medtronic's experiences with the Models 6971/6972 and 6991U. These conditions were as follows:

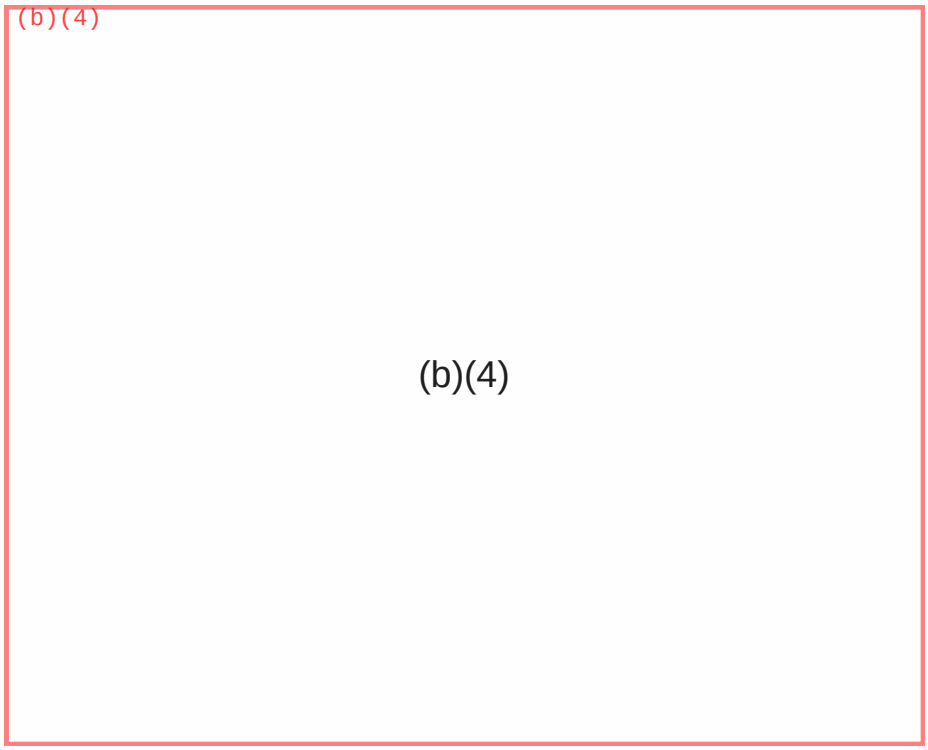
- Use of thicker insulation (tubing).
- (b)(4) (b)(4) for conductor coils versus (b)(4) (b)(4)
- Thermal annealing versus solvent stress relieving of insulation and/or the assembled device. Typically polyurethane tubings were solvent stress relieved and lubricated in order to facilitate manufacture of the lead. However, newer configurations (b)(4) (b)(4) lead tubing prior to or after device assembly to relieve residual stress thereby minimizing the potential for ESC.
- Assured clearance between insulation and conductor coil versus potential for interference fit.

The Models 6957/6957J incorporated thicker insulation and (b)(4) (b)(4) of tubing. The Models 4011/4511 and 4012/4512 incorporated thicker insulation and (b)(4) (b)(4) of the assembled device. As shown in the Product Performance Report (Figures IV and V), these leads are performing well.

Survival probabilities of unipolar leads (after 6971) are as follows:

Unipolar Polyurethane Leads

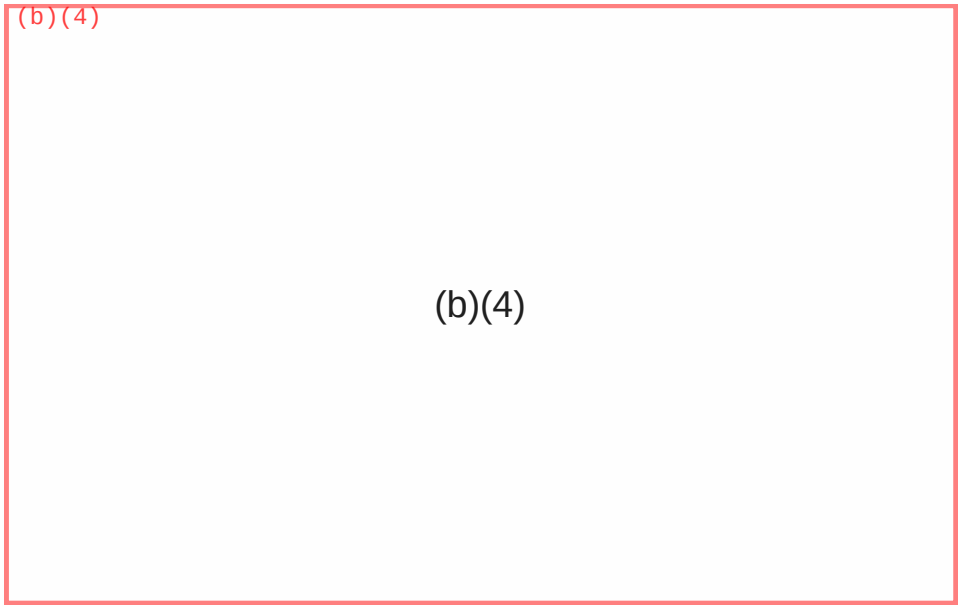
(b)(4)



Survival probabilities of bipolar leads (after 6972) are as follows:

Bipolar Polyurethane Leads

(b)(4)



Tables e-VI-3 and e-VI-4 further demonstrate the improvements with respect to polyurethane biostability.

Table e-VI-3
Insulation Failures*

Model	Initial+ Implants	Active Implants	Insulation Failures
(b)(4)	(b)(4)		

Table e-VI-4
Insulation Failures*

Model	Initial+ Implants	Active Implants	Insulation Failures
Ventricular			
(b)(4)	(b)(4)		

Note the excellent survival probabilities and low occurrence of insulation failures. Reference Appendix B for additional descriptions of lead insulation performance.

In addition to the aforementioned conditions, state-of-the-art during development of the Models 4003/4503 also included the use of thermal forming mandrels for joint construction to eliminate residual stress in joints. In order to facilitate tubing overlaps in lead joint construction, mandrels are used to thermally preform the tubing to the appropriate size. Adhesive is then applied to the joint to assure a secure fit.

Long-term clinical data on the Models 4003/4503 are not yet available. However, the Models 4003/4503 incorporated the positive features of the Models 6957/6957J and therefore clinical performance is expected to be comparable. Twelve month clinical data indicate this is true, see Figure e-VI-1 (Appendix C) and Table e-VI-1.

In conclusion, the Models 4003/4503 as state-of-the-art pacing leads differ from the Models 6971/6972 in the following respects which

Medtronic considers as positive attributes in terms of lead biostability:

- (b)(4)
- (b)(4)
- (b)(4)
- (b)(4)
- (b)(4)

State-of-the-art bipolar leads, i.e., Models 4004/4504, are identical to the unipolar Models 4003/4503 with the following additional improvements:

- (b)(4)
- (b)(4)
- (b)(4)

These additional features cannot yet be proven clinically, however, accelerated testing information (presented later in this section) will confirm this improved performance expectation.

In order to further demonstrate that polyurethane as used in Medtronic pacing leads is biostable and, therefore, a safe and effective insulation material for long-term implant, the following information relative to Medtronic polyurethane pacing leads is provided:

- A detailed comparison of lead configuration, materials, and processing for Medtronic's major line of bipolar and unipolar polyurethane pacing leads.

  Tables e-VI-5 and 6, and e-VI-7 and 8, present configuration, materials and processing characteristics for unipolar and bipolar polyurethane pacing leads. In comparing unipolar leads, Models 4003/4503 are the most current state-of-the-art in polyurethane lead development and for the bipolar leads, Models 4004/4504 are the most current state-of-the art.

Table e-VI-5

Unipolar Ventricular Pacing Leads
Comparison of Configuration, Materials, Processing

Model 4003	Model 6957	Model 4011	Model 6971
(b)(4)			

(b)(4)

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Table e-VI-6

Unipolar Atrial Pacing Leads
Comparison of Configuration, Materials, Processing

Model 4503	Model 6957J	Model 4511	Model 6993
(b)(4)			

(b)(4)

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Table e-VI-7

Bipolar Ventricular Pacing Leads
Comparison of Configuration, Materials, Processing

CONFIGURATION	Model 4004	Model 4016A	Model 4016	Model 4012	Model 6972
(b)(4)					

(b)(4)

Table e-VI-8

Bipolar Atrial Pacing Leads
Comparison of Configuration, Materials, Processing

CONFIGURATION	Model 4504	Model 4512	Model 6990U
(b)(4)	(b)(4)		

DETAILED COMPARISON: CONFIGURATION, MATERIALS, PROCESSING--UNIPOLAR VENTRICULAR AND ATRIAL PACING LEADS, MODELS 4003, 4011, 6957, 6971, 4503, 4511, 6957J, 6993, and BIPOLAR VENTRICULAR AND ATRIAL PACING LEADS, MODELS 4004, 4012, 4016, 4016A, 4504, 4512, 6990U.

Only those characteristics relative to polyurethane are discussed. Other features are presented in the tables for completeness purposes only.

Configuration Similarities

- All incorporate (b)(4) (b)(4) polyurethane insulation (tubing) over the conductor coil(s) and/or memory coil (atrial leads).

Configuration Differences

- The comparative models all differ with respect to minimal insulation (wall) thickness. These differences are primarily due to the desired lead body diameters. The Model 4003's insulation thickness is between that of the Model 6971 and 6957 and larger than the Model 4011. The Model

4503's insulation thickness is between that of the Models 6993 and 6957J, and identical to the Model 4511. The thicker insulation of the Models 6957 and 6957J was a result of desired mechanical characteristics, e.g., torque transfer. Models 4004, 4012, 4016 and 4016A outer insulation thicknesses are significantly larger than the Model 6972. Models 4004 and 4012 inner insulation thickness are identical, as are Models 4504 and 4512 and 4016 and 4016A. Lead insulation thickness is one factor of the lead design that is important in terms of lead biostability. Thicker insulation is not deformed as much when tight ligatures are placed on it. Thus stress applied at implant (securing lead to vein or muscle facia) is less than that which would occur if a thinner insulation were used.

- The Models 4003, 4503 and comparative leads differ with respect to interference fit (tubing-to-coil clearance). As noted in the tables, the Models 4003/4503, 6957/6957J and 4511 leads have clearance between the conductor coil or no interference fit. The unipolar Models

4011, 6971 and 6993, and bipolar Models 4012/4512, 6972 and 6990U have/had the potential, due to the dimensional tolerances associated with the conductor coil and insulation, of creating a situation where interference fit between the conductor coil and insulation exist(ed). The importance here is that relative to ESC, when there is interference fit, there is a potential for stresses of the lead insulation to occur, and if these stresses weren't subsequently relieved, could potentially cause environmental stress cracking of the insulation. As mentioned earlier, the Models 4003/4503, 6957/6957J, and 4511 do not have interference fit and therefore no residual stresses are imposed upon the lead insulation. The Models 4011 and 4012/4512 have the potential for interference fit but are thermally annealed after lead assembly to relieve any residual stresses in the insulation.

- Models 4004/4504 and 4016A incorporate a barrier coating between the conductor coil and insulation. All other lead models do not have a barrier coating.

Material Similarities

- All incorporate (b)(4) as the outer insulation (tubing) material. (Unipolar leads have only outer insulation.)

Material Differences

- All Models except the Models 6971/6972 and 6993 have (b)(4) conductor coils. Models 6971/6972 and 6993 leads had (b)(4) (b)(4) (b)(4) conductor coils. (The 6993 had an (b)(4) outer memory coil.) (b)(4) (b)(4) conductor coils reduce the possibility of stylet perforation because (b)(4) is a more (b)(4) conductor.

- Models 4016 and 4016A use (b)(4) (b)(4) for the inner insulation. All other bipolar leads incorporate (b)(4) (b)(4) for both the inner and outer insulation.

- The barrier coating on the Models 4004/4504 and 4016A is a sputter coat of platinum. All other leads do not have a barrier coating.

Processing Similarities

- All models incorporate manufacturing operations that are intended to relieve residual stresses that may have been introduced during the extrusion process. The Models 4003/4503 and 4004/4504 insulation is thermally annealed as are the Models 6957/6957J, 4016, 4016A (and Models 4011/4511, 4012/4512 after device assembly) to reduce stress.

Processing Differences

- The Models 6971/6972, 6990U and 6993 leads underwent a stress relieving operation in which the insulation was soaked in solvent to relieve residual stresses that may have been introduced during the extrusion process. The Models 4003/4503, 4004/4504, 4016 and 4016A do not use solvent for stress relieving.

- Expansion (b)(4) (b)(4) on the Models 4003/4503, 4004/4504, 4016 and 4016A are formed by using mandrels of specified diameters during the thermal stress relieving/ annealing process. This is not

applicable to the Models 6957/6957J, 6971/6972, 6990U, 6993, 4011/4511 and 4012/4512. (Note: Models 4011/4511 and 4012/4512 are thermally annealed after device assembly to reduce residual stresses.)

- Models 4004/4504 and 4016A insulation (tubing) is thermally stress relieved in an inert atmosphere. Thermal annealing in an inert atmosphere protects the tubing surface from oxidative degradation during the annealing proces.

In summary, Models 4003/4503 and 4004/4504 differ from the very early designs of polyurethane leads (Models 6971/6972 and 6993/6990U) in the following respects. Medtronic considers these to be positive attributes, in terms of lead biostability:

1) Thicker insulation,

2) Assured clearance between insulation and conductor coil versus potential interference fit,

3) (b)(4) versus (b)(4) conductor,

4) Thermal annealing instead of solvent stress relieving.

5) Thermal forming mandrels instead of solvent dilation/lubrication for joint construction,

In addition, the Models 4004/4504 also incorporate:

6) A protective barrier coating between conductor coil and insulation, and

7) Thermal annealing in an inert atmosphere.

More Recent Polyurethane Lead Research

There has been significant research data generated on polyurethane (b)(4) (b)(4) since the Model 6972 lead, focusing on two failure mechanisms, MIO and ESC.

MIO

In order to better understand MIO, Medtronic developed an accelerated bench test to reproduce in-vitro a condition seen in-vivo, and to use this test as a predictor for polyurethane lead performance with respect to MIO. This Medtronic

test is known as (b)(4) (b)(4) is a (b)(4) solution to which (b)(4) (b)(4) is added to make it (b)(4) saline.

Results of (b)(4) testing have demonstrated that MIO can be minimized by preventing certain metal ions from contacting polyurethane. An effective method of preventing (b)(4) (b)(4) polyurethane contact is through the use of a barrier coating between conductor coil and insulation. An effective barrier coating is platinum. In addition, thermally annealing polyurethane in an inert atmosphere has been proven to enhance polyurethane (b)(4) resistance to MIO.

Therefore, two improvements incorporated into the Models 4004/4504 are:

- Barrier coating the conductor coils with platinum, and
- Thermal annealing tubing in an inert atmosphere (e.g., (b)(4)

Both of these improvements have been proven by (b)(4) The Model 4016A pacing lead also incorporated these improvements (reference Document Control Number K873962, Judged substantially equivalent on February 2, 1988).

(b)(4) Test Validation

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4) Test Validation: Non-Paced Tubing Coil Assemblies

(b)(4)

(b)(4)

(b)(4)

(b)(4)

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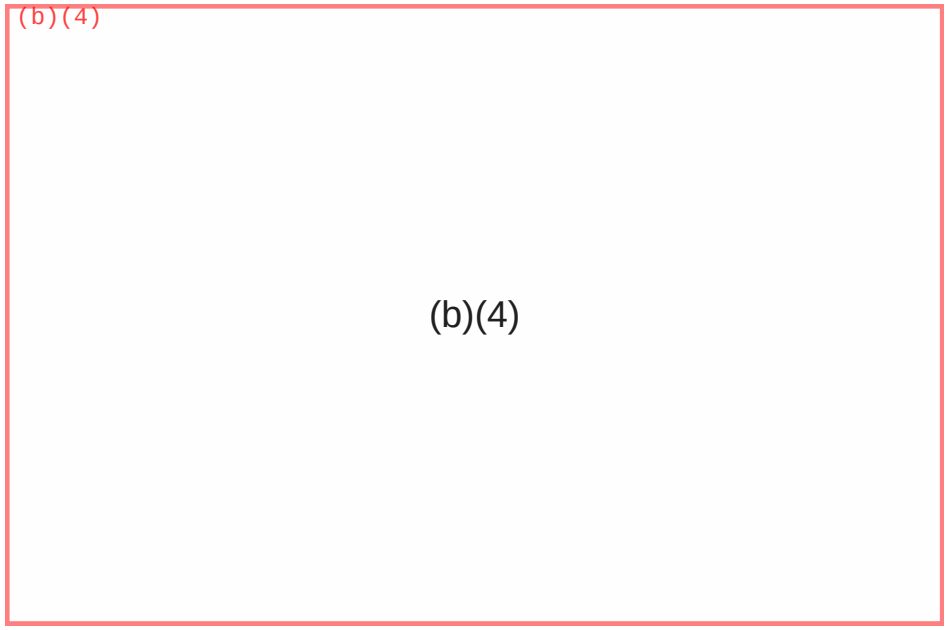
Figure e-VI-5

Tubing/Coil Assembly for Testing Platinum Sputtered (b)(4) Coil in (b)(4)



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(b)(4)

(b)(4)

Objective: To determine the effectiveness of platinum as a barrier coating in reducing MIO in (b)(4)

Test Samples:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Controls:

(b)(4)

(b)(4)

Methods:

(b)(4)

(b)(4)

Results:

Barrier Coated Test Samples

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)
Tubing Coil Assembly

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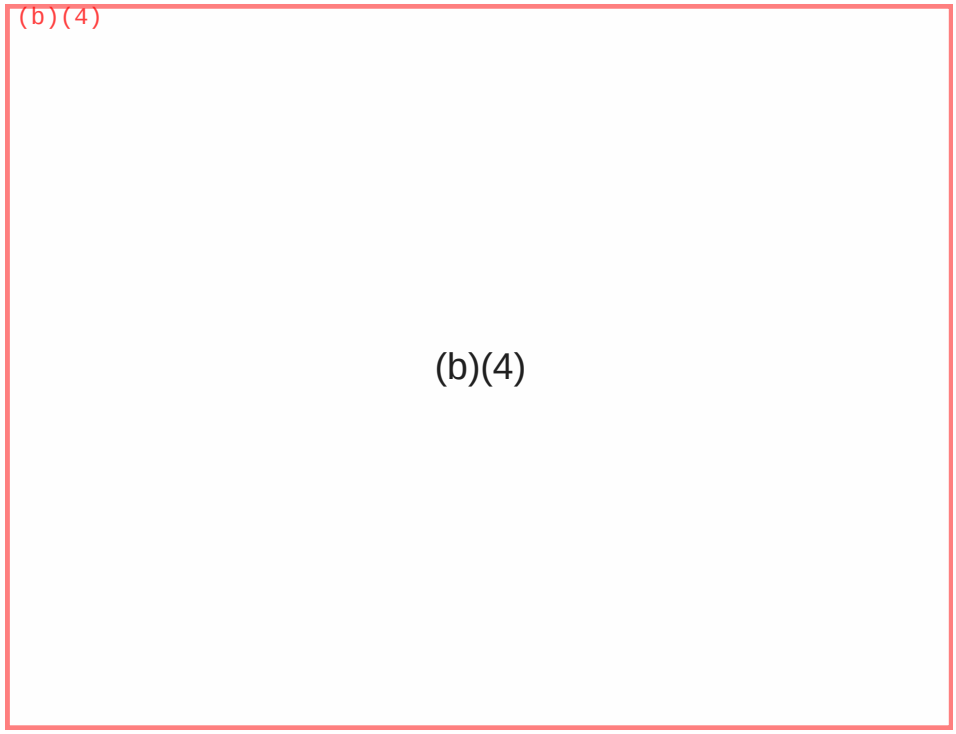

Figure e-VI-6
(b)(4) Tubing Lumen Surface From Platinum
Sputter Coated (b)(4) Coil Assembly After (b)(4) Days in (b)(4) —(b)(4)

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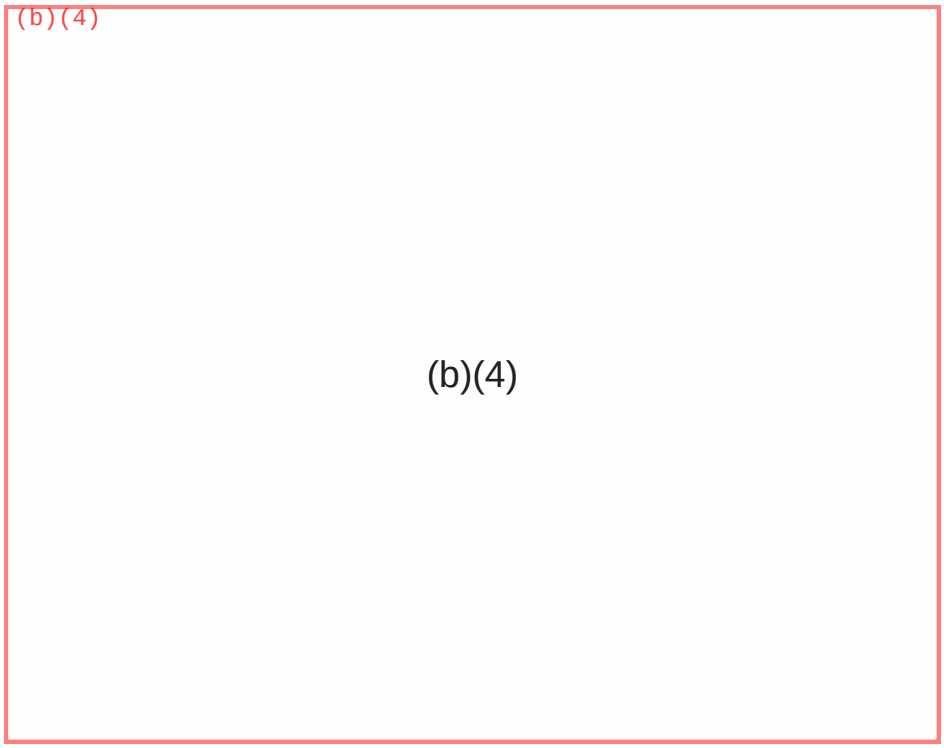

Figure e-VI-7
(b)(4) Tubing Lumen Surface From Platinum
Sputter Coated (b)(4) Coil Assembly After (b)(4) Days in (b)(4) —(b)(4)

140

(b)(4) Controls

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Conclusions:

(b)(4)

(b)(4)

(b)(4) Test Validation: Model 4016A Pacing Lead

(b)(4)

(b)(4)

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(b)(4)

Results:

(b)(4)

(b)(4)

Conclusions:

(b)(4)

(b)(4)

(b)(4) Test Data: Models 4004/4504

(b)(4)

(b)(4)

Models 4004/4504 (b)(4) test and results are as follows:

Objective: (b)(4)

(b)(4)

Test Samples: (b)(4)

(b)(4)

Controls: (b)(4)

(b)(4)

Methods: (b)(4)

(b)(4)

MEDTRONIC CONFIDENTIAL

(b)(4)

(b)(4)

Results:

(b)(4)

(b)(4)

Conclusions:

(b)(4)

(b)(4)

(b)(4) Biostability Testing

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

MIO and Thermal Annealing

(b)(4)

(b)(4)

Process Condition	Time First TCA Failure Observed (days)	TCAs Failed After (b)(4) Days (%)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

ESC

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Biostability Conclusions

(b)(4)

(b)(4)

(b)(4)

(b)(4)

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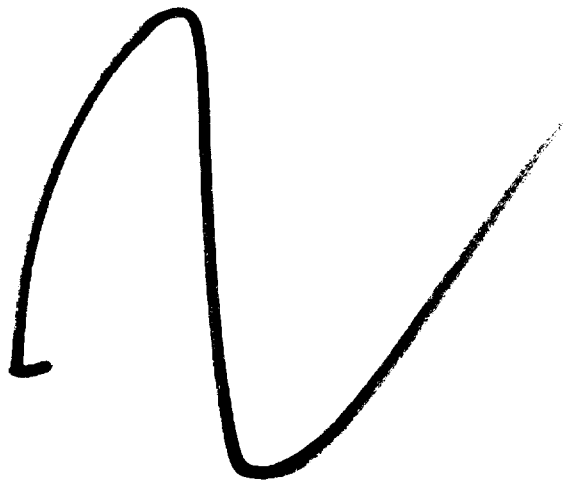
(b)(4)



(b)(4) Biostability

(Reference P830061/S10 and S12)

One Plac------ Text Could Go (See Documentation Section 6)

SECTION II: (b)(4) BIOSTABILITY STUDIES
OF (b)(4) INSULATORS

SECTION II
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(b)(4) Biostability Studies

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F. Appendix

1. Canine Lead Biostability Data

2. Statistical Methods

A. Introduction and Study Design

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Table II-A1 illustrates the chronology of these studies and the polyurethane processing enhancements. The methodology and findings of these five studies is the subject of this complete and in-depth report. A discussion of the study design immediately follows.

Table II-A1. Chronology of Implemented Polyurethane Processing Lead Enhancements

	Polyurethane Lead Enhancements and Year Canine Study Initiated				
	1984	1984	1987	1988	1989
(b)(4)	(b)(4)				
(b)(4)	(b)(4)				

Specific polyurethane tubing insulation wall thickness and (b)(4) resin formulation are presented in Table II-A2. This table is organized to indicate specific tubing insulator factors that were subjected to canine biostability implants in each model studied.

Table II-A2. Test and Control Lead Devices Used in the Canine Study Design

	Polyurethane Tubing Factor Evaluated in Each Lead Studied
(b)(4)	(b)(4)

(b)(4)

(b)(4)

(b)(4) Leads as Experimental Control Devices

(b)(4)

(b)(4)

Model 4023/4523 Prototype Test and Control Devices

(b)(4)

(b)(4)

(b)(4)

- (b)(4)
- (b)(4)

Prototype Model 4004/4504 Control Devices

(b)(4)

(b)(4)

Model 4016A Control Devices

(b)(4)

(b)(4)

Model 4024/4524 Test Devices

(b)(4)

(b)(4)

B. Methods

(b)(4)

(b)(4)

Table II-B1. Canine Implant Studies and Polyurethane Evaluation Methods

Lead Model Studied	Insulation Outer	Insulation Inner	Number of Leads Evaluated	Number of Dogs in Study	Maximum Implant Duration (Months)	Tubing Insulation Evaluation: Visual/ Micro-scopic	Tubing Insulation Evaluation: Tensile
(b)(4)							

(b)(4)

1. Lead Implant Procedures

(b)(4)

(b)(4)

(b)(4)

(b)(4)

2. Lead Removal

(b)(4)

(b)(4)

3. Lead Evaluation

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

4. Tensile Test Procedures

(b)(4)

(b)(4)

5. Scanning Electron Microscopy (SEM) Evaluation

(b)(4)

(b)(4)

6. Statistical Methods

- (b)(4)

(b)(4)

-

c. Canine Biostability Test Results/Discussion

1. Model 6972 Control Leads

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

a. Model 6972 Lead ESC Performance in Canines

(b)(4)

(b)(4)

(b)(4)

(b)(4)

b. Model 6972 Lead MIO Performance in Canines

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

c. Model 6972 Lead Conclusions

(b)(4)

(b)(4)

(b)(4)

(b)(4)

FIGURE IIC1
6972 CANINE ESC RESULTS*

* RESULTS EXCLUDE SUTURE SITE DATA

TABLE II-C1--MODEL 6972 CANINE BIOSTABILITY PERFORMANCE

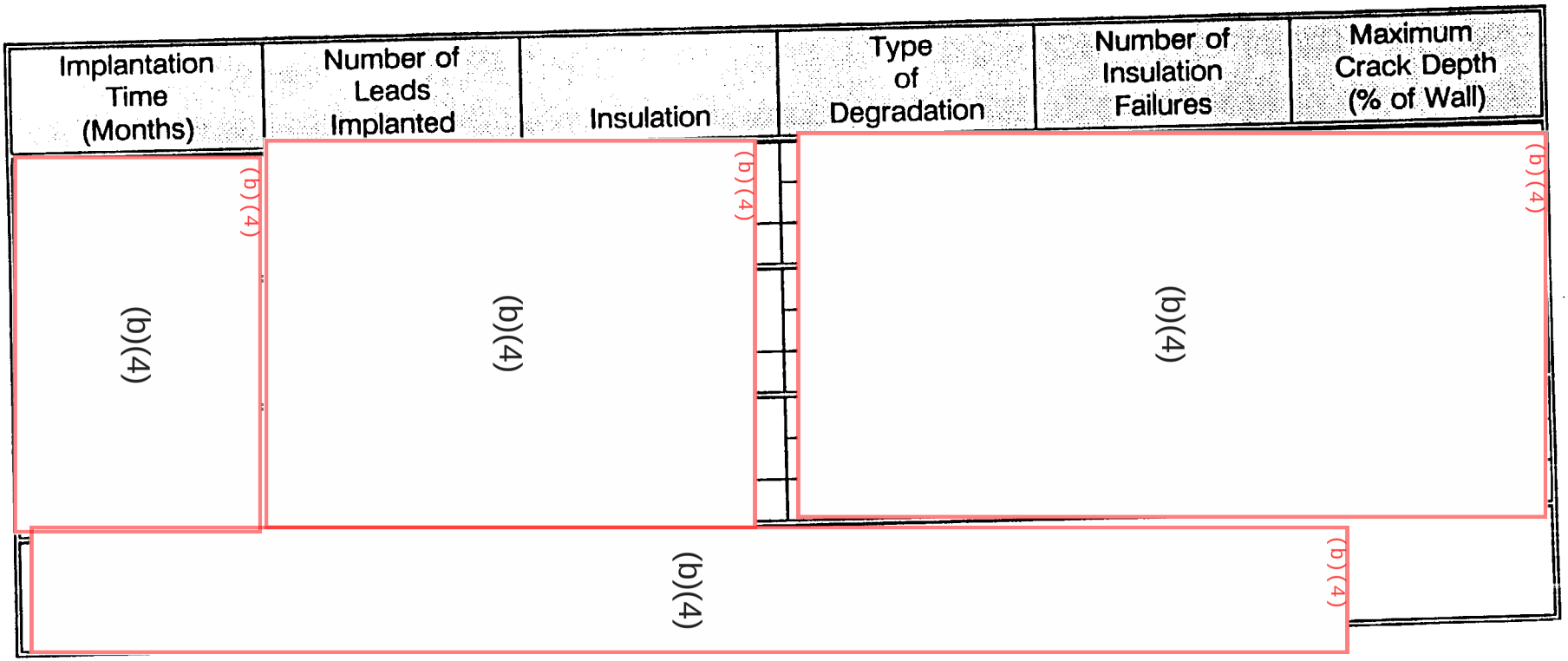

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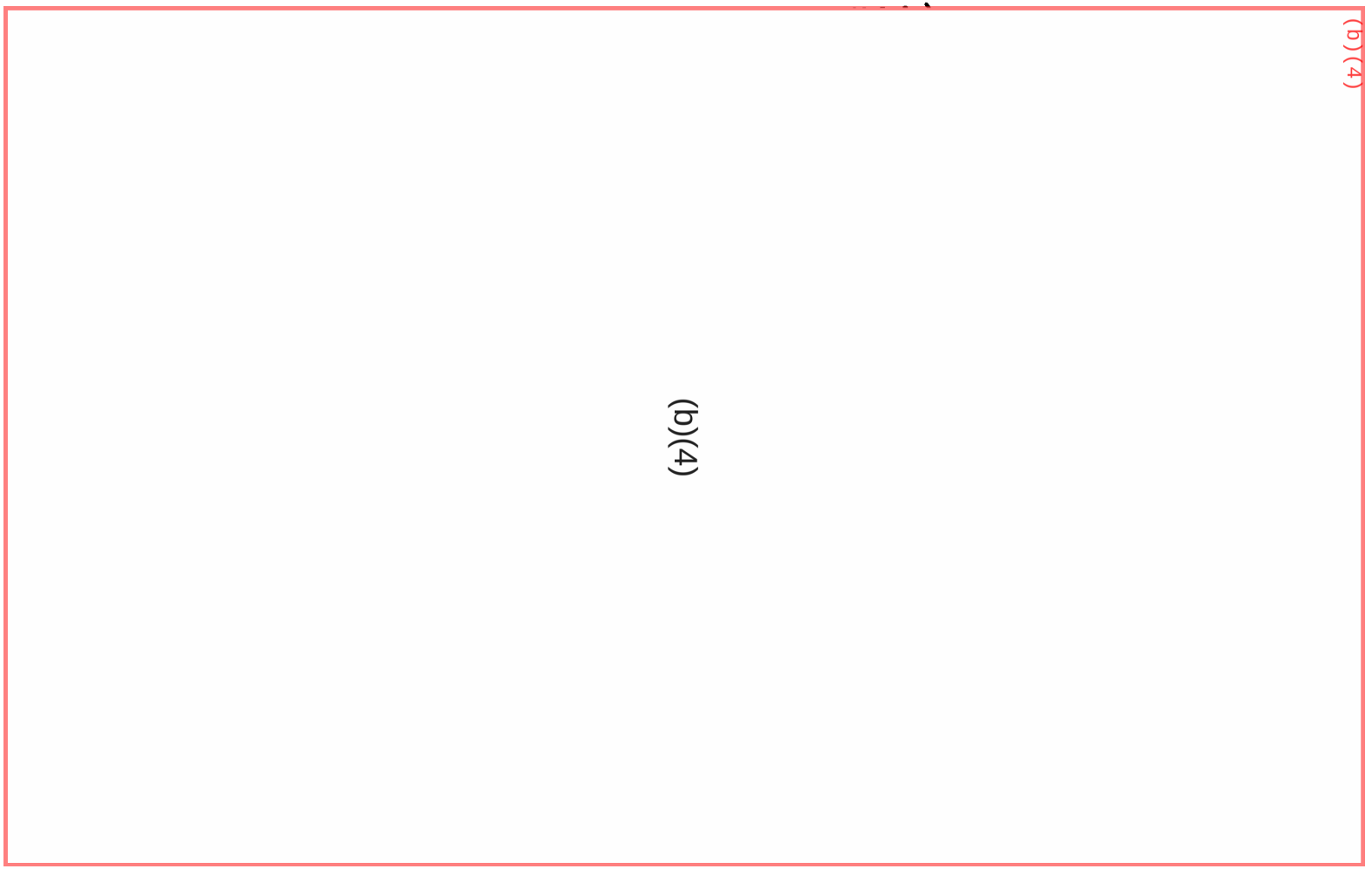
FIGURE IIC2
6972 CANINE MIO RESULTS*



*RESULTS EXCLUDE SUTURE SITE DATA

MEDTRONIC CONFIDENTIAL

(b)(4)

- (b)(4)

2. Model 4023/4523 Prototype and 4004/4504 Prototype Leads: Comparable Past state-of-the-art (b)(4) and (b)(4) Lead Tubing Technology.

(b)(4)

(b)(4)

a. Model 4023/4523 Prototype and 4004/4504 Prototype Lead ESC Performance

(b)(4)

(b)(4)

(b)(4)

(b)(4)

b. Model 4023/4523 Prototype and Model 4004/4504 Prototype Lead MIO Performance

(b)(4)

(b)(4)

FIGURE IIC3
4023/4523,4004/4504 CANINE ESC RESULTS*

(b)(4)

(b)(4)

*RESULTS EXCLUDE SUTURE SITE DATA

FIGURE IIC4
4023/4523,4004/4504 CANINE MIO RESULTS*

(b)(4)

(b)(4)

*RESULTS EXCLUDE SUTURE SITE DATA

(b)(4)

(b)(4)

c. Model 4023/4523 Prototype and Model 4004/4504 Prototype Lead Conclusions

(b)(4)

(b)(4)

- (b)(4)

(b)(4)

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-

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(b)(4)

(b)(4)

(b)(4)

3. Model 6972 and Model 4023/4523 Prototype Lead Canine Biostability: Tubing Insulation Tensile Strength Evaluations

(b)(4)

(b)(4)

TABLE II-C2–SUMMARY OF TENSILE DATA FOR MODEL 4023/4523
PROTOTYPE AND 6972 LEADS

Secant Modulus at	(b)(4)	(b)(4)	(b)(4)
Ultimate	(b)(4)	(b)(4)	(b)(4)
Ultimate Tesile Strength	(b)(4)	(b)(4)	(b)(4)
Tubing Insulation Tested	(b)(4)	(b)(4)	(b)(4)
Canine Implant Time (Months)	(b)(4)	(b)(4)	(b)(4)
Lead Model	(b)(4)	(b)(4)	(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

a. Conclusions for Model 6972 and Model 4023/4523 Prototype Lead Canine Biostability: Tubing Insulation Tensile Strength Evaluation

(b)(4)

(b)(4)

1)

2)

(b)(4)

3)

4)

5) (b)(4)

4. Model 4024/4524 and Model 4016A: Comparable State-of-the-Art Lead Designs for (b)(4) and (b)(4) Lead Technology

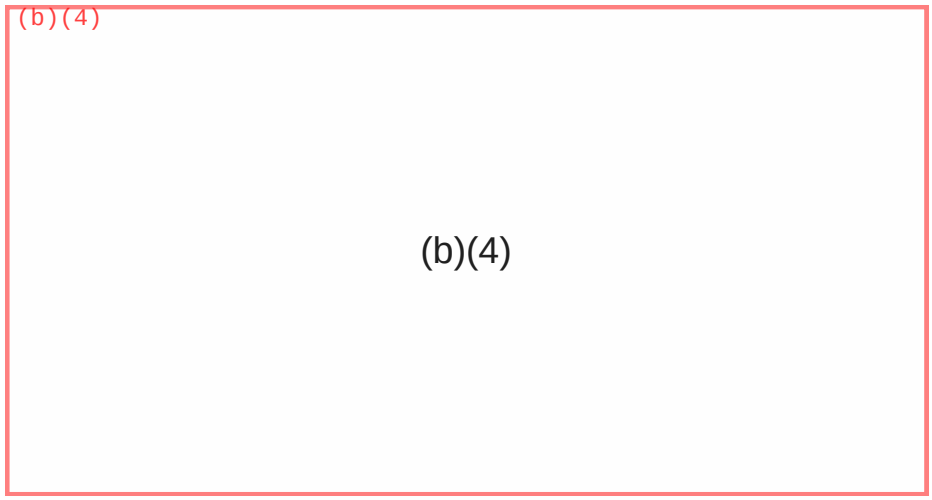
(b)(4)

a. Model 4024/4524 and Model 4016A Lead ESC Performance

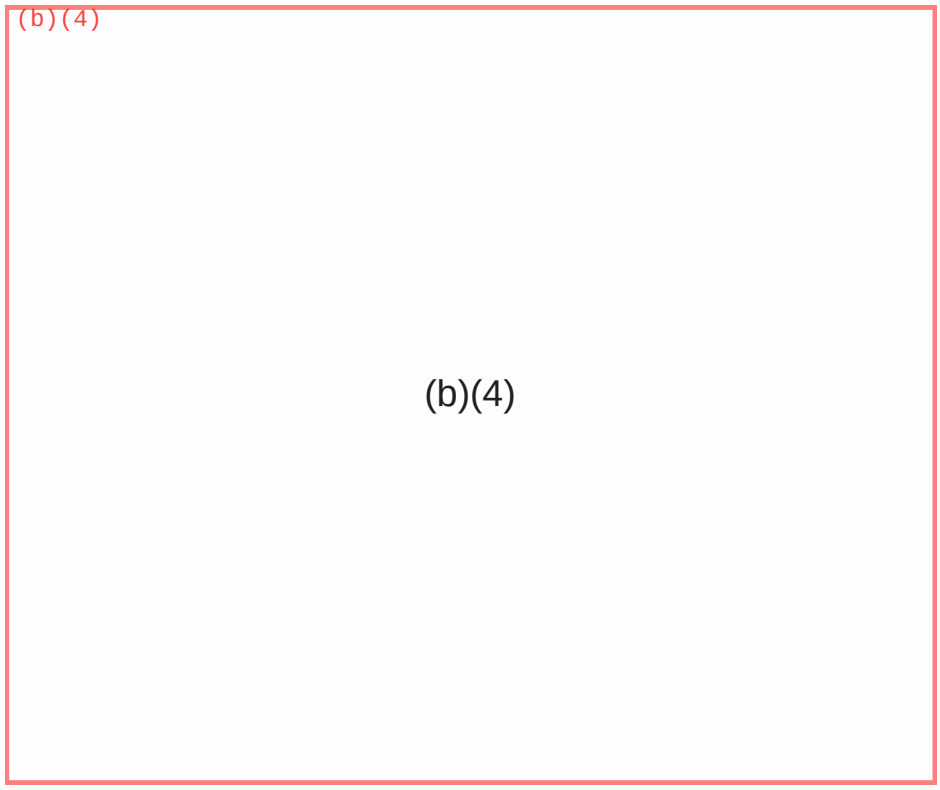
(b)(4)

(b)(4)

(b)(4)

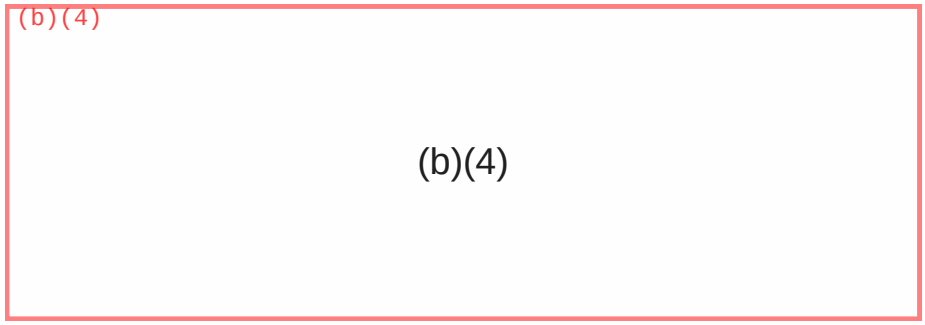


(b)(4)



b. Model 4024/4524 and 4016A Lead MIO Performance

(b)(4)



Figures II-C11 and II-C12 are SEM photographs of typical inner tubing insulation surfaces

(b)(4)

FIGURE IIC5
4024/4524,4016A CANINE ESC RESULTS*

(b)(4)

*RESULTS EXCLUDE SUTURE SITE DATA

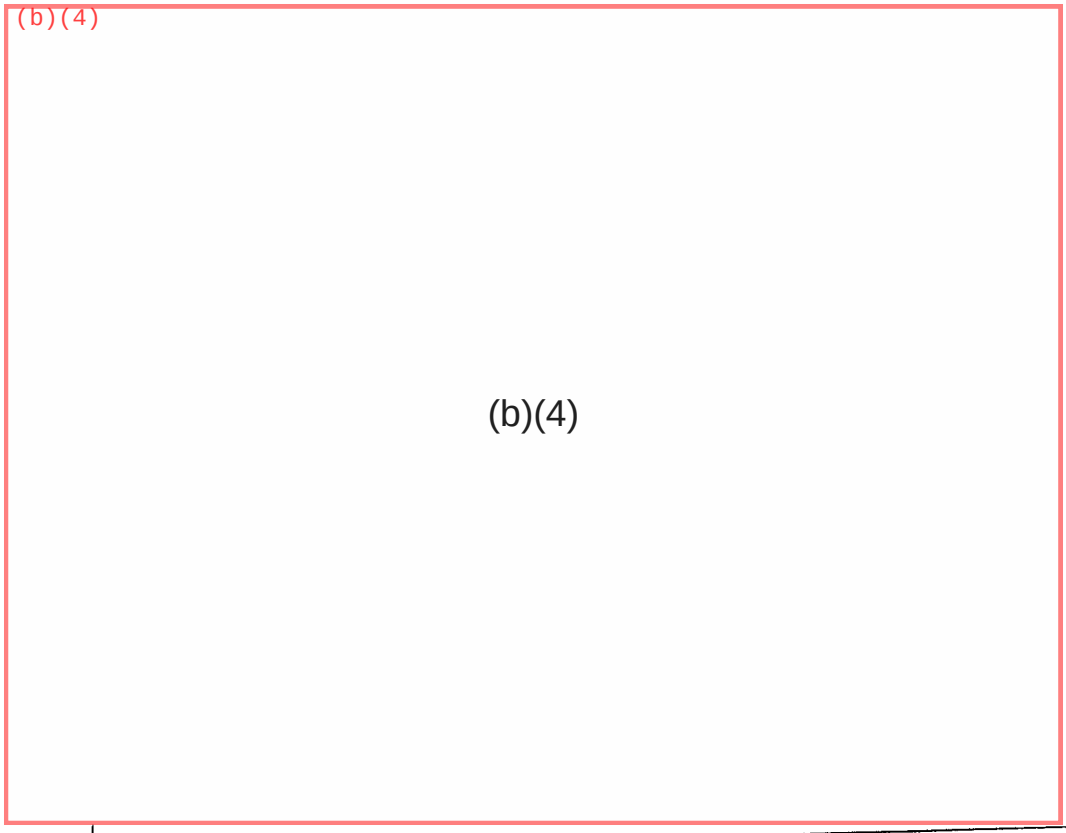


Figure IIC6. SEM photograph of outer (b)(4) tubing insulation removed from a Model 4024 lead implanted (b)(4) months illustrating the maximum ESC (b)(4) observed away from a suture site .... Magnification 1000X.

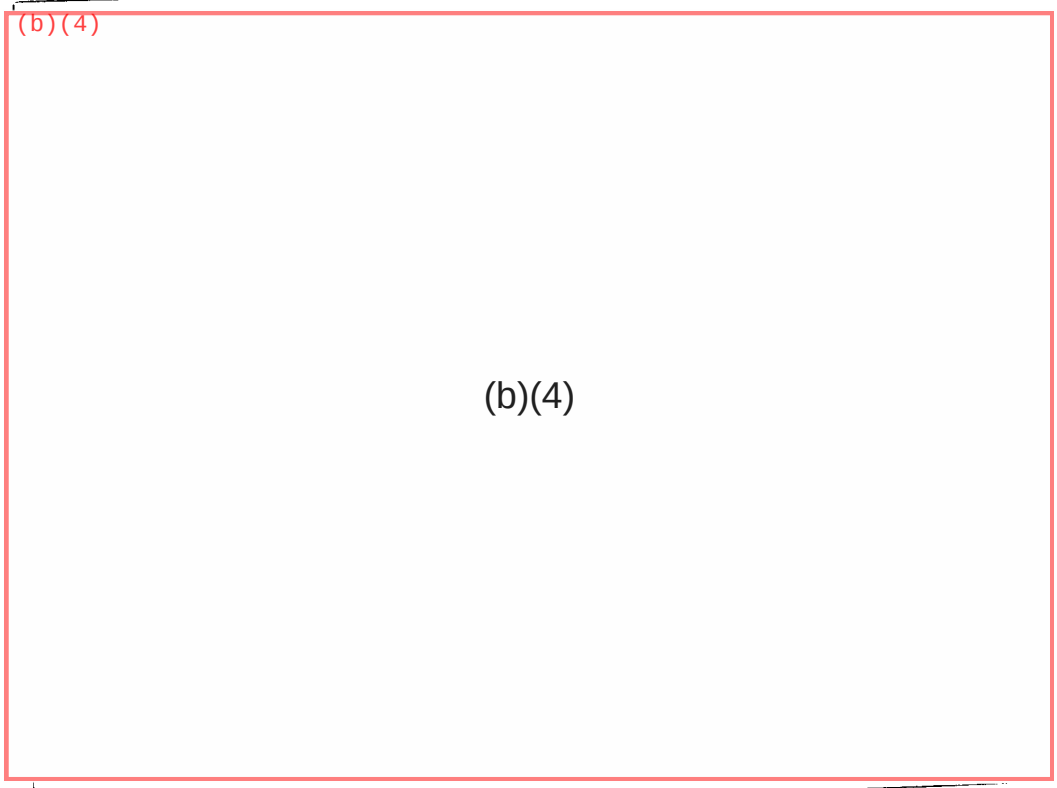


Figure IIC7. SEM photograph of the outer (b)(4) tubing insulation removed from a Model 4524 lead implanted (b)(4) months illustrating shallow ESC (b)(4) .... Magnification 1000X.

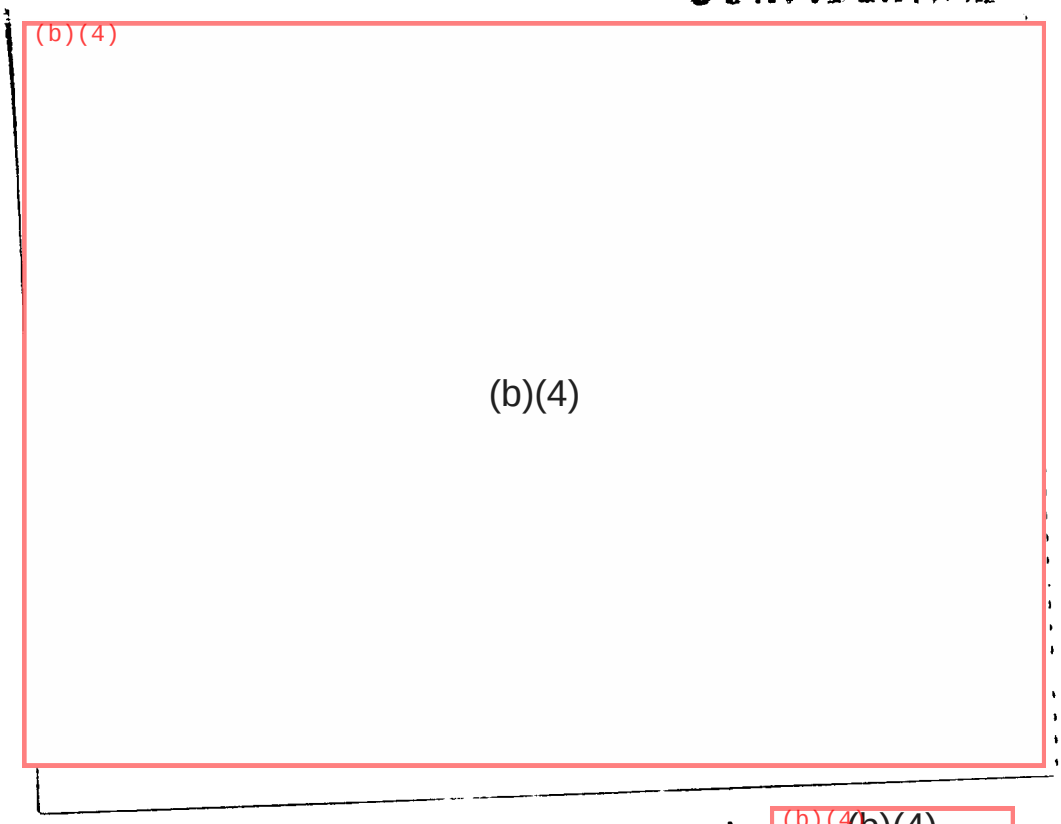


Figure IIC8. SEM photograph of a representative outer (b)(4) (b)(4) tubing insulation removed from a Model 4524 lead implanted (b)(4) months showing the outer surface free of ESC .... Magnification 1000X.

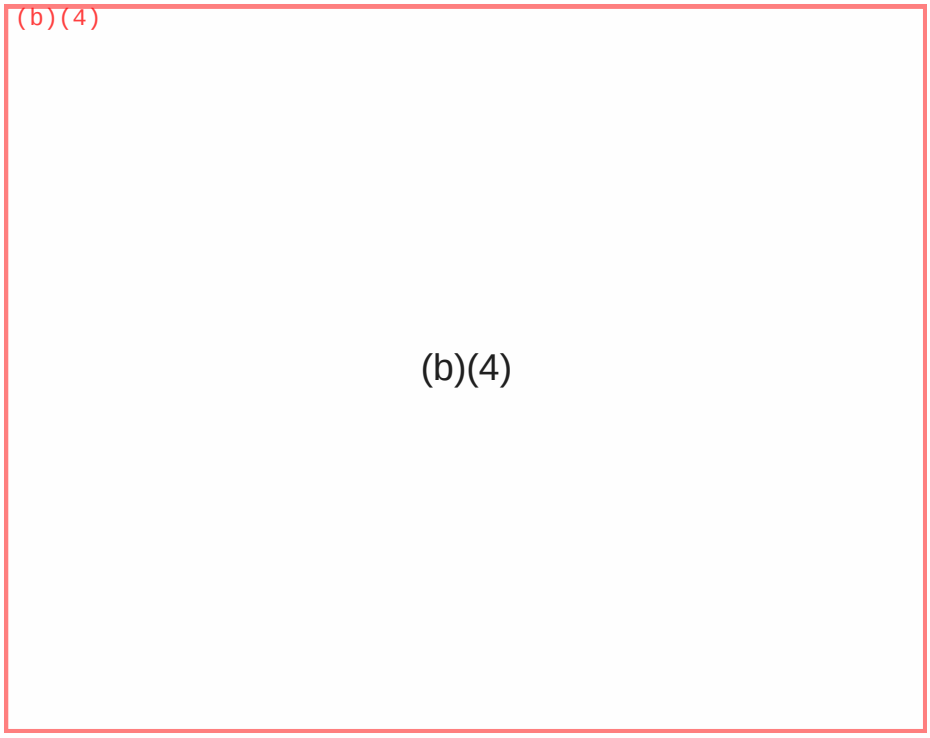


Figure IIC9. ESC degradation (b)(4) (b)(4) of outer (b)(4) (b)(4) tubing insulation removed from a canine explanted Model 6972 control lead after (b)(4) months implantation .... Magnification 480X.

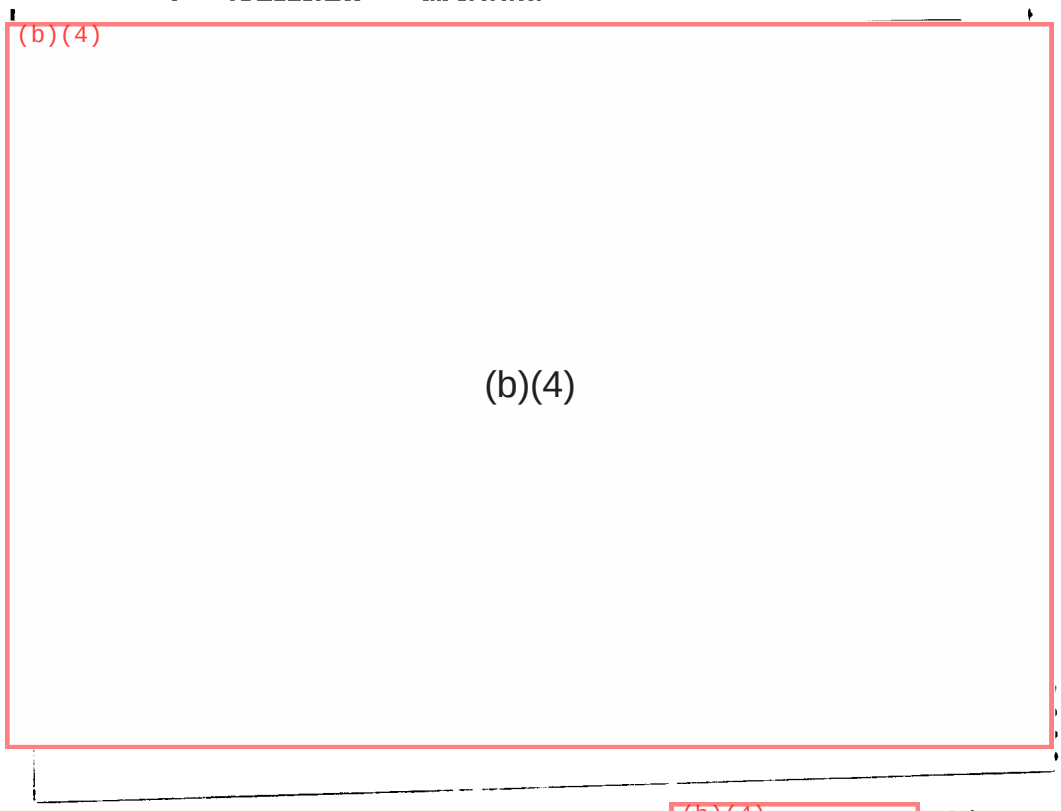


Figure IIC10. SEM photograph of a typical outer (b)(4) tubing insulation lumen (inner) surface from a Model 4524 lead implanted (b)(4) months showing a smooth surface free of MIO cracks .... Magnification 100X.

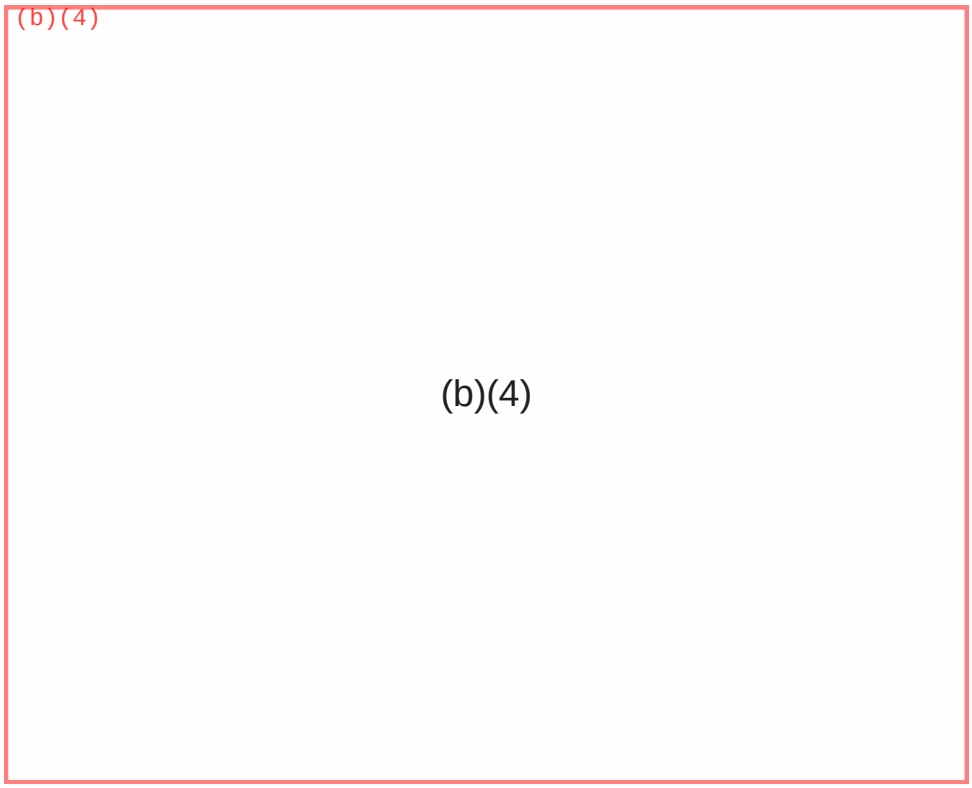


Figure IIC11. SEM photograph of a typical inner (b)(4) tubing insulation (outer) surface from a Model 4524 lead implanted (b)(4) months illustrating a smooth surface free of MIO cracks .... Magnification 100X.

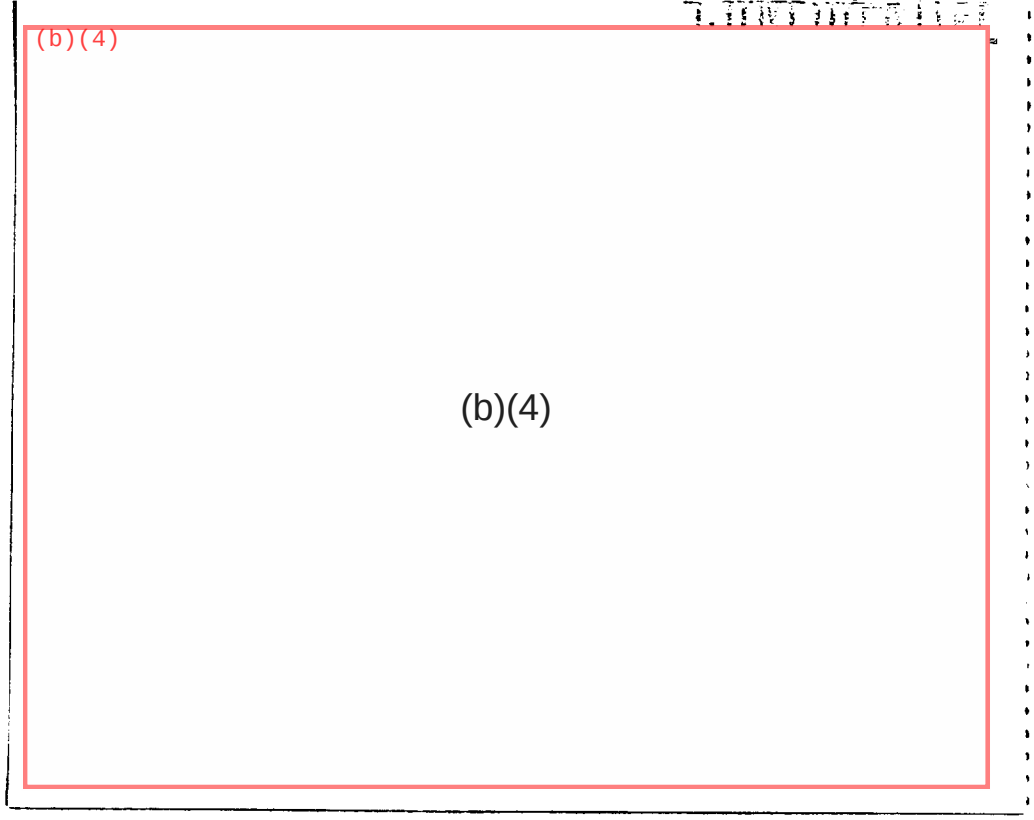


Figure IIC12. SEM photograph of a typical inner (b)(4) tubing insulation lumen (inner) surface removed from a Model 4524 lead implanted (b)(4) months showing a smooth surface free of MIO cracks .... Magnification 100X.

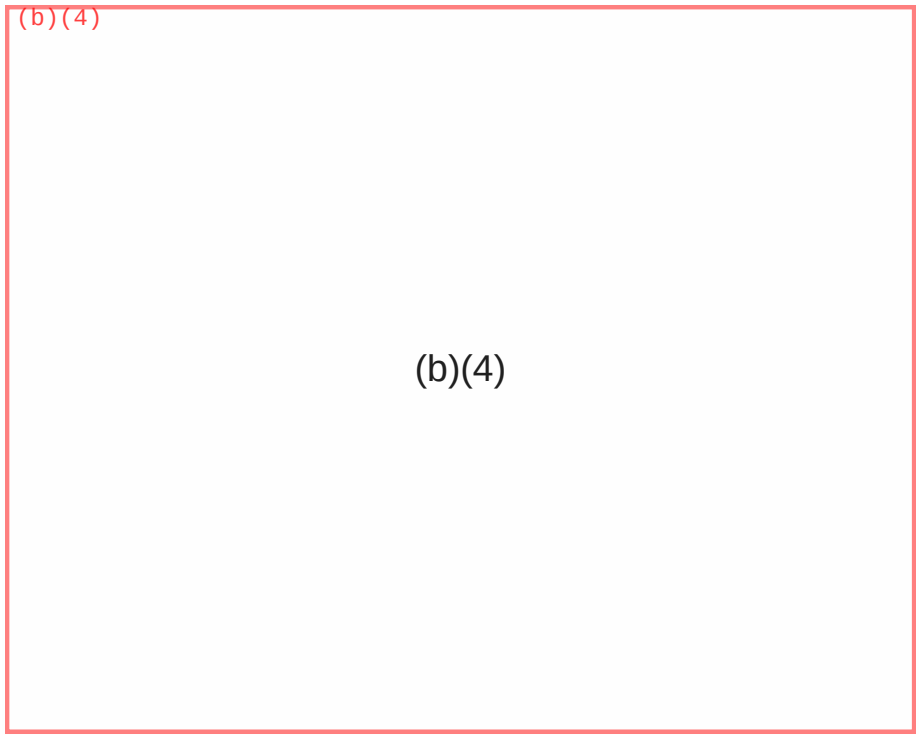


Figure IIC13. MIO degradation of the outer (b)(4) tubing insulation lumen (inner) surface removed from a canine explanted Model 6972 control lead after (b)(4) months implantation .... Magnification 60X.

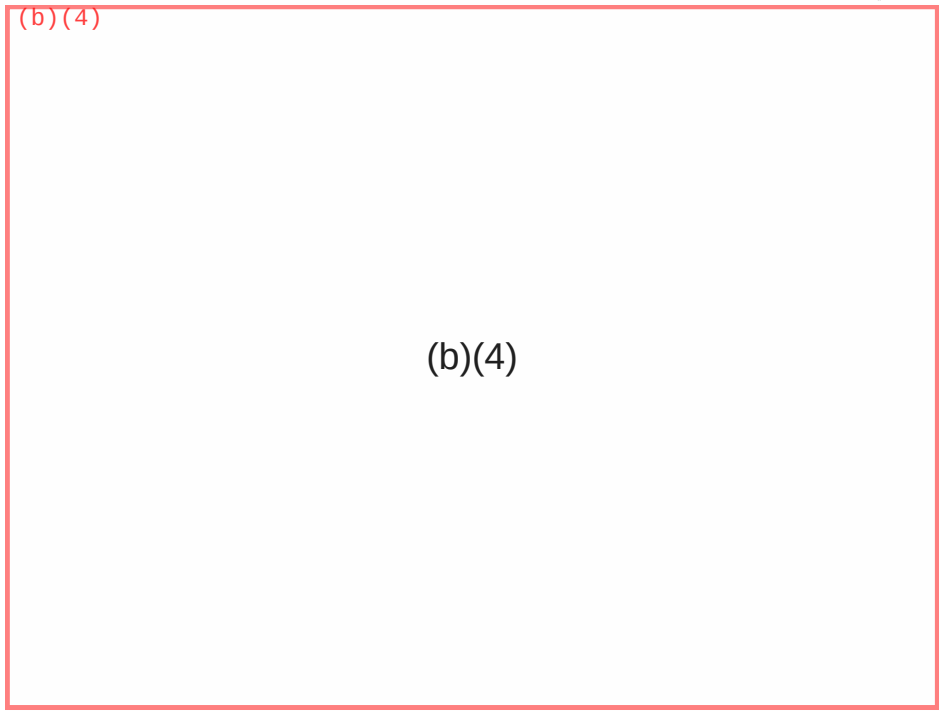


Figure IIC14. **MIO degradation of the inner (b)(4) tubing insulation removed from a canine explanted Model 6972 control lead after (b)(4) months implantation .... Magnification ~10X.**

(b)(4)

(b)(4)

(b)(4)

(b)(4)

c. Conclusions for Model 4024/4524 and Model 4016A Lead Canine Biostability Studies

(b)(4)

(b)(4)

- (b)(4)

-

(b)(4)

(b)(4)

(b)(4)

D. Conclusions for Canine Biostability Studies

The following conclusions were drawn from these canine studies:

1. (b)(4)

2.

3.

4.

(b)(4)

5.

6.

7. (b)(4)

(b)(4)

E. Previously Reported Canine Model 4023/4523 Findings

(b)(4)

(b)(4)

1. Number of leads tested.

Statement Made:

(b)(4)

Correction:

(b)(4)

2. Lead Description.

Statement Made:

(b)(4)

Correction:

(b)(4)

(b)(4)

3. MIO Findings:

Statement Made:

Correction:

(b)(4)

4. ESC Findings:

Statement Made:

Correction:

(b)(4)

(b)(4)

5. Number of Model 6972 Control Leads.

Statement Made:

(b)(4)

(b)(4)

Correction:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

c. Conclusions for Model 4024/4524 and Model 4016A Lead Canine Biostability Studies

(b)(4)

(b)(4)

(b)(4)

(b)(4)

D. Conclusions for Canine Biostability Studies

The following conclusions were drawn from these canine studies:

1. (b)(4)

2.

3.

4.

(b)(4)

5.

6.

7. (b)(4)

(b)(4)

E. Previously Reported Canine Model 4023/4523 Findings

(b)(4)

(b)(4)

1. Number of leads tested.

Statement Made:

(b)(4)

Correction:

2. Lead Description.

Statement Made:

(b)(4)

Correction:

(b)(4)

3. MIO Findings:

Statement Made:

Correction:

(b)(4)

4. ESC Findings:

Statement Made:

Correction:

(b)(4)

(b)(4)

5. Number of Model 6972 Control Leads.

Statement Made:

(b)(4)

(b)(4)

Correction:

(b)(4)

(b)(4)

APPENDIX 1

CANINE LEAD BIOSTABILITY DATA

TABLE 1-1--MODEL 6972 CANINE ESC DATA

Lead Serial Number	Implant Time (Months)	LEAD BODY SECTION							
		A		B		C (Suture Site)	D		E	
		ESC Patch Length (In)	Maximum ESC Crack Depth (%)	ESC Patch Length (In)	Maximum ESC Crack Depth (%)	Maximum ESC Crack Depth (%)	ESC Patch Length (In)	Maximum ESC Crack Depth (%)	ESC Patch Length (In)	Maximum ESC Crack Depth (%)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)

LEAD BODY SECTIONS

(b)(4)

TABLE 1-2–MODEL 6972 CANINE MIO DATA
OUTER INSULATION

Lead Serial Number	Implant Time (Months)	LEAD BODY SECTION								
		A		B		C (Suture Site)	D		E	
		MIO Patch Length (in)	Maximum MIO Crack Depth (%)	MIO Patch Length (in)	Maximum MIO Crack Depth (%)	Maximum MIO Crack Depth (%)	MIO Patch Length (in)	Maximum MIO Crack Depth (%)	MIO Patch Length (in)	Maximum MIO Crack Depth (%)
(b)(4)										

(b)(4)

LEAD BODY SECTIONS

(b)(4)

(b)(4)

TABLE 1-3--MODEL .2 CANINE MIO DATA
INNER INSULATION

Lead Serial Number	Implant Time (Months)	LEAD BODY SECTION							
		A		B		C (Suture Site)	D		E	
		MIO Patch Length (In)	Maximum MIO Crack Depth (%)	MIO Patch Length (In)	Maximum MIO Crack Depth (%)	Maximum MIO Crack Depth (%)	MIO Patch Length (in)	Maximum MIO Crack Depth (%)	MIO Patch Length (In)	Maximum MIO Crack Depth (%)
(b)(4)										

LEAD BODY SECTIONS

(b)(4)

TABLE 1-4--MODEL 4023/45(ROTOTYPE CANINE ESC DATA

Lead Serial Number	Implant Time (Months)	LEAD BODY SECTION						
		A		B		C (Suture Site)	D	
		ESC Patch Length (in)	Maximum ESC Crack Depth (%)	ESC Patch Length (in)	Maximum ESC Crack Depth (%)	Maximum ESC Crack Depth (%)	ESC Patch Length (in)	Maximum ESC Crack Depth (%)

[redacted] (b)(4)

LEAD BODY SECTIONS

[redacted] (b)(4)

TABLE 1-5--MODEL 4023/4523 . PROTOTYPE CANINE MIO DATA

Lead Serial Number	Implant Time (Months)	LEAD BODY SECTION							
		A		B		C (Suture Site)	D		
		MIO Patch Length (In)	Maximum MIO Crack Depth (%)	MIO Patch Length (In)	Maximum MIO Crack Depth (%)	Maximum MIO Crack Depth (%)	MIO Patch Length (In)	Maximum MIO Crack Depth (%)	
(b)(4)									(b)(4)

LEAD BODY SECTIONS

(b)(4) (b)(4)

TABLE 1-6--MODEL 4004/4504 PROTOTYPE CANINE ESC DATA

Lead Serial	Implant Time (Months)	LEAD BODY SECTION							
		A		B		C (Suture Site)	D		E	
		ESC Patch Length (in)	Maximum ESC Crack Depth (%)	ESC Patch Length (in)	Maximum ESC Crack Depth (%)	Maximum ESC Crack Depth (%)	ESC Patch Length (in)	Maximum ESC Crack Depth (%)	ESC Patch Length (in)	Maximum ESC Crack Depth (%)
(b)(4)										

(b)(4)

LEAD BODY SECTIONS

(b)(4)

(b)(4)

TABLE 1-7--MODEL 4004/45 PROTOTYPE CANINE MIO DATA
OUTER INSULATION

Lead Serial Number	Implant Time (Months)	LEAD BODY SECTION									
		A		B		C (Suture Site)	D		E		
		MIO Patch Length (In)	Maximum MIO Crack Depth (%)	MIO Patch Length (In)	Maximum MIO Crack Depth (%)	Maximum MIO Crack Depth (%)	MIO Patch Length (In)	Maximum MIO Crack Depth (%)	MIO Patch Length (In)	Maximum MIO Crack Depth (%)	
(b)(4)											(b)(4)

LEAD BODY SECTIONS

(b)(4) (b)(4)

TABLE 1-8--MODEL 4004/4504 PROTOTYPE CANINE MIO DATA
INNER INSULATION

Lead Serial	Implant Time	LEAD BODY SECTION							
		A		B		C (Suture Site)	D		E	
		MIO Patch Length (in)	Maximum MIO Crack Depth (%)	MIO Patch Length (in)	Maximum MIO Crack Depth (%)	Maximum MIO Crack Depth (%)	MIO Patch Length (in)	Maximum MIO Crack Depth (%)	MIO Patch Length (in)	Maximum MIO Crack Depth (%)
(b)(4)										

LEAD BODY SECTIONS

(b)(4)

TABLE 1-9--MODEL 402 524 CANINE ESC DATA

Lead Serial	Implant Time	LEAD BODY SECTION							
		A		B		C (Suture Site)	D		E	
		ESC Patch Length	Maximum ESC Crack	ESC Patch Length	Maximum ESC Crack	Maximum ESC Crack Depth (%)	ESC Patch Length (In)	Maximum ESC Crack Depth (%)	ESC Patch Length (In)	Maximum ESC Crack Depth (%)
(b)(4)										

LEAD BODY SECTIONS

(b)(4)

TABLE 1-10--MODEL 4024/4524 CANINE MIO DATA
OUTER INSULATION

Lead Serial Number	Implant Time (Months)	LEAD BODY SECTION								
		A		B		C (Suture Site)	D		E	
		MIO Patch Length (in)	Maximum MIO Crack Depth (%)	MIO Patch Length (in)	Maximum MIO Crack Depth (%)	Maximum MIO Crack Depth (%)	MIO Patch Length (in)	Maximum MIO Crack Depth (%)	MIO Patch Length (in)	Maximum MIO Crack Depth (%)

(b)(4)

LEAD BODY SECTIONS

(b)(4)

TABLE 1-11--MODEL 4024/4524 CANINE MIO DATA
INNER INSULATION

Lead Serial	Implant Time	LEAD BODY SECTION								
		A		B		C (Suture Site)	D		E	
		MIO Patch Length	Maximum MIO Crack Depth	MIO Patch Length	Maximum MIO Crack Depth	Maximum MIO Crack Depth	MIO Patch Length (in)	Maximum MIO Crack Depth (%)	MIO Patch Length (in)	Maximum MIO Crack Depth (%)
(b)(4)										

(b)(4)

(b)(4)

LEAD BODY SECTIONS

(b)(4)

(b)(4)

Q12

TABLE 1-12--MODEL 4016A CANINE ESC DATA

Lead Serial Number	Implant Time (Months)	LEAD BODY SECTION							
		A		B		C (Suture Site)	D		
		ESC Patch Length (In)	Maximum Crack Depth (%)	ESC Patch Length (In)	Maximum Crack Depth (%)	Maximum ESC Crack Depth (%)	ESC Patch Length (In)	Maximum Crack Depth (%)	
(b)(4)									

(b)(4)

LEAD BODY SECTIONS

(b)(4)

(b)(4)

TABLE 1-13--MODEL 4076A CANINE MIO DATA
OUTER INSULATION

Lead Serial Number	Implant Time (Months)	LEAD BODY SECTION									
		A		B		C (Suture Site)	D		E		
		MIO Patch Length (in)	Maximum MIO Crack Depth (%)	MIO Patch Length (in)	Maximum MIO Crack Depth (%)	Maximum MIO Crack Depth (%)	MIO Patch Length (in)	Maximum MIO Crack Depth (%)	MIO Patch Length (in)	Maximum MIO Crack Depth (%)	
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)

LEAD BODY SECTIONS

(b)(4)

TABLE 1-14--MODEL 4016A CANINE MIO DATA
INNER INSULATION

Lead Serial Number	Implant Time (Months)	LEAD BODY SECTION									
		A		B		C (Suture Site)	D		E		
		MIO Patch Length (in)	Maximum MIO Crack Depth (%)	MIO Patch Length (in)	Maximum MIO Crack Depth (%)	Maximum MIO Crack Depth (%)	MIO Patch Length (in)	Maximum MIO Crack Depth (%)	MIO Patch Length (in)	Maximum MIO Crack Depth (%)	
(b)(4)											

LEAD BODY SECTIONS

(b)(4)

APPENDIX 2

LITERATURE ON ANALYSIS OF POLYURETHANE BY FOURIER TRANSFORMED INFRARED SPECTROSCOPY

Pages removed for the following reason: Copyright material

APPENDIX 3

LITERATURE ON INJECTION-MOLDED (b)(4) TENSILE STRENGTH

Pages removed for the following reason: Copyright material

POLYMERIC MATERIALS SCIENCE and ENGINEERING

Proceedings of the ACS Division of
Polymeric Materials:
Science and Engineering

VOLUME 53

Fall Meeting 1985
Chicago, Illinois

AMERICAN CHEMICAL SOCIETY
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

Ms. Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

DEC 9 1993

Re: P920015
Medtronic® Transvene® Lead System
Filed: April 1, 1992
Amended: August 27, September 21, October 27 and November 5, 1992,
March 29, June 2, 14, July 9, October 12, and November 3, 1993

Dear Ms. Marrone:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Medtronic® Transvene® Lead System. The Medtronic® Transvene® Lead System (Models 6963, 6966 and 6999), (hereafter referred to as the Transvene® Leads) with Medtronic Pacer-Cardioverter-Defibrillator (PCD®) Model 7217B Multiprogrammable Tachyarrhythmia Control System (hereafter referred to as the PCD™ Transvene® System) is intended for single long-term use and each lead is designed to be used only with a compatible Medtronic implantable tachyarrhythmia control device along with at least one other Medtronic defibrillation lead. The lead system has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated. Current medical research indicates that such patients should: (1) have survived at least one episode of a cardiac arrest presumably due to a ventricular tachyarrhythmia as evidenced by resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; or (2) in the absence of a prior cardiac arrest, have poorly tolerated sustained VT and/or VF, which occurs spontaneously, or can be induced, despite the best antiarrhythmic drug therapy.

The natural history of patients with hemodynamically stable sustained VT is not well defined. While this patient population was included in the Transvene® Lead clinical study, no conclusions were drawn from the data obtained on this specific patient group.

Prior to Transvene® implant, it is strongly recommended that patients undergo a complete cardiac evaluation, which should include extensive electrophysiologic testing. Also, extensive electrophysiologic evaluation and testing of the safety and efficacy of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the Transvene® System.

We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

Expiration dating for this device has been established and approved at 2 years.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act.

The device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the approved labeling specifies the requirements that apply to the training of physicians who may use the device.

In addition to the postapproval requirements, postmarket surveillance should track the explanted Transvene® leads for evidence of metal ion oxidation (MIO).

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

In addition, under Section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under Section 522(a)(1(A) the device cleared for marketing by this order as requiring postmarket surveillance.

Within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you are required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

Submit five (5) copies to:

Postmarket Studies Document Center
Suite 405 (HFZ-107)
1801 Rockville Pike
Rockville, Maryland 20852

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will cause your product to be misbranded and could lead to the imposition of civil money penalties or other regulatory actions. Any distribution of a misbranded device is a violation of the act and may result in a number of FDA enforcement actions, including (but not limited to) withdrawal of your PMA.

If you have questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch at (301) 594-0639.

Under Section 519(e) of the act (as amended by the Safe Medical Devices Act in 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of device user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under Section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonably likely to have serious adverse consequences. FDA has designated your device for tracking.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR § 821.20(b) and the devices that FDA has designated for tracking at 21 CFR § 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705- 10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)).

If you have questions concerning this approval order, please contact Doris Terry at (301) 594-1523 or Arnold Alpert, Ph.D., at (301) 594-2186.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Acting Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

Issued 11-5-93

CONDITIONS OF APPROVAL
FOR IMPLANTABLE DEFIBRILLATORS AND PROGRAMMERS

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 1390 Piccard Drive, Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgement by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgement is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 1390 Piccard Drive, Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

In addition to the above and in order to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use, the annual postapproval reports shall include, separately for each model number (if applicable), the following information known by or reported to the applicant:

(1) The number of pulse generators domestically implanted and the number of reported explants and deaths.

(2) A breakdown of the reported deaths into pulse generator related and non-pulse generator related.

(3) A breakdown of the reported explants into the numbers reported at end of battery life, having complications unresolvable by programming and for other reasons with safety and effectiveness issues which can be derived from the reports stated.

(4) The number of pulse generators returned to the applicant for cause from domestic sources with a breakdown into the numbers currently in analysis, operating properly, at normal battery depletion and failed, with the failure mechanisms described.

(5) A cumulative survival table for the pulse generators.

(6) The number of programmers and modules shipped and the number of returns with a breakdown into the numbers currently in analysis, operating properly and failed, with the failure mechanisms described.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 1390 Piccard Drive, Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984, and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one if its marketed devices

(1) may have caused or contributed to a death or serious injury or

(2) has malfunctioned and that the device or any other device marketed by the manufacturer or imported would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for this PMA, you shall submit the appropriate reports required by the MDR Regulation and identified with the PMA reference number to the following office:

Division of Postmarket Evaluation (HFZ-520)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850
Telephone (301) 594-1144

Events included in periodic reports to the PMA that have also been reported under the MDR Regulation must be so identified in the periodic report to the PMA to prevent duplicative entry into FDA information systems.

Copies of the MDR Regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by written request to the above address or by telephoning (301) 594-1140.

To the Manufacturer:

The attached draft guidance represents an attempt by the Center for Devices and Radiological Health (CDRH) to provide general guidance to manufacturers of a broad spectrum of devices. On review, some have taken this guidance as requiring Phase IV clinical studies. This is not the intention of the attached document nor is it the goal of Required Postmarket Surveillance (RPS) studies. The primary objective of RPS studies is the study of the performance of the device after marketing as it is to be used in the general population for which it is intended.

Generally, the primary variables to be studied are morbidity or mortality in the population on whom the device has been used or in whom the device has been implanted. The major interest lies in device failure and its attendant impact on the patient. Additionally, however, expected major complications should be monitored to be certain that the incidence of such complications is not unacceptably high in the population for which the device was intended when used according to manufacturer's instructions.

You are free to choose whatever design you wish as long as you can persuade CDRH that the study is scientifically sound. For example, a two-tiered approach has been proposed which may be acceptable in some circumstances as a postmarket surveillance study. What appears in the attached draft guidance is a listing of study elements which should be considered in the conduct of a scientifically sound postmarket study. Some studies will incorporate more features than others. When a topic discussed in the draft guidance is not needed for your specific study, it is only necessary to discuss the exclusion of that item in the protocol.

Currently, CDRH is working with industry to redraft the guidance to prevent the misconception that postmarket surveillance under Section 522(a)(1) of the Federal Food, Drug, and Cosmetic Act requires an elaborate extension of the premarket clinical investigation. Until such guidance is available, questions on specific elements of study design may be directed to Anita Rayner at the phone number listed in the draft guidance document.

DRAFT

GUIDANCE TO MANUFACTURERS ON THE DEVELOPMENT OF REQUIRED POSTMARKET SURVEILLANCE STUDY PROTOCOLS UNDER SECTION 522(a)(1) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT

INTRODUCTION

Under Section 522(a)(1) of the Federal Food, Drug, and Cosmetic Act (Act) all manufacturers of certain types of devices identified in the Act are required to conduct postmarket surveillance studies. It has been determined by the Agency that the device cleared for marketing by the attached letter is subject to Section 522(a)(1) of the Act.

Within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce, you are required to submit to the Agency a detailed protocol that describes your proposed postmarket surveillance study, and you are to certify the exact date the device was first introduced or delivered for introduction into interstate commerce. As described in the Act, the protocol must be designed to produce useful information evaluating the safety and effectiveness of the device. The Agency has sixty (60) days to approve or disapprove a protocol and principal investigator. The manufacturer will be notified in writing of the Agency's determination and should wait for this notification before initiating the study. Failure to submit a protocol within the specified timeframe, provide appropriate reports to the Agency, or complete an Agency approved postmarket surveillance study consistent with the protocol will constitute a violation of the Act.

For your reference, the Agency has included this general guidance on preparing a protocol for a postmarket surveillance study. In addition to submitting the protocol, you must also include a detailed profile of the study's principal investigator. This profile should clearly establish the qualifications and experience of the individual to conduct the proposed investigation.

The Agency strongly encourages manufacturers to consult with appropriate professionals experienced in data management, research design, methodology, and statistical analysis in designing a potential postmarket surveillance study. It is usually most cost effective to utilize these individuals as early as possible in the study design process.

PURPOSE OF REQUIRED POSTMARKET SURVEILLANCE

It is recognized that not all device related problems, whether of design, mechanical, electrical, or human origin, are going to be

observed in the limited investigations that usually precede Agency approval to commercially market a device. Moreover, the preliminary estimates of the various performance characteristics, adverse effects, and related parameters obtained in pre-approval testing are also subject to further refinement as actual clinical experience and the size of the data base increases.

The primary purpose of required postmarket surveillance is to provide an early warning system to alert the health care community to any potential problems with a given device within a reasonable time of the initial marketing of the device. This postmarket surveillance is intended to provide crucial information not available in current passive reporting mechanisms such as MDR or user reporting by requiring the manufacturer to conduct active investigations of device performance in actual use. Secondarily, such studies will provide the public, health care professionals, industry, and government with additional useful information regarding device safety and effectiveness.

PURPOSE OF GUIDANCE

The purpose of this guidance document is to assist manufacturers in the preparation and submission of postmarket surveillance study protocols that are required under Section 522(a)(1) of the Federal Food, Drug, and Cosmetic Act.

Please submit five (5) copies of your proposed postmarket surveillance study protocol to:

Postmarket Studies Document Center
Room 408 (HFZ-107)
Center for Devices and Radiological Health
12720 Twinbrook Parkway
Rockville, Maryland 20852

CONTENTS OF THE POSTMARKET SURVEILLANCE SUBMISSION

The Agency recognizes that the planning and conduct of each postmarket surveillance study will be essentially device dependent. Within certain limitations, the basic assumption of postmarket surveillance is that a reasonable assurance of safety and effectiveness (risks and benefits) or substantial equivalence, of a given device has already been demonstrated through the premarket approval or premarket notification process, respectively.

The manufacturer shall address each of the following issues when presenting a proposed protocol to the Agency. While the Agency has offered some suggestions or examples under each heading, no single protocol has been identified to meet the requirements of required

postmarket surveillance. The manufacturer has the flexibility to design a surveillance program appropriate to the subject device provided the inclusion or exclusion of each of the following issues is discussed and justified.

I. ORGANIZATIONAL AND ADMINISTRATIVE ELEMENTS

The first section of the protocol is concerned with organizational and administrative elements of the submission. Most of this information relates to basic manufacturer and device identification (see the attached Checklist for details). This section also requires the manufacturer to certify the date the device was first introduced or delivered for introduction into interstate commerce.

The submission shall be numbered by section and organized according to the outline provided by the enclosed protocol checklist and the entire submission must also be sequentially numbered from the Table of Contents through the last page of text or data. A detailed Table of Contents with appropriate listings of sections, tables, graphs, figures, appendices, etc. is also required. The page numbering sequence in the Table of Contents should correspond to the sequential numbering system.

II. SURVEILLANCE PROTOCOL

A. STUDY OBJECTIVES

The manufacturer shall identify precisely the objectives of the proposed surveillance study in the protocol. The Agency recommends that the manufacturer limit the number of objectives to a well defined minimum in an effort to produce clear data and analyses that are designed to provide reasonable assurance that the device is operating safely and effectively when used as intended in the target population.

B. STUDY VARIABLES

The manufacturer shall clearly define all relevant study variables that are to be included in the investigational plan. As appropriate, the manufacturer should include data on patient survival rates, device failure rates, morbidity and/or mortality associated with the device, etc. Each parameter should be defined in words, and where appropriate, in mathematical terms. Any information which the manufacturer can provide concerning the identified variables will be extremely helpful in the review of the submitted protocol. For example, for each variable, an expected range of values could be presented along with other appropriate statistical summaries and estimates that may be known from earlier

clinical experience.

The Agency believes that if these studies are to be useful in serving as early warning systems designed to avert potential catastrophes, and to evaluate safety and effectiveness on a large scale, the data must be amenable to appropriate statistical evaluation. This requires that the manufacturer collect pertinent denominator data for all study variables (especially important in rate calculations). "Pertinent denominator data" refers to the use of appropriate numbers in all calculations. In general, a pertinent denominator will refer to the actual number of devices in use in the study population (as opposed to number of devices manufactured, shipped, or delivered) during a given phase of the postmarket surveillance study. Conversely, it would be inappropriate to use the large number of shipped devices as the denominator in a ratio-type computation in order to artificially lower the corresponding failure rate, or to incorrectly use a smaller number in the denominator to artificially raise a success rate.

The discussion of appropriate use of denominator data will be considered critical in reviewing the proposed protocol. The Agency believes that analyses without meaningful denominators will not result in obtaining the most reliable information to best serve the interests of the public health.

C. STUDY DESIGN

The primary function of good study design is to control sources of error or bias. In general, the principal objective of good study design is the identification of these potential sources of bias before beginning the study. It is then a matter of determining how to utilize available research techniques to control these factors during the study.

In the case of postmarket surveillance studies, much may already be known about the problems and sources of bias because of previous experience in the non-clinical and clinical trials required to obtain marketing approval. This prior experience should have also highlighted another important aspect of study design - the identification of critical variables and their associated uncertainty.

This type of information allows for more precise formulation of research objectives, hypotheses, and allocation of other resources. For this reason, the Agency strongly recommends that manufacturers devote sufficient time to the planning of postmarket studies and consult with appropriate professionals early in the design process.

Proper study design and a clear presentation of the selected associated methodology to achieve the stated research objectives

will facilitate postmarket protocol approval and thus eliminate unnecessary delays and the associated expense in time and resources. Accordingly, a proposed postmarket study protocol should include: a discussion of design issues such as the type of study to be utilized; the study size; the data collection plan and associated forms; the follow-up plan; data quality control mechanisms; the length and proposed endpoint of the study; and the proposed analytical plan.

The manufacturer should address each of the following items in designing a proposed protocol or provide an explanation as to why a particular section does not apply in a given situation.

1. Type of Study

Discuss the proposed study design including control selection, stratification, matching criteria if needed, etc. For example, morbidity and mortality data may require prospective follow-up, case-control design, etc. A device failure analysis of retrieved implants may require an engineering and/or materials analysis including complete description of test method, specification of all experimental errors, etc. The appropriateness of a given design will vary from device to device and depend on the surveillance objectives. The Agency does not require a specific study type be used during the postmarket study, and recognizes the need to be flexible in allowing for creative, valid strategies. However, it is incumbent upon the manufacturer to fully justify the type of study proposed for a given device.

2. Study Size

The manufacturer should provide a complete description of the proposed sample size. This should include any assumptions or formulas, with references, that are used for sample size determination.

a. Source(s) of Patient or Device Data

Specify identification of study subjects. For example, in a follow-up study, treated and un-treated subjects need to be defined and identified from sources such as hospital logs, physician records, population listings, etc. In case-control studies, the sources of both cases and controls need to be described in detail.

The manufacturer should also supply a full description of subject inclusion/exclusion criteria that will be used in selecting subjects for the actual study.

b. Representativeness of Data

If pooling from different sources, such as private practices, medical centers, or cities is planned, a detailed justification for combining such data must be presented. For example, a single medical center may not provide enough patients to meet the target number, although three centers would. In such a situation, the comparability and uniqueness of each center should be discussed in terms of relevance to the study. Data collection, processing, and analysis strategies are examples of factors that illustrate a common protocol is being used across investigational sites, and should be presented as evidence supporting the pooling of data.

3. Data Collection Plan and Forms

Explain which variables will be collected. For example, patient name, address, age, sex, device serial number, manufacturing date, duration of use etc. Specify how the data will be obtained, for example, from personal interview, hospital medical record, specific laboratory analysis, etc., and the timing of collection of the different variables. For example, some will be obtained at the beginning, while others may be collected at the conclusion of the study. It is suggested the manufacturer include copies of data collection forms if available.

4. Follow-up Plan

For studies requiring follow-up of patients, a plan is needed to describe how subjects will be followed, e.g., through the patient's personal physician, personal interviews, monthly phone calls, relatives, etc. For patients who become "apparently" lost, explain the procedures that will be used to find them.

5. Data Quality Control

Detailed procedures for monitoring data to ensure accuracy should be discussed. For example, a subset of patients may have duplicate data collected by two people, or certain mutually exclusive terms may exist such that records can be compared using automated techniques to rule out data entry error. Techniques for anticipating, identifying, and correcting errors should be described.

6. Length/End of Study

When will data collection end? The conclusion of the study can be in terms of an absolute date, relative date, attainment of minimal sample size or number of person-years of follow-up, etc. However, the manufacturer should justify the selected method.

7. Proposed Analytical Plan

This section should be a description of all on-going, interim, and final analyses to be performed. The discussion of any proposed statistical tests should include assumptions, formulas, references, and a brief explanation of why the selected tests are appropriate for the situation. Interim analyses designed to demonstrate that device performance is within the expected values should be outlined here, along with a proposed reporting schedule for the analyses.

D. REPORTING REQUIREMENTS

The manufacturer is required to submit plans that describe interim, and final reporting mechanisms. Each plan should outline the proposed reporting objectives and the rationale for the selection of each objective, a complete description of what information will be reported, what mechanism the manufacturer will use to report this information, and proposed reporting timeframe(s).

It is important to note that reports to the Agency in these instances must be made in addition to reports submitted in compliance with the Medical Device Reporting Regulation.

1. Interim Reporting

In addition to describing the contents and mechanisms for interim reporting, the manufacturer will identify benchmark points in the study. These benchmark points represent critical phases in the conduct of the postmarket surveillance study and will also serve as report due dates. Unless noted otherwise, these interim communications will require a report of study progress by the Principal Investigator and a summary of the analyses of available data gathered under the protocol. At a minimum, interim reporting should be done at the following study benchmarks: initiation of the study, one-year post-initiation, the mid-point of the study (this may be time or subject dependent depending upon the study design), and the completion of data collection.

2. Final Report

At the conclusion of the study, the manufacturer must submit a final report that shall summarize the results of the study. All analyses and evaluations of these results must directly address the original study objectives. These results must include a clear presentation of patient and/or device data. All data that support statistical results or conclusions must be adequately referenced, and the report will provide detailed patient listings of all available data along with appropriate summary tables.

These summary tables should be concerned with all study variables, timeframes, or other factors as related to study objectives, or

statistical analyses. Where laboratory analyses of devices are performed, the analysis of errors associated with the test method must be included.

III. PRINCIPAL INVESTIGATOR

The law directs the Agency to determine if the proposed principal investigator of the study has sufficient qualifications and experience to conduct this surveillance. Typically, the principal investigator of an investigation is an individual who actually conducts the investigation, that is, under whose direction postmarket investigations of the device are conducted.

In the event of an investigation that is conducted by a team of individuals, the term principal investigator refers to the individual who is the designated leader of the team. For purposes of Section 522 of the Act, the Agency extends this definition to include study monitors, i.e., individuals who are qualified by training and experience to oversee and manage an investigation, but who may not necessarily be active investigators in the study. It should be noted that such individuals must also be qualified by training and experience to conduct these investigations.

The principal investigator or monitor is responsible for ensuring that the investigation is conducted in accordance with any signed agreements, the investigational plan, and any applicable Agency regulations. In addition, if applicable, the principal investigator/monitor protects the rights, safety and welfare of subjects.

In order that the Agency may determine that an individual is qualified by both training and experience to conduct a postmarket surveillance study, the sponsor shall submit a detailed Curriculum Vitae of the proposed investigator; a statement of the investigator's relevant training and experience - including the dates, location, extent, and type of experience; and, if the investigator was ever involved in an investigation or research program that was terminated other than by contractual agreement, an explanation of the circumstances surrounding the termination.

In addition, the manufacturer is required to submit a statement signed by the investigator who has agreed to conduct the investigation in accordance with the protocol, applicable Agency regulations and guidance, and conditions of approval that may have been imposed by the Agency. Finally, the investigator shall submit a disclosure of financial interests that are directly or indirectly affected by the sales and distribution of the device that is the subject of this postmarket investigation. Any subsequent change in financial interest should also be reported to the Agency.

CHANGES TO THE POSTMARKET SURVEILLANCE STUDY

The manufacturer will notify the Postmarket Surveillance Studies Branch of any proposed changes in ongoing studies. A proposed change must be submitted for Agency approval prior to execution. For example, if there is a change in the principal investigator of the study, the manufacturer must submit information regarding the qualifications and experience of the proposed replacement.

THE PROTOCOL CHECKLIST

A copy of the Postmarket Surveillance Protocol Checklist is attached to this guidance document. This checklist summarizes the topics listed in the Contents of the Postmarket Surveillance Submission section. A presentation and discussion of these issues are necessary to evaluate any study that is designed to comply with the law and result in the collection of useful data or other information necessary to protect the public health and to provide safety and effectiveness information for the device.

The purpose of the protocol checklist is to provide Agency reviewers and manufacturers alike with an outline of what the Agency believes are the essential administrative and research issues that must be addressed by any proposed surveillance protocol. This checklist in effect represents those general items that the Agency considers the minimum information it would need in order to evaluate the scientific validity of a proposed postmarket surveillance study.

In a protocol submission, the manufacturer must include a discussion of each item on the checklist or explain why a particular issue is not applicable to a postmarket surveillance study of the subject device. A protocol submitted for review that does not address the minimum requirements as specified in the checklist will be considered administratively incomplete and not approved. Protocols that are found to be administratively complete will be reviewed by an appropriate scientific and technical review committee.

Satisfying the immediate administrative requirements of the protocol checklist does not necessarily imply that a proposed protocol will be subsequently approved by the review committee. Approval of the postmarket surveillance study will be based upon the appropriate selection of study objectives relative to critical device variables, the scientific and technical merits of the proposed research design as it relates to the stated objectives, and the qualifications of the proposed principal investigator.

AGENCY CONTACT OFFICE

This guidance is subject to future revision, and the Agency welcomes any suggestions to improve either the document or the associated review process. If there are any comments or questions regarding this guidance, please contact the Postmarket Surveillance Studies Staff at the address below:

Division of Biometric Sciences (HFZ-160)
Center for Devices and Radiological Health
12200 Wilkins Avenue
Rockville, Maryland 20852

Telephone: 301-443-7120
FAX: 301-443-0097

DRAFT

SECTION 522 POSTMARKET SURVEILLANCE
PROTOCOL CHECKLIST

DATE:_____

REVIEWER:_____

	YES	NO	COMMENT
I. Organizational and Administrative			
A. General Information			
1. Device Generic Name	____	____	_____
2. Device Trade Name	____	____	_____
3. Manufacturers Name and Address	____	____	_____
4. Contact Person Address & Telephone	____	____	_____
5. PMA or 510(k) Number	____	____	_____
6. Date of PMA Approval or 510(k) Decision	____	____	_____
7. Certification of Date Device First Introduced or Delivered for Introduction into Interstate Commerce	____	____	_____
B. Table of Contents with Page Numbers	____	____	_____
C. Device Description			
1. System Description			
a. Identification of Critical Components	____	____	_____
b. Materials Used	____	____	_____
2. Indications for Use	____	____	_____
3. Claims for the Device	____	____	_____

DRAFT

	YES	NO	COMMENT
I. Surveillance Protocol			
A. Study Objectives	____	____	_____
B. Study Variables	____	____	_____
1. Discussion of Denominator Data	____	____	_____
C. Study Design			
1. Type of Study	____	____	_____
2. Study Size			
a. Source(s) of Patient or Device Data	____	____	_____
b. Pooling	____	____	_____
3. Data Collection Plan and Forms	____	____	_____
4. Follow-up Plan	____	____	_____
5. Data Quality Control	____	____	_____
6. Length/End of Study	____	____	_____
7. Proposed Analytical Plan	____	____	_____
D. Reporting Requirements			
1. Interim Reporting	____	____	_____
2. Final Report	____	____	_____
III. Principal Investigator			
A. Description of Qualifications	____	____	_____
B. Description of Experience	____	____	_____
C. Curriculum Vitae Included	____	____	_____
D. Signed Copy of Investigator Agreement	____	____	_____
E. Disclosure of Financial Interests	____	____	_____

Agency Sec. 522 RPS

Protocol Checklist

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

[DOCKET NO. _____]

PREMARKET APPROVAL OF MEDTRONIC® TRANSVENE® LEAD SYSTEM

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by Medtronic, Inc., Minneapolis, MN, for premarket approval, under section 515 of the Federal Food, Drug, and Cosmetic Act (the act), of Medtronic® Transvene® Lead System. After reviewing the recommendation of the Circulatory System Devices Panel, FDA's Center for Devices and Radiological Health (CDRH) notified the applicant by letter on DEC 9 1988, of the approval of the application.

DATE: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESS: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review to the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Doris Terry

Center for Devices and Radiological Health (HFZ-450)

Food and Drug Administration

1390 Piccard Drive

Rockville, MD 20850

301-594-1523.

SUPPLEMENTARY INFORMATION: On April 1, 1992, Medtronic, Inc., Minneapolis, MN, 55432, submitted to CDRH an application for premarket approval of Medtronic® Transvene® Lead System. The device is a transvenous defibrillation lead system and is intended for single long-term use and each lead is designed to be used only with a compatible Medtronic implantable tachyarrhythmia control device along with at least one other Medtronic defibrillator lead. The lead system has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated. Current medical research indicates that such patients should: (1) have survived at least one episode of a cardiac arrest, presumably due to a ventricular tachyarrhythmia as evidenced by resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; or (2) in the absence of a prior cardiac arrest, have poorly tolerated sustained VT and/or VF, which occurs spontaneously, or can be induced, despite the best antiarrhythmic drug therapy.

The natural history of patients with hemodynamically stable sustained VT is not well defined. While this patient population was included in the Transvene® Lead clinical study, no conclusions were drawn from the data obtained on this specific patient group.

Prior to Transvene® implant, it is strongly recommended that patients undergo a complete cardiac evaluation, which should include extensive electrophysiologic testing. Also, extensive electrophysiologic evaluation and testing of the safety and efficacy of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the Transvene® system.

On August 2, 1993, the Circulatory System Devices Panel, an FDA advisory panel, reviewed and recommended approval of the application. On , CDRH approved the application by a letter to the applicant from the Acting Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

OPPORTUNITY FOR ADMINISTRATIVE REVIEW

Section 515(d)(3) of the act (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act (21 U.S.C. 360e(g)), for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under Part 12 (21 CFR Part 12) of FDA's administrative practices and procedures regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under 10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. This notice is issued under the Federal Food, Drug, and Cosmetic Act Section 520(h), 90 Stat. 554-555, 571 (21 U.S.C. 360e(d), 360j(h)) and under authority

delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated:_____.

_____

D. Bruce Burlington, M.D.
Director
Center for Devices and
Radiological Health

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL

_____

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. General Information

Device Generic Name: Transvenous Defibrillation Lead System

Device Trade Name: Medtronic® Transvene® Lead System

Applicant's Name and Address: Medtronic, Inc.
7000 Central Avenue N.E.
Minneapolis, MN 55432

Premarket Approval (PMA) Application Number: P920015

Date of Panel Recommendation: August 2, 1993

Date of Notice of Approval to the Application: DEC 9 1993

II. Indications for Use

The Medtronic® Transvene® Lead System (Models 6963, 6966 and 6999), (hereafter referred to as the Transvene® Leads) with Medtronic Pacer-Cardioverter-Defibrillator (PCD®) Model 7217B Multiprogrammable Tachyarrhythmia Control System (hereafter referred to as the PCD® Transvene® System) is intended for single long-term use and each lead is designed to be used only with a compatible Medtronic implantable tachyarrhythmia control device along with at least one other Medtronic defibrillation lead. The lead system has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated. Current medical research indicates that such patients should: (1) have survived at least one episode of a cardiac arrest presumably due to a ventricular tachyarrhythmia as evidenced by resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; or (2) in the absence of a prior cardiac arrest, have poorly tolerated sustained VT and/or VF, which occurs spontaneously or can be induced, despite the best antiarrhythmic drug therapy.

The natural history of patients with hemodynamically stable sustained VT is not well defined. While this patient population was included in the Transvene® Lead clinical study, no conclusions were drawn from the data obtained on this specific patient group.

Prior to Transvene® implant, it is strongly recommended that patients undergo a complete cardiac evaluation, which should include extensive electrophysiologic testing. Also, extensive electrophysiologic

evaluation and testing of the safety and efficacy of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the Transvene® system.

III. Device Description

The PCD® Transvene® System consists of the following:

- Model 6963 Unipolar, Endocardial, Coronary Sinus or Superior Vena Cava Lead;
- Model 6966 Tripolar, Endocardial, Screw-In Ventricular Lead;
- Model 6999 Unipolar, Subcutaneous, Oval Patch Lead;
- commercially available Model 7217B PCD®,
- commercially available Model 5355 External Tachyarrhythmia Control Device (ETCD) and ETCD™ accessories such as the Model 5418 and 5419 Patient Cables, Model 5414 Test Load, Model 5417 Electrogram Cable and Model 6701 Lead End Cap; and
- commercially available Model 9788 MemoryMod™ Software Module.

The PCD® Transvene® Lead System is implanted using a transvenous approach to the right heart. This means that PCD® therapy may be provided without the necessity of a thoracotomy (open chest surgical procedure) for lead placement.

The PCD® Transvene® System may be programmed to deliver cardioversion and defibrillation therapies in 1 of 3 different configurations. The configurations include the following: single (a single pulse delivered over one pathway; a simultaneous pulse delivered over two pathways; and, two sequential pulses separated by a very short interval delivered over two different pathways.

The lead configurations to be used depend on the desired pathway and the physician's placement preference. The available configurations involve using 2 or 3 leads to deliver therapies. A PCD® Transvene® System using two leads delivers cardioversion and defibrillation pulses between two electrodes. The lead system consists of either of the following combinations: right ventricle and coronary sinus; right ventricle and superior vena cava; or right ventricle and subcutaneous patch. A system using three leads delivers cardioversion and defibrillation pulses either simultaneously or sequentially from the anode electrodes to the COMMON (designated PCD® connection) defibrillation electrode. The lead system may have the following combinations: right ventricle, superior vena cava and subcutaneous patch; right ventricle, coronary sinus and subcutaneous patch; and right ventricle, coronary sinus and superior vena cava.

A. Model 6963 Unipolar, Endocardial, Coronary Sinus or Superior Vena Cava Lead

The Model 6963 Unipolar, Coronary Sinus or Superior Vena Cava, Transvenous Lead (hereafter referred to as the Model 6963 Lead) is designed for the delivery of cardioversion and defibrillation pulses in the coronary sinus or superior vena cava.

The Model 6963 Lead has a platinum alloy electrode and silicone insulation which surrounds a low resistance platinum alloy conductor coil. The Model 6963 Lead has a 6.5 mm connector.

B. Model 6966 Tripolar Endocardial, Screw-In Ventricular Lead

The Medtronic Transvene Model 6966 Tripolar, Endocardial, Screw-In Ventricular Lead (hereafter referred to as the Model 6966 Lead) is designed for pacing, sensing, and delivering cardioversion and defibrillation pulses in the ventricle. The Model 6966 Lead has three electrodes: the helix, ring and coil. The helix tip electrode and the ring electrode may be used for bipolar pacing and sensing; the coil electrode is intended to be used for delivery of cardioversion and defibrillation pulses. The Model 6966 Lead has a 6.5 mm connector.

The helix is made of platinum alloy that can be actively fixed in the endocardium. The helix can be extended or retracted by rotating the lead connector pin with a special fixation tool.

The ring electrode is made of platinum alloy and is located proximal to the helix and connects electrically to the connector ring of the bipolar leg of the bifurcation.

The defibrillating coil electrode is made of platinum and is most proximal to the pulse generator and connects electrically to the connector pin of the unipolar leg of the bifurcation.

C. Model 6999 Unipolar, Subcutaneous, Oval, Patch Lead

The Medtronic Model 6999 Unipolar, Subcutaneous, Oval, Patch Lead (hereafter referred to as the Model 6999 Patch Lead) is designed for the delivery of cardioversion and defibrillation pulses in the subcutaneous or submuscular space of the left lateral chest wall.

The Model 6999 Patch Lead has a low resistance MP35N conductor coil and platinum alloy electrode coils for cardioversion and defibrillation. The Model 6999 lead has a 6.5 mm unipolar connector.

IV. Contraindications

The PCD® Transvene® System is contraindicated in the following:

- patients with transient ventricular tachyarrhythmias due to reversible causes, e.g., drug intoxication, electrolyte imbalance, sepsis or hypoxia; and

- patients with transient ventricular tachyarrhythmias due to other factors, e.g., myocardial infarction and electrocution.

When tricuspid valvular disease or a mechanical heart valve is present, use of a ventricular endocardial lead (the Model 6966) is contraindicated.

The PCD® Transvene® Lead System is also contraindicated for the sole use of detection and treatment of atrial arrhythmias.

V. Warnings

The warnings for the Transvene Leads include the following:

- Use only battery-powered equipment during lead implantation and testing to protect against fibrillation that may be caused by alternating currents. Line-powered equipment used in the vicinity of the patient must be properly grounded. Lead connector pins must be insulated from any leakage currents that may arise from line-powered equipment.

- Do not attempt to use the Transvene® Lead system with any device other than a Medtronic implantable tachyarrhythmia control device for which it has been tested. While there has been no testing of the Transvene® leads with a non-Medtronic device, the potential adverse consequences of using such a combination may include, but are not limited to, undersensing cardiac activity and failure to deliver necessary therapy.

- Two anchoring sleeves are provided with the leads (Models 6963 and 6966). Both anchoring sleeves should be used as described in the section of the manual "Anchoring the Lead" to assure adequate fixation.

- If patients do not meet the implant criteria (demonstration of a 10 Joule safety margin) for a transvenous lead system, physicians should consider implanting an epicardial cardioversion/defibrillation lead system. If an epicardial system is to be implanted after testing a transvenous system, consider performing the procedure at a later date. The Transvene® clinical study showed a 9.3 percent perioperative death rate for patients failing the implant criteria for a Transvene® system and receiving

an epicardial system. This compares to 0.7 percent for those patients receiving a Transvene® system without the additional epicardial surgical procedure.

In addition the following warnings apply to the Model 6999 Lead.

- The Model 6999 Lead is not intended for epicardial or pericardial placement since testing has not been performed to determine if epicardial or pericardial use is safe or effective.

- The Model 6999 Leads have palpable nodes on the insulation side of the patch which must face the skin surface to assure the electrode surface is facing the heart. If the insulation side of the patch is facing the heart cardioversion/defibrillation energy may be inadequate to reliably convert arrhythmias.

- Placement of the patch over nerve tissue may result in nerve damage.

VI. Precautions

The precautions for use of the Transvene® Leads include the following:

- Defibrillation equipment should be kept nearby for immediate use during the acute lead system testing, implantation procedure, or whenever arrhythmias are possible or intentionally induced during post-implant testing.

- Carefully inspect the lead sterile package prior to opening; if the seal or package is damaged, contact your local Medtronic representative.

- Leads should be handled with great care at all times. Any severe bending, kinking, stretching, or handling with surgical instruments may cause permanent damage to the lead.

- Lead insulators attract small particles such as lint and dust. Therefore, protect the lead from materials shedding these substances. Handle the lead with sterile surgical gloves that have been wiped with a sterile moist sponge or equivalent.

- Do not immerse leads in mineral oil, silicone oil, or any other liquid.

- Use ethylene oxide only. Do not resterilize more than one time.

- Do not use surgical instruments to grasp the lead or connector pin when tunneling.

- Chronic repositioning or removal of the lead may be difficult because of the fibrotic tissue. However, if a lead must be

removed or repositioned, proceed with extreme caution. If a lead is abandoned, it should be capped to avoid transmitting electrical signals. Return all removed or unused leads or portions thereof to Medtronic.

The following precautions apply to the Model 6963 and 6966 Leads:

- Given the body diameter of transvenous defibrillation leads, insertion via a subclavian approach should be done as far lateral as possible to avoid clamping the lead body between the clavicle and the first rib. Clamping the lead can eventually cause the conductor to fracture, can cause damage to the insulation, or can cause other damage to the lead. This can result in complications such as loss of detection, loss of pacing therapies, or loss of cardioversion/defibrillation therapy. Certain anatomical abnormalities, such as thoracic outlet syndrome, can also precipitate pinching and subsequent fracture of the lead. If the subclavian approach is required, avoid techniques that can damage the lead. Specifically, do not force the lead if significant resistance is encountered. Do not use techniques such as adjusting the patient's posture (i.e., raising the arm or putting a towel behind the person's back) to facilitate the passage of the lead. If resistance is encountered, it is recommended that an alternate venous entry site be used, e.g., the cephalic vein.

- To avoid damage to the lead or body tissue, do not use excessive force or surgical instruments to insert a stylet into the lead. When handling a stylet, avoid overbending, kinking, or blood contact.

- Repeated insertions of a stylet increases the chance that blood or other fluids may accumulate on it, which may cause difficulty in passing the stylet through the lead and may cause damage to the lead.

- Avoid placing the lead under extreme tension or angulation to prevent dislodgement and possible lead fracture. Do not grip the lead with surgical instruments.

- To avoid damage to the stylet, do not use a sharp object to impart a curve to the distal end.

- Do not use the anchoring sleeve tabs for suturing.

- Do not use surgical instruments to grasp the lead or connector pin when tunneling.

- Always remove the stylet before connecting the lead to the pulse generator. Failure to remove the stylet may result in lead failure.

The following precaution applies only to the Model 6966 Lead: The maximum number of revolutions of the electrode fixation tool needed to extend or retract the helix is 20. Exceeding the maximum revolutions may damage the lead.

VII. Alternative Practices and Procedures

Cardioversion and defibrillation is an accepted treatment for the indications described in Section II above. The most reliable method for increasing the survival of persons at high risk of sudden cardiac death is the prompt treatment of ventricular fibrillation and hemodynamically unstable ventricular tachycardias by the application of a high energy electrical discharge to the heart. The most widespread alternative chronic treatment is the suppression of ventricular tachyarrhythmias with antiarrhythmic drug therapy. Other commercially available automatic implantable pacer cardioverter defibrillator systems, may also meet the needs of the patients with the conditions described in Section II above.

VIII. Marketing History

On November 1991, Medtronic, Inc. began marketing the PCD® Transvene® System outside the United States. Approximately 2000 PCD® Transvene® Systems were marketed with no adverse effects reported. The system has not been removed from any market for reasons of safety and effectiveness.

IX. Potential Adverse Effects

The potential adverse effects related to the use of endocardial leads include, but are not limited to the following patient-related conditions: fibrillation or other arrhythmias, air embolism, cardiac perforation, heart wall rupture, cardiac tamponade, infection, endocarditis, constrictive pericarditis, pneumothorax, hemothorax, and tissue necrosis.

Other potential adverse effects known to be related to the lead system, include the following: lead dislodgement, lead conductor or electrode fracture, insulation failure, and poor connection which may lead to loss of detection, cardioversion, defibrillation, or pacing therapies.

X. Summary of Studies

A. Electrical Testing

Electrical resistance testing was performed to ensure proper functioning of the Transvene® Leads. Seventeen Model 6963 Leads, 35 Model 6966 Leads and 18 Model 6999 Leads were tested.

Electrical resistance was measured on all of the Transvene Leads at 21 degrees Centigrade (C). All samples met the design specifications.

B. Environmental Analysis Testing

Environmental Analysis testing was performed to determine the leads' resistance to thermal stresses (shocks) when subjected to temperature extremes. Fifteen Transvene® Leads of each model were subjected to a temperature range of 45 degrees C to 70 degrees C. After shock testing, visual inspection and electrical resistance measurements were performed. There were no visual defects and the electrical resistance of all the samples met the design specifications.

C. Mechanical Testing

The mechanical integrity of the Transvene® Leads was assessed. The leads and/or assemblies were subjected to the following:

- flex testing;
- composite pull strength testing;
- crimp and weld pull strength testing;
- insertion and withdrawal force testing; and
- leakage testing;

1. Flex Testing

Flex testing was performed to evaluate the integrity of the leads when subjected to bending stresses intended to simulate in vivo conditions. The flex testing consisted of mounting 11 samples of insulated conductor coils and 11 samples of uninsulated electrode coils of each of the Transvene® Leads in a lead flex test fixture. The insulated conductor coils and uninsulated electrode coils were flexed at 21 degrees C and at a bend radius of 00.236 inches. All samples exceeded the specifications.

2. Composite Pull Strength Testing

Composite pull strength testing was performed to evaluate the overall pull strength of the lead and connections. Fifteen Transvene® Leads of each model were boiled in Ringer's solution or soaked in normal saline and pull tested while wet, utilizing a tensile testing machine. The samples were pulled until failure at a rate of 5 inches per minute. The initial failures were then analyzed statistically for the confidence level in meeting the specification for the composite lead which is 1.0 pound (lb) minimum. All samples met or exceeded specifications.

3. Crimp and Weld Pull Strength Testing

Crimp and weld pull strength testing was performed to evaluate the strength of the connections of the PCD® Transvene® System. Fifteen subassemblies of each Transvene® Lead were pull tested by using a tensile testing machine. The samples were pulled until failure at a rate of 4 inches per minute with forces from 1 lb to 3.0 lbs. All samples met or exceeded the design specifications.

4. Insertion and Withdrawal Force Testing

Insertion and withdrawal force testing was performed to ensure compatibility of the Transvene Leads with the PCD® Model 7217B. Twenty-five samples of each Transvene® Lead were tested at an insertion force greater than or equal to 3.0 lbs and a withdrawal force less than or equal to 2.5 lbs. The results of testing demonstrated no physical changes. All measurements were within specifications.

5. Leakage Testing

Fluid leakage tests were conducted on the lead assemblies and the connector of the Model 7217 B PCD® to determine if there was fluid leakage. Ten samples of each Transvene® Lead were tested. Electrical impedance was measured from the case of the Model 7217B PCD® to the lead connections while immersed in fluid. All samples met specifications.

D. Life Testing

In addition to the above tests, life testing was performed to assess the overall integrity of the Transvene® Leads. Testing included subjecting 15 samples of each Transvene® Lead model to soaking, flexing and high-voltage pulsing. A separate test which involved crushing the leads was performed on 10 samples each of the Models 6963 and 6966 leads. Electrical resistance values were measured before and after all tests. The results demonstrated that all of the Transvene® Lead models met the acceptance criteria.

E. Biocompatibility

The biocompatibility of the tissue contact materials used in the Transvene® Leads has been well established historically. These materials include polyurethane, silicone rubber, silicone rubber/titanium dioxide and platinum/iridium. The results of USP/Tripartite testing (hemolysis, toxicity, pyrogenicity, mutagenicity tests) demonstrated that all of the materials were non-hemolytic, non-pyrogenic, non-toxic, non-mutagenic and biocompatible.

F. Animal Studies

The Transvene® Leads were evaluated in acute and chronic animal studies to assess the toxicity of the leads as well as its stability over a minimum of 2 years. One acute study and 3 chronic studies were performed.

The objective of the acute study was to quantify the amount and nature of shock-induced damage to the myocardial tissue resulting from multiple, high energy defibrillation shocks delivered via the Transvene® Leads. The results of the study of 7 canines revealed only minimal shock-induced necrosis (less than 0.1-0.5 percent by weight), which did not result in functional impairment of the cardiac tissue. The findings demonstrated that the Transvene® Leads did not cause significant myocardial damage in canines and could be safely implanted in humans.

The objective of the chronic studies was to evaluate the suitability for human clinical use, and to evaluate the chronic stability of the Transvene® Leads by monitoring defibrillation and pacing thresholds. The studies also assessed the amount and nature of shock-induced damage to the myocardial tissue resulting from defibrillation energy. The results of the studies on 16 canines demonstrated that the performance of the PCD® Transvene® System conformed to specifications and design requirements. Stable pacing and defibrillation thresholds and appropriate intracardiac sensing over at least a 2-year period were demonstrated.

G. Clinical Studies

The primary objectives of the study of the PCD® Transvene® System include the following: evaluating and monitoring the system in the detection and treatment of ventricular tachycardia (VT) and ventricular fibrillation (VF); estimating the survival from sudden cardiac death and overall survival.

A total of 78 investigative centers participated in the clinical study. There were 35 centers in the United States and 43 outside the United States. The clinical experience covered a total of 762 implants of the PCD® Transvene® System in 757 patients as of February 1, 1993. The performance of the patients was compared to the Ventak® Model 1600 AICD™ population (historical control with 292 patients, approved for marketing on May 2, 1991) and the Medtronic PCD® Epicardial System population (concurrent control with 742 patients, approved for marketing on February 11, 1993).

1. Follow-up Schedule

All patients enrolled in the clinical study underwent extensive pre-implant testing as well as operative testing. In addition, patients were evaluated prior to hospital

discharge, 1 month post implant, 3 months post implant and then at intervals of every 3 months. At implant, an evaluation was performed to demonstrate proper detection and termination of VF by the PCD® Transvene® System. At the follow-up intervals, regular testing was performed to evaluate chronic stability of the programmed therapy and sensing parameters. This testing included the following: assessing the relative stability of the energy required for patient treatment; evaluating manual charge times; measuring battery voltage; and evaluating the stability of the implanted Transvene® Leads. In some cases additional testing, which included inductions of arrhythmias, was performed at the physician's discretion to evaluate spontaneous events.

2. Patient Population

The patient population enrolled in the clinical study was predominately male (610, 80.6 percent) with a mean age of 59.4 years. In 377 (49.8 percent) patients, the primary indication for implant was recurrent, sustained VT without an episode of sudden cardiac death. Coronary artery disease was the primary disease process in 561 (74.1 percent) patients. These patients had a mean reported ejection fraction of 35.6 percent.

The mean documented implant duration for the patient population was 11.7 months and ranged from implant to 37.4 months. The documented cumulative implant duration was 8,895 months. There are 657 (86.8 percent) patients with implant durations equal to or greater than 6 months.

Patients may use either 2 or 3 Transvene® Leads to deliver therapy. All 757 patients were implanted with 3 Transvene® Leads. Of these, 574 patients (75.8 percent) were programmed to a sequential defibrillation pathway (3-lead system), 178 patients (23.5 percent) were programmed to a simultaneous defibrillation pathway (3-lead system), and 10 patients (1.3 percent) were programmed to a single defibrillation pathway (2-lead system). The configuration chosen was dependent on the patient's history, condition, and anatomy, and the pathway which would deliver the least energy to defibrillate. Both the 2 and 3-lead systems can be used, and were used successfully to treat the patient's ventricular tachyarrhythmia. This was determined by assessing the patient's defibrillation threshold (DFT) prior to implant. In the patient population, the mean DFT was 14.8 Joules (J).

Prior to implanting the PCD® Transvene® System, the patient had to have 3 out of 4 successful defibrillations at 18 J or less. The need for a change in this implant criteria was

demonstrated during the clinical study. Subsequently, approval was received under the investigational device exemptions (IDE) regulation to make the change. This change allowed implant when there are 2 consecutive successful terminations at 24 J or less, or 3 out of 4 successful defibrillations at 24 J or less. Even though the patient population was comprised of patients who were subject to the original implant criteria, adequate data were provided to support the new implant criteria.

3. Spontaneous and Induced Episode Experience

Of the 757 patients who received a PCD® Transvene® System, 597 (78.9 percent) patients either experienced a spontaneous VT and/or VF episode or had VT and/or VF induced during a post-implant electrophysiological (EP) study (354 of the 597 patients had induced episodes of either VT or VF or VT and VF during the follow-up periods). A total of 458 of the 757 patients (60.5 percent) experienced 12,009 episodes of spontaneous VT and VF that were detected and treated by the PCD® Transvene® System. Of these 458 patients, 141 patients (18.6 percent) experienced VT only, 142 patients (18.8 percent) experienced VF only, and 175 patients (23.1 percent) experienced VT and/or VF. The overall success rate of the PCD® Transvene® System in terminating these spontaneous episodes included the following: for VT only, 98.3 percent (9,864 of 10,027); for VF only, 98.4 percent (1,951 of 1,982) and for VT and/or VF, 98.4 percent (11,815 of 12,009).

The incidence of unsuccessful termination of a "true" (no indication of atrial fibrillation or sinus tachycardia) spontaneous episode of VT despite delivery of all four therapies was 0.7 percent (68 of 10,027). The remaining 0.9 percent (95 of 10,027) were episodes of sinus tachycardia or atrial fibrillation where the device responded appropriately based on the programmed detection parameters, however, the device was unsuccessful in terminating the arrhythmia.

The incidence of unsuccessful termination of a "true" episode of VF despite delivery of all four therapies was 0.3 percent (5 of 1,982). The remaining 1.3 percent (26 of 1,982) were episodes of sinus tachycardia and atrial fibrillation.

4. Complications and Observations

For purposes of the clinical study, the reported medical events were identified as complications and observations. A complication was defined as a symptomatic or asymptomatic clinical event with potential adverse effects, which can not be treated or resolved by reprogramming the device, and

requires invasive intervention. An observation was defined as a symptomatic or asymptomatic clinical event which either does not require invasive intervention, or which can be corrected by reprogramming the device.

There have been a total of 176 complications identified in 147 patients and 212 observations identified in 178 patients. Thus 19.4 percent (147 of 757) of the patients have experienced a complication and 23.5 percent (178 of 757) have experienced an observation. The most frequently reported complications were pocket infection (3.2 percent, 24 of 757), lead fractures (1.2 percent, 9 of 757), and lead dislodgement (11.4 percent, 86 of 757). In an attempt to reduce the lead dislodgement, modifications were made to the lead anchoring sleeve and a second sleeve was added to the lead. Analysis on 439 patients implanted with the two anchoring sleeves showed a dislodgement rate of 2.3 percent (10 of 439). Within the first 30 days of implant 34.8 percent (135 of 388) of the complications and observations occurred; 42.8 percent (166 of 388) occurred between 1 and 6 months and the remaining 22.4 percent (87 of 388) occurred at or greater than 6 months.

5. Explants

There have been 63 (8.3 percent) pulse generators explanted. Reasons for explant were patient deaths (22), infection (22), cardiac transplant (9), device performance (6), and lead system issues (4) which included 1 case each of twiddler's syndrome, fractured RV lead, increased DFT and dislodged RV lead. Of the 6 cases related to device performance, the reasons were: failure of an integrated circuit in 3 devices; hermetic leakage at the input to one of the integrated circuits in 1 device; and random component failure in 2 devices.

There were 77 patients who had received a pulse generator and were no longer active in the study. The reasons included the following: patient death (51), explant due to infection (17) and heart transplant (9).

6. Survival Data

There were 51 patient deaths reported (6.7 percent, 51 of 757). For the entire study, 5 deaths were classified as sudden cardiac (0.7 percent, 5 of 757), 31 were classified as non-sudden cardiac (4.1 percent, 31 of 757) and 15 were classified as non-cardiac (2.0 percent, 15 of 757). Of the 51 deaths, 7 patients had the PCD® programmed OFF at the time of death (includes 1 of the 5 sudden cardiac deaths). Thus, there were 7 patient deaths where PCD® therapy was unavailable due to the device being programmed OFF. The

decision to deactivate the device is usually made when the physician is concerned about the potential development of atrial fibrillation with rapid ventricular response or sinus tachycardia that might be detected as a ventricular tachyarrhythmia which can result in delivering inappropriate therapy.

Actuarial survival analysis was done on all patients who were either evaluated for implantation or in whom the PCD® Transvene® System was implanted. Thus the analysis was done from the perspective of intention to treat. Those patients in whom the PCD® was programmed OFF at the time of death or in whom no PCD® was implanted were included in the survival analysis. The 1 year survival probabilities for the intention to treat were as follows: sudden cardiac death (99.5 percent); non-sudden cardiac (96.2 percent); all cardiac (95.8); and non-cardiac (98.1 percent). These probabilities were calculated using the Kaplan Meier statistical package. Overall survival (from death due to all causes) was 93.3 percent. The actuarial projections did not include perioperative deaths (deaths which occurred within 30 days of implant), except in the calculation of 1 year survival from death due to all causes. The perioperative mortality was 0.7 percent (5 of 757): 2 sudden cardiac deaths; 2 non-sudden cardiac deaths; and 1 non-cardiac death.

The 1 year sudden cardiac death actuarial survival rate for the PCD® Transvene® System was 99.5 percent as compared to 98.6 percent for the historical control and 98.9 percent for the concurrent control. The 1 year survival rate from death due to all causes was 93.3 percent for the PCD® Transvene® System, 90.8 percent for the historical control and 88.6 percent for the concurrent control.

XI. Conclusions Drawn From Studies

The results of the laboratory and animal testing and the clinical study of the PCD® Transvene® Lead System demonstrated that the system, including all the associated components, performs according to its design intent and is safe and effective for use. One year survival rates from sudden cardiac death included the following: PCD® Transvene® System (99.5 percent), historical control (98.6 percent) and concurrent control (98.9 percent).

XII. Panel Recommendations

The Circulatory System Devices Panel reviewed this application at a public meeting on August 2, 1993, and recommended approval for the PCD® Transvene® Lead System. The recommendation for approval was based on

modifications to the labeling which should include the following: diagrams which show proper insertion of the endocardial Transvene® Leads and how the Model 6999 Patch lead should be applied to the subcutaneous tissue; a warning which states that the Model 6999 Patch lead is not for use on the pericardium or epicardium; pictures or diagrams of the various electrode configurations which serve as a guide for selection; a reference about using 5-minute intervals between VF inductions during testing; a warning which states that after extensive testing with a nonthoracotomy lead system a thoracotomy should be delayed at least 2 days (the clinical data showed that when a thoracotomy was performed immediately after testing, the perioperative mortality rate was increased from 0.7 percent to 9.3 percent); guidance regarding separating pacemaker leads from the Transvene® Leads; a statement which emphasizes the need for x-rays and pace/sense threshold testing at follow-up to check for lead dislodgement; and information regarding placing the leads via the cephalic vein when possible. In addition, the panel recommended that postmarket surveillance track the explanted Transvene® Leads for evidence of metal ion oxidation (MIO).

XIII. FDA Decision

On October 27, 1993, FDA found Medtronic Inc.'s facilities in compliance with the Device Good Manufacturing Practices regulation (21 CFR part 820).

FDA concurred with the recommendation of the Circulatory System Devices Panel. In addition, on September 23, 1993, in an approvable letter to the applicant, FDA required that the labeling should be modified to include the following: effectiveness data on the different lead configurations via the different pathways; information and/or recommendations about implanting the leads and testing the different configurations (for example, when to use a 2-lead versus a 3-lead configuration and when to implant in the SVC versus the CS); information or recommendations regarding implanting in patients who do not have the 10 J safety margin; information about how the incidence of infection can be reduced; a warning regarding the use of dual anchoring sleeves on the RV, SVC and CS leads; and an explanation regarding the necessity for explant and return of the lead upon the patient's death. In addition, FDA requested that the manufacturer note the following: The indications and contraindications for use of the Medtronic® Transvene® Lead System must be the same (with certain modifications) as those for the Medtronic® PCD® Epicardial System. Modifications pertaining to the labeling included the following: The second indication was changed to read as follows: "poorly tolerated, sustained ventricular tachycardia and/or fibrillation which recurs spontaneously or can be induced despite the best antiarrhythmic drug therapy". The following note in the labeling was also recommended: "The clinical outcome of hemodynamically stable, sustained VT patients is not fully known. The safety and effectiveness of the PCD® System in this subgroup of VT patients has not been determined." The technical manuals for Transvene® Leads must state that the leads are for use together as a system. The labeling (where

appropriate) must be consistent in all Transvene® Lead manuals. The information regarding the Transvene® Leads in the Medtronic® PCD® Epicardial manual must also be included in the Transvene® Lead manuals. There should be an identifying mark on the package label of the Transvene® Leads which distinguishes nonthoracotomy leads from thoracotomy leads. The Warnings and Precautions in the labeling must be identified and reported separately according to FDA's Blue Book Memorandum of March 8, 1991. The manufacturer should also provide a copy of the Patient's Manual which includes a reference to the use of nonthoracotomy leads with the PCD® models.

On October 12, and November 3, 1993, Medtronic, Inc. submitted an amendment to the application providing the information recommended by the panel and required by FDA.

FDA approval is subject to the applicant's compliance with the "Conditions of Approval for Implantable Defibrillators and Programmers" (Attachment A), and the conditions that (1) the sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520 (e) of the Federal Food, Drug and Cosmetic Act (the act) under the authority of section 515 (d) (1) (B) (ii) of the Act; and (2) that the device is further restricted within the meaning of section 520 (e) under the authority of section 515 (d) (1) (B) (ii) insofar as the approved labeling specifies the requirements that apply to the training of physicians who may use the device.

XIV. Approval Specifications

The post approval recommendations are discussed above in Section XIII.

Ms. Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

DEC 9 1993

Re: P920015
Medtronic® Transvene® Lead System
Filed: April 1, 1992
Amended: August 27, September 21, October 27 and November 5, 1992,
March 29, June 2, 14, July 9, October 12, and November 3, 1993

Dear Ms. Marrone:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Medtronic® Transvene® Lead System. The Medtronic® Transvene® Lead System (Models 6963, 6966 and 6999), (hereafter referred to as the Transvene® Leads) with Medtronic Pacer-Cardioverter-Defibrillator (PCD®) Model 7217B Multiprogrammable Tachyarrhythmia Control System (hereafter referred to as the PCD™ Transvene® System) is intended for single long-term use and each lead is designed to be used only with a compatible Medtronic implantable tachyarrhythmia control device along with at least one other Medtronic defibrillation lead. The lead system has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated. Current medical research indicates that such patients should: (1) have survived at least one episode of a cardiac arrest presumably due to a ventricular tachyarrhythmia as evidenced by resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; or (2) in the absence of a prior cardiac arrest, have poorly tolerated sustained VT and/or VF, which occurs spontaneously, or can be induced, despite the best antiarrhythmic drug therapy.

The natural history of patients with hemodynamically stable sustained VT is not well defined. While this patient population was included in the Transvene® Lead clinical study, no conclusions were drawn from the data obtained on this specific patient group.

Prior to Transvene® implant, it is strongly recommended that patients undergo a complete cardiac evaluation, which should include extensive electrophysiologic testing. Also, extensive electrophysiologic evaluation and testing of the safety and efficacy of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the Transvene® System.

We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval for Implantable Defibrillators and Programmers" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

Expiration dating for this device has been established and approved at 2 years.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act.

The device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the approved labeling specifies the requirements that apply to the training of physicians who may use the device.

In addition to the postapproval requirements, postmarket surveillance should track the explanted Transvene● leads for evidence of metal ion oxidation (MIO).

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

In addition, under Section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under Section 522(a)(1(A) the device cleared for marketing by this order as requiring postmarket surveillance.

Within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you are required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

Submit five (5) copies to:

Postmarket Studies Document Center
Suite 405 (HFZ-107)
1801 Rockville Pike
Rockville, Maryland 20852

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will cause your product to be misbranded and could lead to the imposition of civil money penalties or other regulatory actions. Any distribution of a misbranded device is a violation of the act and may result in a number of FDA enforcement actions, including (but not limited to) withdrawal of your PMA.

If you have questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch at (301) 594-0639.

Under Section 519(e) of the act (as amended by the Safe Medical Devices Act in 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of device user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under Section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonably likely to have serious adverse consequences. FDA has designated your device for tracking.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR § 821.20(b) and the devices that FDA has designated for tracking at 21 CFR § 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705-10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)).

If you have questions concerning this approval order, please contact Doris Terry at (301) 594-1523 or Arnold Alpert, Ph.D., at (301) 594-2186.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Acting Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

cc: HFZ-107
HFZ-401
HFZ-403
HFZ-450 Prepared by:DTERRY:jau:11/02/93
D.O. Revised:JDONELSON:jau:11/30/93
Revised:AALPERT:jau:12/03/93

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450	Terry	12/3/93		Kahn	12/3/93	402	A Alpert	12/3/93
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450	Leamer	12/3/93			12/3/93			

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

DEC 9 1993

Acting Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)

Premarket Approval of Medtronic® Transvene® Lead System - ACTION

The Director, CDRH
Through: ORA ________

ISSUE. Publication of a notice announcing approval of the subject PMA.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

(1) a premarket approval order for the above referenced medical device (Tab B); and

(2) the availability of a summary of safety and effectiveness data for the device (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.

Susan Alpert, Ph.D., M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION

DEC 9 1993

Approved ________ Disapproved ________ Date ________
prepared by CDRH, HFZ-450, Doris Terry, 8/26/93, 594-~~2018~~ 1523

cc: HFC-10 (w/original attachments and one copy)
HFZ-401 DMC (with attachments)
HFZ-402 PMA (with attachments)
HFZ-450 (with attachments)
typed by:jau:10/29/93

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OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450	[illegible]	11/29/93	450	Reamer	11/29/93	400	[illegible]	11/29/93
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[illegible] 12/3/93

[illegible] 12/8/93
402 A. Alpert 12/9/93

U.S. GOVERNMENT PRINTING OFFICE

SEP 23 1993

Ms. Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

RE: P920015
Medtronic® Transvene® Lead System
Filed: April 1, 1992
Amended: August 27, September 21, October 27 and November 5, 1992, March 29, June 2, 14, and July 9, 1993

Dear Ms. Marrone:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA). The Circulatory System Devices Panel which also reviewed your PMA, recommended to CDRH at the August 2, 1993, panel meeting that the PMA be considered approvable. CDRH is pleased to inform you that the PMA is approvable subject to your submission of the following:

1. The labeling should be modified to include the following directions for use:

   a. diagrams which demonstrate the proper insertion technique and final anatomic position of the intravascular leads and the Sub-Q patch;

   b. defibrillation efficacy data on the different lead configurations, various polarity combinations and sequential versus simultaneous discharges;

   c. information and/or recommendations regarding specific implantation techniques and methods of testing the different configurations. For example, when is it recommended to use a two-lead configuration versus a three-lead configuration, when to implant in the superior vena cava (SVC) versus the coronary sinus (CS), and how the most advantageous position of the Sub-Q patch is determined;

   d. information or recommendations, based on your experience, regarding implantation in patients who do not have at least a 10 Joule safety margin;

   e. information aimed at reducing the incidence of infection;

   f. instructions stressing the importance of pausing between inductions of ventricular fibrillation (VF) at the time of implantation for at least a specified period of time in order to

decrease morbidity and mortality. The comments and the pause duration suggested should be based on the experience of the primary investigators in your study;

g. information regarding the change in defibrillation thresholds that one may expect with time as based on the experience of your investigators in your study;

h. guidance and techniques for separating permanent pacemaker leads from the Transvene® leads to minimize the interaction between the two devices, and diagnostic methods which can be employed at implant or predischarge to confirm the absence of adverse interaction;

i. a statement which emphasizes the need for x-rays and pace/sense threshold testing at follow-up to check for lead dislodgement (x-rays should be done at 3-month intervals for 1 year);

j. information regarding techniques for placing the leads via the cephalic vein when possible; and

k. an explanation regarding the necessity for explant and return of the leads upon the patient's death.

2. The labeling should be modified to include the following warnings:

a. a statement that the Sub-Q patch lead is not for use on the pericardium or epicardium, because it is too inflexible to be used as such;

b. stronger and more specific language regarding the use of dual anchoring sleeves on the right ventricle (RV), SVC, and CS leads. Based on the experience of your investigators, please describe the techniques used to fixate the lead at the insertion into the vein to minimize dislodgment; and

c. information which states that after extensive VF inductions at implant testing with the nonthoracotomy lead system, serious consideration should be given to delaying the thoracotomy for at least 2 days. Please include a statement which states that the clinical data showed that when a thoracotomy was performed immediately after testing, the perioperative mortality rate was increased from 0.7 to 9.3 percent.

3. In addition you should note the following:

a. The indications and contraindications for use of the Medtronic® Transvene® Lead System must be identical (except for certain modifications which pertain to the Transvene® Leads and those described below) to those for the PCD™ Epicardial System. Please change your second indication to read: Poorly tolerated,

sustained ventricular tachycardia and/or fibrillation which recurs spontaneously or can be induced despite the best antiarrhythmic drug therapy. Please also include the following statement in your indications section:

Note: The clinical outcome of hemodynamically stable, sustained VT patients is not fully known. The safety and effectiveness of the PCD● Transvene System in this subgroup of VT patients has not been determined.

b. The technical manuals for the Transvene● Leads must state that the leads are for use together as a system. The labeling (where appropriate) must be consistent in all of the Transvene● Lead manuals. The information regarding the Transvene● Leads in the PCD● Manual must also be included in the Transvene● Lead manuals.

c. There should be an identifying mark on the package label which distinguishes nonthoracotomy leads from thoracotomy leads.

d. The Warnings and Precautions in the labeling must be identified and reported separately according to FDA's Blue Book Memorandum of March 8, 1991, (a copy of this memorandum was previously sent to you).

4. Provide a copy of the Patient's Manual which includes a reference to use of the non-thoracotomy leads with the PCD● models.

The PMA must be amended to include your concurrence with, or suggested revision of, the enclosed "Conditions of Approval for Implantable Defibrillators and Programmers."

The condition that the sale, distribution and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act.

The device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the approved labeling specifies the requirements that apply to the training of physicians who may use the device.

In addition to the above, an FDA inspection must find that the manufacturing facilities, methods and controls comply with applicable device Good Manufacturing Practice Regulations (21 CFR Part 820). If applicable, amend the PMA to include required manufacturing information not previously submitted.

This is to advise you that, following receipt of an approvable letter, an applicant is required by 21 CFR 814.20(e) to update its pending PMA with new safety and effectiveness information learned about the device from ongoing or completed studies that may reasonably affect an evaluation of the safety or effectiveness of the device or that may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling. This updated reporting is limited to studies sponsored by the applicant or to which the applicant has reasonable access. The update report shall be consistent with the data reporting provisions of the protocol. Any update report shall be submitted in three copies as an amendment to the PMA and shall include the FDA reference number assigned to the PMA.

CDRH will issue an approval order after the requested information has been reviewed and determined to be acceptable. You may not begin commercial distribution of the device until you have received an approval order.

As provided by 21 CFR 814.44(e)(2), you may amend your PMA as requested, or withdraw it, or you may treat this letter as a formal denial of approval. If you choose the latter, you may request administrative review,.either through a hearing or review by an independent advisory committee, under section 515(d)(3) and 515(g) of the act by filing a petition with the Food and Drug Administration, Dockets Management Branch (HFA-305), Room 1-23, 12420 Parklawn Drive, Rockville, Maryland 20857, within 30 days of the date you receive this letter. A petition for administrative review must be submitted in accordance with general administrative procedures for submission of documents to the Dockets Management Branch (21 CFR 10.20) and in the form of a petition for reconsideration (21 CFR 10.33). After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issues to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

The above requested information must be submitted in the form of an amendment (3 copies). Unless you amend this PMA to request an extension, and the extension is approved, FDA will consider the PMA to have been withdrawn voluntarily if you fail to respond in writing to this request for an amendment within 180 days of the date of this letter as provided under 21 CFR 814.44(g). Any request for an extension must be submitted within the 180-day period, justify the need for the extension, and provide a reasonable estimate as to when the requested information will be submitted.

All amendments to the PMA must be submitted in triplicate to the address below and shall reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

In addition, under Section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under Section 522(a)(1)(A) the above noted device as requiring postmarket surveillance.

Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study to include the evaluation of the explanted leads for evidence of metal ion oxidation (MIO), and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

Postmarket Studies Document Center
Room 408 (HFZ-107)
12720 Twinbrook Parkway
Rockville, Maryland 20852

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will cause your product to be misbranded and could lead to the imposition of civil money penalties or other regulatory actions. Any distribution of a misbranded device is a violation of the act and may result in a number of FDA enforcement actions, including (but not limited to) withdrawal of your PMA.

If you have questions concerning postmarket surveillance study requirements, contact Postmarket Surveillance Studies Branch at (301) 594-0639.

Finally, on August 16, 1993, the Final Rule for Device Tracking was published in the FEDERAL REGISTER, pages 43442-43455 (enclosed). FDA is required to provide notice to PMA applicants in an approvable letter that their device is

subject to the regulation. Therefore, be advised that under Section 519(e) of the act, FDA has identified the above device as a device which requires tracking. You are required to adopt a method of tracking that follows the devices through the distribution chain and then identifies and follows the patients who receive them. The specific requirements of the regulation are found in 21 CFR 821 as described in the August 16, 1993, FEDERAL REGISTER beginning on page 43447.

If you have questions concerning this approvable letter please contact Doris Terry at (301) 594-2018 or Arnold Alpert, Ph.D., at (301) 594-2186.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Acting Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

cc: HFZ-300
HFZ-331
HFZ-107
HFZ-401
HFZ-402
HFZ-450
D.O.
501:4-22-91
Prepared by:DTERRY:jau:8/23/93
Revised:JDONELSON:jld:8/25/93
Revised:KLUNDSTEN:jld:9/2/93
Revised:JJONES:jau:9/9/93

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OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450	Terry	9/15/93	450		9/15/93	402		
450	Reamer	9/15/93			9/16	402		
					9/20	400		

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

Ms. Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

SEP 23 1993

RE: P920015
Medtronic® Transvene® Lead System
Filed: April 1, 1992
Amended: August 27, September 21, October 27 and November 5, 1992,
March 29, June 2, 14, and July 9, 1993

Dear Ms. Marrone:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA). The Circulatory System Devices Panel which also reviewed your PMA, recommended to CDRH at the August 2, 1993, panel meeting that the PMA be considered approvable. CDRH is pleased to inform you that the PMA is approvable subject to your submission of the following:

1. The labeling should be modified to include the following directions for use:

   a. diagrams which demonstrate the proper insertion technique and final anatomic position of the intravascular leads and the Sub-Q patch;

   b. defibrillation efficacy data on the different lead configurations, various polarity combinations and sequential versus simultaneous discharges;

   c. information and/or recommendations regarding specific implantation techniques and methods of testing the different configurations. For example, when is it recommended to use a two-lead configuration versus a three-lead configuration, when to implant in the superior vena cava (SVC) versus the coronary sinus (CS), and how the most advantageous position of the Sub-Q patch is determined;

   d. information or recommendations, based on your experience, regarding implantation in patients who do not have at least a 10 Joule safety margin;

   e. information aimed at reducing the incidence of infection;

   f. instructions stressing the importance of pausing between inductions of ventricular fibrillation (VF) at the time of implantation for at least a specified period of time in order to

decrease morbidity and mortality. The comments and the pause duration suggested should be based on the experience of the primary investigators in your study;

g. information regarding the change in defibrillation thresholds that one may expect with time as based on the experience of your investigators in your study;

h. guidance and techniques for separating permanent pacemaker leads from the Transvene® leads to minimize the interaction between the two devices, and diagnostic methods which can be employed at implant or predischarge to confirm the absence of adverse interaction;

i. a statement which emphasizes the need for x-rays and pace/sense threshold testing at follow-up to check for lead dislodgement (x-rays should be done at 3-month intervals for 1 year);

j. information regarding techniques for placing the leads via the cephalic vein when possible; and

k. an explanation regarding the necessity for explant and return of the leads upon the patient's death.

2. The labeling should be modified to include the following warnings:

a. a statement that the Sub-Q patch lead is not for use on the pericardium or epicardium, because it is too inflexible to be used as such;

b. stronger and more specific language regarding the use of dual anchoring sleeves on the right ventricle (RV), SVC, and CS leads. Based on the experience of your investigators, please describe the techniques used to fixate the lead at the insertion into the vein to minimize dislodgment; and

c. information which states that after extensive VF inductions at implant testing with the nonthoracotomy lead system, serious consideration should be given to delaying the thoracotomy for at least 2 days. Please include a statement which states that the clinical data showed that when a thoracotomy was performed immediately after testing, the perioperative mortality rate was increased from 0.7 to 9.3 percent.

3. In addition you should note the following:

a. The indications and contraindications for use of the Medtronic® Transvene® Lead System must be identical (except for certain modifications which pertain to the Transvene® Leads and those described below) to those for the PCD™ Epicardial System. Please change your second indication to read: Poorly tolerated,

sustained ventricular tachycardia and/or fibrillation which recurs spontaneously or can be induced despite the best antiarrhythmic drug therapy. Please also include the following statement in your indications section:

Note: The clinical outcome of hemodynamically stable, sustained VT patients is not fully known. The safety and effectiveness of the PCD® Transvene System in this subgroup of VT patients has not been determined.

b. The technical manuals for the Transvene® Leads must state that the leads are for use together as a system. The labeling (where appropriate) must be consistent in all of the Transvene® Lead manuals. The information regarding the Transvene® Leads in the PCD® Manual must also be included in the Transvene® Lead manuals.

c. There should be an identifying mark on the package label which distinguishes nonthoracotomy leads from thoracotomy leads.

d. The Warnings and Precautions in the labeling must be identified and reported separately according to FDA's Blue Book Memorandum of March 8, 1991, (a copy of this memorandum was previously sent to you).

4. Provide a copy of the Patient's Manual which includes a reference to use of the non-thoracotomy leads with the PCD® models.

The PMA must be amended to include your concurrence with, or suggested revision of, the enclosed "Conditions of Approval for Implantable Defibrillators and Programmers."

The condition that the sale, distribution and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act.

The device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the approved labeling specifies the requirements that apply to the training of physicians who may use the device.

In addition to the above, an FDA inspection must find that the manufacturing facilities, methods and controls comply with applicable device Good Manufacturing Practice Regulations (21 CFR Part 820). If applicable, amend the PMA to include required manufacturing information not previously submitted.

This is to advise you that, following receipt of an approvable letter, an applicant is required by 21 CFR 814.20(e) to update its pending PMA with new safety and effectiveness information learned about the device from ongoing or completed studies that may reasonably affect an evaluation of the safety or effectiveness of the device or that may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling. This updated reporting is limited to studies sponsored by the applicant or to which the applicant has reasonable access. The update report shall be consistent with the data reporting provisions of the protocol. Any update report shall be submitted in three copies as an amendment to the PMA and shall include the FDA reference number assigned to the PMA.

CDRH will issue an approval order after the requested information has been reviewed and determined to be acceptable. You may not begin commercial distribution of the device until you have received an approval order.

As provided by 21 CFR 814.44(e)(2), you may amend your PMA as requested, or withdraw it, or you may treat this letter as a formal denial of approval. If you choose the latter, you may request administrative review, either through a hearing or review by an independent advisory committee, under section 515(d)(3) and 515(g) of the act by filing a petition with the Food and Drug Administration, Dockets Management Branch (HFA-305), Room 1-23, 12420 Parklawn Drive, Rockville, Maryland 20857, within 30 days of the date you receive this letter. A petition for administrative review must be submitted in accordance with general administrative procedures for submission of documents to the Dockets Management Branch (21 CFR 10.20) and in the form of a petition for reconsideration (21 CFR 10.33). After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issues to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

The above requested information must be submitted in the form of an amendment (3 copies). Unless you amend this PMA to request an extension, and the extension is approved, FDA will consider the PMA to have been withdrawn voluntarily if you fail to respond in writing to this request for an amendment within 180 days of the date of this letter as provided under 21 CFR 814.44(g). Any request for an extension must be submitted within the 180-day period, justify the need for the extension, and provide a reasonable estimate as to when the requested information will be submitted.

All amendments to the PMA must be submitted in triplicate to the address below and shall reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

In addition, under Section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under Section 522(a)(1)(A) the above noted device as requiring postmarket surveillance.

Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study to include the evaluation of the explanted leads for evidence of metal ion oxidation (MIO), and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

Postmarket Studies Document Center
Room 408 (HFZ-107)
12720 Twinbrook Parkway
Rockville, Maryland 20852

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will cause your product to be misbranded and could lead to the imposition of civil money penalties or other regulatory actions. Any distribution of a misbranded device is a violation of the act and may result in a number of FDA enforcement actions, including (but not limited to) withdrawal of your PMA.

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If you have questions concerning this approvable letter please contact Doris Terry at (301) 594-2018 or Arnold Alpert, Ph.D., at (301) 594-2186.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Acting Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

MAR 17 1993

Ms. Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

RE: P920015
Transvene™ Lead System
Filed: April 1, 1992
Amended: September 21, 1992

Dear Ms. Marrone:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial scientific review of the above referenced premarket approval application (PMA). We regret to inform you that on the basis of this review, we have concluded that the PMA lacks information needed to complete the review and determine whether there is reasonable assurance that the device is safe and effective for its intended use.

We recognize the potential public health significance of this device and acknowledge the separate discussions underway to expedite the review. However, because of this lack of information, review of the PMA cannot continue and, accordingly, we have listed the following significant deficiencies which require the responses as indicated:

1. To clearly establish the purpose of the clinical data in the PMA application, please provide the following:

   a. the hypothesis and the objectives of your clinical study;

   b. a discussion of (i) how your clinical study addresses the use of a control, which is relevant to all clinical studies, (ii) the appropriateness of the AICD™ as a historical control, and (iii) your rationale for not using a concurrent control during an implantable cardioverter defibrillator (ICD) study;

   c. the endpoints of your study; and

   d. how the data provided in the PMA application support the specified endpoints.

2. Based on data provided in your PMA application, please prepare table(s) which include a side-by-side comparison of the PCD® Transvene™ and the PCD® Epicardial System and the PCD® Transvene™ and Ventak P AICD™ populations. The table must also include the inclusion and exclusion criteria which were used for each study. You must include a discussion of how these data may or may not represent a valid comparison, and other comments which justify and support the use of these groups as controls.

3. An update of the PMA clinical study population must be provided. The update must include the data as presented in the PMA application, and must include the clinical experience in the use of the new anchoring sleeves, which are aimed at decreasing the incidence of dislodgement, and a summary of the clinical experience (spontaneous treatment efficacy of ventricular tachycardia (VT) and ventricular fibrillation (VF), observations and complications, number of patient deaths and overall survival) of the patients followed for a year or more.

4. Please provide a clear description of how you identified the "patient who did not meet the implant criteria." Please discuss your implant criteria and how implant testing attempted to satisfy protocol requirements.

5. Of the 214 patients who did not meet the implant criteria and yet were implanted with the device, 170 patients had successful defibrillation with 24 Joules (J). Please provide an update of the clinical experience on these patients, as described in item 3 above. Also, please discuss how your proposed labeling will address this protocol deviation. Will implant criteria be changed?

6. There were 20 patients among the 214 who did not meet the implant criteria and were implanted without the 10 J safety margin. An update of the spontaneous episode experience in the treatment of VT and VF in these patients and the overall survival must be provided.

7. Table IK-4, page 151, compares the patients meeting the implant criteria to those who did not meet the criteria. However, many of the percentages were presented without numerical support. Please provide the appropriate numbers.

8. Please provide an update on the patients who are implanted with the Transvene™ System and were not counted in the PMA population. The update must include a summary of the clinical experience as referenced in item 3 above.

9. Based on your study protocol, please differentiate between defibrillation threshold (DFT) testing and lowest energy to defibrillate (LED) testing. Based on the individual patient report forms of the 757 patients, how many patients underwent what is described as DFT testing and how many had LED testing? Samples of the patient report forms showing the scheme of testing which was

categorized as DFT and LED testing must be provided. Please discuss how the DFT and LED data were reported and presented in the PMA application.

10. There is a statistically significant difference between the mean DFT obtained with the RV-CS-SQ lead configuration and the mean DFT obtained with the other lead configurations. How do you account for this difference? Was the DFT as reported and discussed for all lead configurations obtained using an identical or similar scheme? Please discuss. You must document that there were no significant differences between the scheme for performing DFT and LED testing between the Transvene™ and PCD® Epicardial patient populations, if that is the case.

11. Please elaborate on how the comparison of DFTs obtained from the PCD® Epicardial Lead study and the Transvene™ study can be considered as a valid comparison in that the majority of the patients (574 (75.3 percent)) in the Transvene™ study were programmed with the sequential pathway and 178 (23.4 percent) were programmed via the simultaneous pathway. The majority of the patients (496 (65.2 percent)) in the PCD® Epicardial study were programmed with the single pathway. Based on your PCD® Epicardial study, please discuss the DFTs or energy requirements obtained with the use of the single defibrillation pathway versus the sequential and simultaneous pathways.

12. Please discuss the time between detection and delivery of therapy of the Transvene™ System versus the PCD® Epicardial System.

13. On page 125 of the application, please explain and/or discuss what is meant by "a 2:1 VF sensing margin", how it is determined, and if the patients met the criteria.

14. Of the 329 patients who were followed for 6 months, 130 patients had spontaneous episodes. What was the average number of VT and VF episodes per patient? Of the patients followed for a year, how many had spontaneous episodes of VT and VF and what was the mean number of episodes per patient in this group?

15. On page 130, Table IF-4, you report that there were 5362 episodes of VT successfully terminated. On page 131, paragraph 2, you state that 25 patients experienced 45 (0.8 percent) episodes of sinus tachycardia or atrial fibrillation. Are these patients included in the success or failure category? Nine hundred and sixty-four episodes of VF were reported, however, 75 episodes were not actual VF. You must clarify how the successful and ineffective therapies and failures are discerned and categorized. Please prepare a table which includes a category of ineffective therapies with actual patient numbers and percentages. In addition, what assurance is there that an episode of supraventricular tachycardia or atrial fibrillation is not misinterpreted as VT or VF by the physician and considered a successful therapy?

16. Table IM-6, page 173 must be modified to include a column on inappropriate therapy or therapies delivered as the device was programmed so that the percentages add up to 100 percent.

17. On page 162, Table IL-2 lists a category "Fail to Cardiovert/Defibrillate" as 0.8 percent. Please clarify. If a patient survives an episode of an inappropriate therapy, is it categorized as a success? Please discuss. The tables must include percentages with the representative numerical support.

18. There were 38 inactive patients reported in Table IH-1, however, 34 patients were reported to be no longer active. Please clarify.

19. Please discuss how the 1 year sudden cardiac death survival, as reported in Table IF-2 page 128, was calculated. The numbers and an explanation of patient classification must be included. Was every patient included who had a prior cardiac arrest regardless of the arrhythmia?.

20. On page 177, the number of patients must be provided so that the percentages and calculated p-values can be confirmed.

21. Table IV-C, page 649 of the original submission shows a comparison of patient variables for the three lead systems and provides p-values for the variables tested, but the hypothesis was not clearly stated. Please state the hypothesis and discuss the p-values obtained when reporting by primary indication, and the chi-square test of the data set and how it was computed.

22. For purposes of justification of data pooling and data analysis of Table IV-C, please discuss why the multiple statistical significant difference was not adjusted at a 0.05 significance level using a more widely accepted procedure such as the Hochberg procedure (Dunnett and Tarnhoue: A Step-up Multiple Test Procedure, Journal of the American Statistical Association, March, 1992, Vol 87: pp.162-170).

23. You claim that confidence interval analysis was performed to compare the overall mortality of the PCD® and AICD™ populations. What was the confidence interval?

24. Please clarify and/or discuss the following regarding Table XB-1, page 378, Volume 2:

    a. the total number of patients in the Ventak P population (292) versus those reported by primary indication (291); and

    b. a chi-square test of primary indication, using the [redacted] (b)(4) computer software, yields a p-value of nearly 0. This is statistically significant, indicating the PCD® and Ventak P populations are significantly different.

25. Please discuss the incidence of inappropriate therapies reported as observations in the Transvene™ study. It appears as if there has only been a slight improvement over the PCD® Epicardial study as it relates to programming and patient management (drug therapy). Please discuss the experience of both studies and how the labeling supports effective programming of the device parameters and the use of the Onset and Stability algorithms. How many patients in the Transvene™ study have the Onset and Stability algorithms programmed ON? At what interval during the study were the majority of patients programmed with the algorithms? Your experience in the treatment of induced and spontaneous episodes with use of the algorithms must be discussed.

26. Please discuss the "device related" complications reported for the Transvene™ and the PCD® Epicardial System.

27. Please describe in detail the complications reported in the patients followed for a year.

28. There was a substantial increase in the number of infections reported in the Transvene™ study. Even though you discussed why there was an increase, based on your experience, how will your labeling address the procedures for reduction in the number of infections? Please validate these procedures.

29. A discussion of your experience in the use of the different entry sites for the placement of the Transvene™ leads, and how your labeling assists in the selection of an entry site, must be provided.

30. Of the 22 deaths, 15 systems were explanted and returned for analysis. The results of the analyses (PCD® and Transvene™ leads) must be provided. What did device interrogation reveal? How many of the 41 Transvene™ lead systems which were explanted were returned and analyzed? How long were the leads implanted? A description of the protocol for analysis and the results of the analyses on all leads and devices must be provided. The PMA application must document how your study has addressed the need for the return and analysis of all Transvene™ leads and the PCD®.

31. Please discuss the circumstances surrounding the death of the patient who died (b)(4) months post implant. What did interrogation of the device reveal?

32. Of the perioperative deaths, how many devices were programmed OFF? Please discuss the circumstances surrounding each death. The number of perioperative deaths must be reported in a table and be identified as sudden cardiac, non-sudden cardiac or non-cardiac. Were there other deaths when the device was programmed OFF?

33. You state that there have been no reported patient deaths in the group with a 1 year sudden cardiac death survival and overall

actuarial survival of 100 percent. Does this include the perioperative deaths and the patients who have been followed out for a year?

34. Please provide an engineering drawing of each Transvene™ lead model which identifies the segments of the lead and a description of the tests that each segment and the full lead body underwent.

35. Since flex testing exerts a considerable amount of stress on the lead, and is essential to life testing, why was it considered that (b)(4) cycles at a bend radius of (b)(4) inch per lead model over (b)(4) month period would be sufficient? Describe how the full lead and different segments were flexed. Did you do a finite element stress analysis to validate the flex testing stress?

36. In light of the failure of your platinum sputtered polyurethane bradycardia pacing leads, and since the Transvene™ lead Model 6966 is also a platinum sputtered polyurethane lead, please provide documentation regarding the failure mechanism of the pacing leads and all relevant information pertaining to these cases. How can we be assured that the failure may be restricted to the bradycardia pacing leads? Based on your testing to date regarding the pacing leads and the testing of the Model 6966 lead, discuss the potential and the probability of failure of the Model 6966 lead. A side by side comparison of the Model 6966 and the 4,000 series bradycardia pacing leads must be provided. The comparison must include material, design, dimensions, function, tests performed and a schematic drawing.

37. A copy of the Summary of Safety and Effectiveness which includes the updated data must be provided.

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period up to 180 days. As provided by 21 CFR 814.37(c), you may decline to submit a major amendment requested by FDA in which case the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

As provided under 21 CFR 814.44(g), FDA will consider this PMA to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA amendment. You may, however, amend the PMA within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA with in the 180-day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA and will be assigned a new number.

You may amend the PMA to provide the above requested information (12 copies), voluntarily withdraw the PMA (3 copies), direct CDRH to complete processing the PMA without the submission of additional information (3 copies) or request an extension. The required copies of the amended PMA should include the FDA reference number for this PMA and should be submitted to the following address:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

Upon receipt of an amendment adequately addressing the above requests or a written response declining to submit the requested amendment, CDRH may schedule an advisory panel meeting at which your PMA will be reviewed. You will be notified of the location and date of this meeting should one be necessary. In order to provide adequate time for CDRH and advisory panel review, information received by FDA less than 6 weeks in advance of any scheduled advisory committee meeting will not be considered or reviewed at the meeting and may delay consideration of your PMA until a subsequent advisory committee meeting.

If you have questions concerning this deficiency letter, please contact Doris Terry at (301) 427-1018 or Arnold Alpert, Ph.D., at (301) 427-1186.

Sincerely yours,

F. Alan Andersen, Ph.D.
Acting Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Page 8 - Ms. Jennifer M. Marrone

cc: HFZ-331
HFZ-401
HFZ-402
HFZ-450
D.O.
402:4-22-91

Final Prepared by:DTERRY:cdh:3/16/93
Revised:DTerry:3/16/93
Spellck:3/16/93

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

MAR 17 1993

Ms. Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

RE: P920015
Transvene™ Lead System
Filed: April 1, 1992
Amended: September 21, 1992

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7. Table IK-4, page 151, compares the patients meeting the implant criteria to those who did not meet the criteria. However, many of the percentages were presented without numerical support. Please provide the appropriate numbers.

8. Please provide an update on the patients who are implanted with the Transvene™ System and were not counted in the PMA population. The update must include a summary of the clinical experience as referenced in item 3 above.

9. Based on your study protocol, please differentiate between defibrillation threshold (DFT) testing and lowest energy to defibrillate (LED) testing. Based on the individual patient report forms of the 757 patients, how many patients underwent what is described as DFT testing and how many had LED testing? Samples of the patient report forms showing the scheme of testing which was

categorized as DFT and LED testing must be provided. Please discuss how the DFT and LED data were reported and presented in the PMA application.

10. There is a statistically significant difference between the mean DFT obtained with the RV-CS-SQ lead configuration and the mean DFT obtained with the other lead configurations. How do you account for this difference? Was the DFT as reported and discussed for all lead configurations obtained using an identical or similar scheme? Please discuss. You must document that there were no significant differences between the scheme for performing DFT and LED testing between the Transvene™ and PCD® Epicardial patient populations, if that is the case.

11. Please elaborate on how the comparison of DFTs obtained from the PCD® Epicardial Lead study and the Transvene™ study can be considered as a valid comparison in that the majority of the patients (574 (75.3 percent)) in the Transvene™ study were programmed with the sequential pathway and 178 (23.4 percent) were programmed via the simultaneous pathway. The majority of the patients (496 (65.2 percent)) in the PCD® Epicardial study were programmed with the single pathway. Based on your PCD® Epicardial study, please discuss the DFTs or energy requirements obtained with the use of the single defibrillation pathway versus the sequential and simultaneous pathways.

12. Please discuss the time between detection and delivery of therapy of the Transvene™ System versus the PCD® Epicardial System.

13. On page 125 of the application, please explain and/or discuss what is meant by "a 2:1 VF sensing margin", how it is determined, and if the patients met the criteria.

14. Of the 329 patients who were followed for 6 months, 130 patients had spontaneous episodes. What was the average number of VT and VF episodes per patient? Of the patients followed for a year, how many had spontaneous episodes of VT and VF and what was the mean number of episodes per patient in this group?

15. On page 130, Table IF-4, you report that there were 5362 episodes of VT successfully terminated. On page 131, paragraph 2, you state that 25 patients experienced 45 (0.8 percent) episodes of sinus tachycardia or atrial fibrillation. Are these patients included in the success or failure category? Nine hundred and sixty-four episodes of VF were reported, however, 75 episodes were not actual VF. You must clarify how the successful and ineffective therapies and failures are discerned and categorized. Please prepare a table which includes a category of ineffective therapies with actual patient numbers and percentages. In addition, what assurance is there that an episode of supraventricular tachycardia or atrial fibrillation is not misinterpreted as VT or VF by the physician and considered a successful therapy?

16. Table IM-6, page 173 must be modified to include a column on inappropriate therapy or therapies delivered as the device was programmed so that the percentages add up to 100 percent.

17. On page 162, Table IL-2 lists a category "Fail to Cardiovert/Defibrillate" as 0.8 percent. Please clarify. If a patient survives an episode of an inappropriate therapy, is it categorized as a success? Please discuss. The tables must include percentages with the representative numerical support.

18. There were 38 inactive patients reported in Table IH-1, however, 34 patients were reported to be no longer active. Please clarify.

19. Please discuss how the 1 year sudden cardiac death survival, as reported in Table IF-2 page 128, was calculated. The numbers and an explanation of patient classification must be included. Was every patient included who had a prior cardiac arrest regardless of the arrhythmia?.

20. On page 177, the number of patients must be provided so that the percentages and calculated p-values can be confirmed.

21. Table IV-C, page 649 of the original submission shows a comparison of patient variables for the three lead systems and provides p-values for the variables tested, but the hypothesis was not clearly stated. Please state the hypothesis and discuss the p-values obtained when reporting by primary indication, and the chi-square test of the data set and how it was computed.

22. For purposes of justification of data pooling and data analysis of Table IV-C, please discuss why the multiple statistical significant difference was not adjusted at a 0.05 significance level using a more widely accepted procedure such as the Hochberg procedure (Dunnett and Tarnhoue: A Step-up Multiple Test Procedure, Journal of the American Statistical Association, March, 1992, Vol 87: pp.162-170).

23. You claim that confidence interval analysis was performed to compare the overall mortality of the PCD● and AICD™ populations. What was the confidence interval?

24. Please clarify and/or discuss the following regarding Table XB-1, page 378, Volume 2:

    a. the total number of patients in the Ventak P population (292) versus those reported by primary indication (291); and

    b. a chi-square test of primary indication, using the (b)(4) computer software, yields a p-value of nearly 0. This is statistically significant, indicating the PCD● and Ventak P populations are significantly different.

25. Please discuss the incidence of inappropriate therapies reported as observations in the Transvene™ study. It appears as if there has only been a slight improvement over the PCD® Epicardial study as it relates to programming and patient management (drug therapy). Please discuss the experience of both studies and how the labeling supports effective programming of the device parameters and the use of the Onset and Stability algorithms. How many patients in the Transvene™ study have the Onset and Stability algorithms programmed ON? At what interval during the study were the majority of patients programmed with the algorithms? Your experience in the treatment of induced and spontaneous episodes with use of the algorithms must be discussed.

26. Please discuss the "device related" complications reported for the Transvene™ and the PCD® Epicardial System.

27. Please describe in detail the complications reported in the patients followed for a year.

28. There was a substantial increase in the number of infections reported in the Transvene™ study. Even though you discussed why there was an increase, based on your experience, how will your labeling address the procedures for reduction in the number of infections? Please validate these procedures.

29. A discussion of your experience in the use of the different entry sites for the placement of the Transvene™ leads, and how your labeling assists in the selection of an entry site, must be provided.

30. Of the 22 deaths, 15 systems were explanted and returned for analysis. The results of the analyses (PCD® and Transvene™ leads) must be provided. What did device interrogation reveal? How many of the 41 Transvene™ lead systems which were explanted were returned and analyzed? How long were the leads implanted? A description of the protocol for analysis and the results of the analyses on all leads and devices must be provided. The PMA application must document how your study has addressed the need for the return and analysis of all Transvene™ leads and the PCD®.

31. Please discuss the circumstances surrounding the death of the patient who died (b)(4) months post implant. What did interrogation of the device reveal?

32. Of the perioperative deaths, how many devices were programmed OFF? Please discuss the circumstances surrounding each death. The number of perioperative deaths must be reported in a table and be identified as sudden cardiac, non-sudden cardiac or non-cardiac. Were there other deaths when the device was programmed OFF?

33. You state that there have been no reported patient deaths in the group with a 1 year sudden cardiac death survival and overall

actuarial survival of 100 percent. Does this include the perioperative deaths and the patients who have been followed out for a year?

34. Please provide an engineering drawing of each Transvene™ lead model which identifies the segments of the lead and a description of the tests that each segment and the full lead body underwent.

35. Since flex testing exerts a considerable amount of stress on the lead, and is essential to life testing, why was it considered that (b)(4) cycles at a bend radius of (b)(4) inch per lead model over a (b)(4) month period would be sufficient? Describe how the full lead and different segments were flexed. Did you do a finite element stress analysis to validate the flex testing stress?

36. In light of the failure of your platinum sputtered polyurethane bradycardia pacing leads, and since the Transvene™ lead Model 6966 is also a platinum sputtered polyurethane lead, please provide documentation regarding the failure mechanism of the pacing leads and all relevant information pertaining to these cases. How can we be assured that the failure may be restricted to the bradycardia pacing leads? Based on your testing to date regarding the pacing leads and the testing of the Model 6966 lead, discuss the potential and the probability of failure of the Model 6966 lead. A side by side comparison of the Model 6966 and the 4,000 series bradycardia pacing leads must be provided. The comparison must include material, design, dimensions, function, tests performed and a schematic drawing.

37. A copy of the Summary of Safety and Effectiveness which includes the updated data must be provided.

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period up to 180 days. As provided by 21 CFR 814.37(c), you may decline to submit a major amendment requested by FDA in which case the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

As provided under 21 CFR 814.44(g), FDA will consider this PMA to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA amendment. You may, however, amend the PMA within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA with in the 180-day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA and will be assigned a new number.

You may amend the PMA to provide the above requested information (12 copies), voluntarily withdraw the PMA (3 copies), direct CDRH to complete processing the PMA without the submission of additional information (3 copies) or request an extension. The required copies of the amended PMA should include the FDA reference number for this PMA and should be submitted to the following address:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

Upon receipt of an amendment adequately addressing the above requests or a written response declining to submit the requested amendment, CDRH may schedule an advisory panel meeting at which your PMA will be reviewed. You will be notified of the location and date of this meeting should one be necessary. In order to provide adequate time for CDRH and advisory panel review, information received by FDA less than 6 weeks in advance of any scheduled advisory committee meeting will not be considered or reviewed at the meeting and may delay consideration of your PMA until a subsequent advisory committee meeting.

If you have questions concerning this deficiency letter, please contact Doris Terry at (301) 427-1018 or Arnold Alpert, Ph.D., at (301) 427-1186.

Sincerely yours,

F. Alan Andersen

F. Alan Andersen, Ph.D.
Acting Director
Office of Device Evaluation
Center for Devices and
Radiological Health

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date December 16, 1992

From Mathematical Statistician (T. C. Lu) HFZ-162
Statistical Branch, Division of Biometric Sciences, OST

Subject Statistical Review of PMA P920015 Amendment, Medtronic Multiprogrammable Tachyarrhythmia Control System with Non-thoracotomy Cardvioversion and Defibrillation Electrodes, Medtronic, Inc.

To

Doris Terry - HFZ-450
Division of Cardiovascular, Respiratory, and Neurological Devices
Through: Director, Division of Biometric Sciences, OST MKB for RPC
Through: Chief, Statistics Branch, DBS, OST CSL for HFZ

1. Background

Per our telephone conversation on December 7, 1992, you requested a statistical review of this PMA amendment. This amendment was received at FDA on September 21, 1992. I wasn't notified of any action until December 7. This amendment was sent to me on December 8, 1992. You indicate that you would like to receive my comments before December 18, 1992. With the limited time frame, I can only concentrate on the sponsor's response to the deficiency letter dated August 6 from FDA to the sponsor.

2. Reviewer's Comments

2.1. Item 21. Sponsor provided the p-values for Tables IV-B and IV-C of the original PMA. This reviewer recomputed the p-values and found them identical to those of the sponsor's. However, there is a problem, sample sizes are 18 for 7216A and 739 for 7217B. With such a large difference in sample size, this will cause very low statistical power, then the small difference is very difficult to detect.

2.2. Table IV-C shows comparisons of patient variables for the three lead systems. All the p-values computed by this reviewer is identical to those of the sponsor's. The total numbers of patients of primary indication are 329 for RV/SVC/SQ (of which 187 for SCD, 114 for VT, and 28 for SCDlVT), which are not in agreement with a total sample size of 496 (403 males and 93 females). The sponsor provided p-values for variables tested in Table IV-C. The hypothesis was not clearly stated. After recomputing the p-values listed in the table, all are in agreement except primary indication. The chi-square test of this data set, computed using (b)(4) computer software, yield a p-value of nearly 0, which is also different from that of sponsor's computed p-value of (b)(4)

2.3. The sponsor, for the purpose of justification of data pooling and data analysis of Table IV-C, adjust the multiple statistical significant difference at 0.05 significance level using Hochberg procedure (Dunnett & Tarnhoue: A Step-up Multiple Test Procedure, Journal of the American Statistical Association, March 1992, 87:162-170). Although this is a published, peer reviewed article, the sponsor's multiple test adjustment procedure is not widely accepted by the biostatistical and clinical community.

2.4. Comparison of Mortality Between One PCD and the AICD

Item 25. The sponsor compared the end points of the two devices. Sponsor claimed that confidence interval analysis was performed but that confidence interval was not given. Confidence interval should be computed by the sponsor to support this claim.

Sponsor provided a table for the comparison of patient characteristics, PCD versus ventak-P. I have two questions about Table XB-1, Page 378, Vol. 2:

(i) The total numbers of patients of primary indication, 291 for Ventak-P (49 for SCD, 169 for VT, and 73 for SCD/VT) are not equal to the total number of patients of Ventak-P of 292.

(ii) A chi-square test of primary indication, using (b)(4) computer software, yield a p-value of nearly 0. This is statistically significant, indicating that PCD and Ventak-P are significantly different.

The inclusion and exclusion criteria for patients of PCD and AICD studies are not discussed by the sponsor.

Conclusion

The sponsor needs to adequately address the issues raised in Section 2 above before the safety and effectiveness of the PCD transvene system can be evaluated from a statistical perspective.

T. C. Lu

T. C. Lu

cc: Abhijit Acharya, Ph.D. - HFZ-450
Donald F. Dahms - HFZ-450
Lynne A. Reamer - HFZ-450
PMS Group - HFZ-402
DCC - HFZ-401
Medical Device File
Board File

Ms. Jennifer Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

AUG - 6 1992

Re: P920015
Transvene™ Lead System
Filed: April 1, 1992

Dear Ms. Marrone:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial scientific review of the above referenced premarket approval application (PMA). We regret to inform you that on the basis of this review, we have concluded that the PMA lacks information needed to complete the review and determine whether there is reasonable assurance that the device is safe and effective for its intended use.

Because of this lack of information, review of the PMA cannot continue and, accordingly, we have listed the following significant deficiencies which require the responses as indicated:

1. Discuss how the use of a silicone adhesive prevents tissue in-growth in the Model 6963 lead. Where is the adhesive placed? From experience, discuss the use of polyurethane and silicone in leads to prevent tissue in-growth.

2. Please provide the results of mutagenicity testing for the (b)(4) and the (b)(4) (anchor sleeve). If the tests have not been done please provide a justification for not doing so.

3. Provide a description of the helix electrode fixation tool and of the tests to verify the torsional force for implanting the helix electrode.

4. Based on your experience, identify the minimum number of flex cycles that a lead should withstand. Also, give the stress level exerted on the Model 6907 lead (from which the median failure time of (b)(4) cycles was observed), and on the Transvene™ leads.

5. Since the electrode coil is flexed separately from the insulated conductor, discuss the reliability of the section where the electrode is coaxial to the conductor. Is there friction between the electrode and the conductor when the section is flexed?

6. The Model 6999's (b)(4) electrode coil fails at a much lower flex cycle than the (b)(4) electrode coil. Discuss the reliability of the (b)(4) electrode coil, and the effects of its failure on the performance of the lead.

7. Please discuss how patient treatment is affected if one or two of the electrode coils of the Model 6999 patch lead becomes damaged.

8. Please specify the section of each lead assembly that was flexed during life testing. Does this section include the electrode coil? The results of the tests should be included.

9. Provide an update of the (b)(4) month life test.

10. The data indicate that a new lead is used for each (temperature tolerance, crush load, or life) test. Correlate the results from those tests to the worst case condition where the same lead has to face temperature differences, crushing, and flexing. Why was sequential testing not performed?

11. Discuss the differences in battery life or energy requirements between the epi-lead system and the Transvene™ system.

12. An update of the chronic animal studies should be provided.

13. An update of the clinical experience of the Transvene™ Lead System should be provided. The update should include all additional patients and the clinical experience to date. The data should be presented as done in your original PMA application, and should include, e.g., implant and follow-up data, lead orientations including patch location, spontaneous episode experience, analyses by different groups, complications/observations, and survival analysis. All remaining deficiencies listed below which pertain to your patient population should be addressed using the updated patient group.

14. Please discuss your clinical data which support the claim which states that the Transvene™ Lead System improves both perioperative and long term patient morbidity.

15. Based on your experience and on the data as reported in the literature, what is the percentage of patients who have been found unable to withstand a thoracotomy?

16. Data such as treatment efficacy, complications and survival analysis on the patients followed for 6 months should be provided.

17. Please discuss your clinical experience (treatment efficacy, lead orientation, complications and survival rates) of the patients who have been followed for 1 year and more.

18. Provide a detailed discussion of the clinical experience (implant duration, lead orientations, spontaneous episodes, treatment efficacy, survival analysis, complications, etc.) of the patients who did not meet the implant criteria and were implanted with the Transvene™ System. Also discuss the experience of the patients who were implanted without the 10 Joule safety margin.

19. A breakdown of the different lead orientations within the patient population, and the treatment efficacy reported for each configuration should be included.

20. Based upon your clinical experience, the Physician's Manual should recommend the sequence of testing with the different lead orientations during implant.

21. Please provide the P-values as listed in Table IV B and IV C of the original PMA application for the new patient population.

22. Please discuss the reasons why some patients dropped out of the study, either withdrawn alive or lost to follow-up. There were 224 patients at 1 month and only 154 patients at 3 months. Please explain the difference of 70 patients during this 2 month period.

23. For the comparison of complications/observations rates for the PCD™ versus the AICD™, please provide the following:

    a. the number of complications and patients for the PCD™ and AICD™ populations;

    b. the clinical success/failure criteria used for "Failure to Cardiovert/Defibrillate and Inappropriate Problematic VT/VF Therapy Delivery"; and

    c. a discussion of the pocket infection rate of the PCD™ and the AICD™ and the lead related complications of the PCD™ Transvene™ System versus the PCD™ Epicardial System.

24. Some Transvene™ patients were also evaluated with the Model 10388 hollow can electrode. Please compare the infection rate of these patients to those who did not undergo the hollow can evaluation.

25. Please discuss and/or provide the following regarding the 1 year actuarial survival comparison of mortality between the PCD™ and the AICD™:

    a. the statistical test that was used to compare survival; and

    b. the two survival or life tables by year of follow-up.

26. Please discuss the statistical techniques used to derive the P-values in Table XI G-2, page 862, Vol. 5 and Table J-2, page 54, Vol. 1.

The following additional deficiencies were noted in this initial scientific review and the indicated responses should be provided:

1. Discuss the properties of polyurethane which make it the ideal insulation material for the 6966 lead. Why was silicone not chosen?

2. Discuss the biostability tests (stress cracking, metal induced oxidation, etc.) performed on the two types of polyurethane. Why was a different polyurethane chosen for the inner coil?

3. Based on the results of the life test, what is the life expectancy of the leads? Please include your assumptions.

4. Provide a side-by-side comparison between the Model 6999 and the epicardial patch lead.

5. Discuss the possible interactions between implanted pacemaker leads and the Transvene™ leads. Also, discuss the effects of the leads on the tricuspid valve and the host vein.

6. The Transvene™ leads seem to tolerate crush testing better than the pacing leads. Please discuss the properties of the Transvene™ leads which support this capability.

7. Are there patients currently implanted with the Model 6895 and 10317 patch leads? If so, please provide a breakdown of the clinical data, e.g., complications, survival, etc. for each lead.

8. Please list the reasons for not performing pre-hospital discharge testing.

9. The number of spontaneous episodes of the patients followed for 6 months and beyond should be provided.

10. A copy of the Summary of Safety and Effectiveness with the updated clinical data should be submitted.

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period up to 180 days. As provided by 21 CFR 814.37(c), you may decline to submit a major amendment requested by FDA in which case the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

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If you have questions concerning this deficiency letter, please contact Doris Terry at (301) 427-1018 or Arnold Alpert, Ph.D., at (301) 427-1186.

cc: HFZ-331
HFZ-401
HFZ-402
HFZ-450 (DCRND)
HFR-MW300
402:4-22-91

Sincerely yours,

F. Alan Andersen, Ph.D.
Acting Director
Office of Device Evaluation
Center for Devices and
Radiological Health

DTerry:P2 PMA/doc.#7
Draft:crd/6/11/92
Final:crd/6/16/92
Revised Draft:crd/7/16/92
Revised/Final:crd/7/20/92
Revised:crd/7/24/92
Decspell:crd/7/20/92
Proofread:

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450	Reamer	7/28/92	402	[illegible]	8/3/92			

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville MD 20850

Ms. Jennifer Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

AUG - 6 1992

Re: P920015
Transvene™ Lead System
Filed: April 1, 1992

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    a. the statistical test that was used to compare survival; and

    b. the two survival or life tables by year of follow-up.

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2. Discuss the biostability tests (stress cracking, metal induced oxidation, etc.) performed on the two types of polyurethane. Why was a different polyurethane chosen for the inner coil?

3. Based on the results of the life test, what is the life expectancy of the leads? Please include your assumptions.

4. Provide a side-by-side comparison between the Model 6999 and the epicardial patch lead.

5. Discuss the possible interactions between implanted pacemaker leads and the Transvene™ leads. Also, discuss the effects of the leads on the tricuspid valve and the host vein.

6. The Transvene™ leads seem to tolerate crush testing better than the pacing leads. Please discuss the properties of the Transvene™ leads which support this capability.

7. Are there patients currently implanted with the Model 6895 and 10317 patch leads? If so, please provide a breakdown of the clinical data, e.g., complications, survival, etc. for each lead.

8. Please list the reasons for not performing pre-hospital discharge testing.

9. The number of spontaneous episodes of the patients followed for 6 months and beyond should be provided.

10. A copy of the Summary of Safety and Effectiveness with the updated clinical data should be submitted.

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period up to 180 days. As provided by 21 CFR 814.37(c), you may decline to submit a major amendment requested by FDA in which case the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

As provided under 21 CFR 814.44(g), FDA will consider this PMA to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA amendment. You may, however, amend the PMA within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180-day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA and will be assigned a new number.

You may amend the PMA to provide the above requested information 12 copies, voluntarily withdraw the PMA (3 copies), direct CDRH to complete processing the PMA without the submission of additional information (3 copies) or request an extension. The required copies of the amended PMA should include the FDA reference number for this PMA and should be submitted to the following address:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

Upon receipt of an amendment adequately addressing the above requests or a written response declining to submit the requested amendment, CDRH may schedule an advisory panel meeting at which your PMA will be reviewed. You will be notified of the location and date of this meeting should one be necessary. In order to provide adequate time for CDRH and advisory panel review, information received by FDA less than 8 weeks in advance of any scheduled advisory committee meeting will not be considered or reviewed at the meeting and may delay consideration of your PMA until a subsequent advisory committee meeting.

If you have questions concerning this deficiency letter, please contact Doris Terry at (301) 427-1018 or Arnold Alpert, Ph.D., at (301) 427-1186.

Sincerely yours,

for F. Alan Andersen, Ph.D.
Acting Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Ms. Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

JUL 17 1992

Re: P920015
Medtronic® Transvene Lead System
Filed: April 1, 1992

Dear Ms. Marrone:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial review of your premarket approval application (PMA). We are pleased to inform you that we have made a threshold determination that the PMA is sufficiently complete to permit a substantive review and is, therefore, suitable for filing. The filing date is April 1, 1992, which is the date of CDRH receipt of the PMA.

Following receipt of a filing letter, an applicant is required by 21 CFR 814.20(e) to update their pending PMA 3 months after the filing date with new safety and effectiveness information learned about the device from ongoing or completed studies when the information may reasonably affect an evaluation of the safety or effectiveness of the device or may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling.

This updated reporting is limited to studies sponsored by the applicant or to which the applicant has reasonable access. The update report should be consistent with the data reporting provisions of the protocol. Please submit update reports in three copies as an amendment to the PMA and include the above PMA reference number assigned to the PMA.

This letter reflects the current progress of our review of your application. Please be advised that continued review of your application or any response to this letter may result in additional deficiencies.

The PMA cannot be approved until FDA has determined that the manufacturing facilities, methods and controls comply with applicable device Good Manufacturing Practice regulations (21 CFR Part 820). If you have not already done so, please notify CDRH as soon as possible in the form of an amendment to the PMA if there will be a delay in setting up your manufacturing facility for production of the device and provide the expected date that the facility will be prepared for an FDA inspection.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

A meeting of the Circulatory System Devices Panel will be held at which your PMA will be reviewed. You will be notified of the location and date of this meeting. Any additional information to be included in your PMA must be submitted in the form of a PMA supplement amendment and be received by FDA at least 6 weeks in advance of the scheduled advisory committee meeting in order for FDA and the panel members to have adequate time to review the new information. Information received by CDRH less than 6 weeks in advance of a scheduled advisory committee meeting will not be considered or reviewed at the meeting.

For your information, there is an industry representative on this FDA advisory committee whose name, address and telephone number you can obtain by contacting the Committee Management Staff at (301) 443-4016. CDRH believes that the industry representatives will be better prepared to participate in panel discussions if they have been provided with a copy of the Summary of Safety and Effectiveness for review prior to the panel meeting. In accordance with 21 CFR 14.86(b), all panel members are subject to all rules and regulations adopted by FDA and the committee; therefore, even though the industry representatives usually are not given access to trade secret and confidential, commercial information, they are bound to protect the confidentiality of documents that would be sent to them in preparation for panel review of a PMA. If you would like the industry representative to have access to any portion of your PMA, including the Summary of Safety and Effectiveness, please provide a copy for that purpose and notify the executive secretary of the panel at (301) 427-1205. However, review of your PMA will not be prejudiced if you elect not to provide a Summary for industry representative review.

All correspondence regarding this PMA should be submitted in 3 copies in the form of a PMA amendment. Please address all submissions to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

If you have questions, please contact Doris Terry at (301) 427-1018 or Arnold Alpert, Ph.D., at (301) 427-1186.

Sincerely yours,

Philip J. Phillips
Director
Program Operations Staff
Office of Device Evaluation
Center for Devices and Radiological Health

for Phillips

cc: HFZ-116 (Statistics Staff)
HFZ-331 (DCP) + HFZ-320 (Grayson)
HFZ-401 (DMC)
HFZ-402
HFZ-450 (DCRND)
DO
302:4-22-91

DTerry:P2 PMA Disk/doc.#3
Draft:crd/5/29/92
Final:crd/6/2/92
Decspell:crd/6/2/92
Proofread:

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OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
450	Terry	6/3/92	DRAD	[illegible]	6/10			
"	Johns	6/3	402	Alpert	6/2/92			
450	Reamer	6/4	7402	Lewis	6/16/92			

☆ U.S. GOVERNMENT PRINTING OFFICE 1991-519-771

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

JUN 17 1992

Ms. Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015
Medtronic® Transvene Lead System
Filed: April 1, 1992

Dear Ms. Marrone:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial review of your premarket approval application (PMA). We are pleased to inform you that we have made a threshold determination that the PMA is sufficiently complete to permit a substantive review and is, therefore, suitable for filing. The filing date is April 1, 1992, which is the date of CDRH receipt of the PMA.

Following receipt of a filing letter, an applicant is required by 21 CFR 814.20(e) to update their pending PMA 3 months after the filing date with new safety and effectiveness information learned about the device from ongoing or completed studies when the information may reasonably affect an evaluation of the safety or effectiveness of the device or may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling.

This updated reporting is limited to studies sponsored by the applicant or to which the applicant has reasonable access. The update report should be consistent with the data reporting provisions of the protocol. Please submit update reports in three copies as an amendment to the PMA and include the above PMA reference number assigned to the PMA.

This letter reflects the current progress of our review of your application. Please be advised that continued review of your application or any response to this letter may result in additional deficiencies.

The PMA cannot be approved until FDA has determined that the manufacturing facilities, methods and controls comply with applicable device Good Manufacturing Practice regulations (21 CFR Part 820). If you have not already done so, please notify CDRH as soon as possible in the form of an amendment to the PMA if there will be a delay in setting up your manufacturing facility for production of the device and provide the expected date that the facility will be prepared for an FDA inspection.

A meeting of the Circulatory System Devices Panel will be held at which your PMA will be reviewed. You will be notified of the location and date of this meeting. Any additional information to be included in your PMA must be submitted in the form of a PMA supplement amendment and be received by FDA at least 6 weeks in advance of the scheduled advisory committee meeting in order for FDA and the panel members to have adequate time to review the new information. Information received by CDRH less than 6 weeks in advance of a scheduled advisory committee meeting will not be considered or reviewed at the meeting.

For your information, there is an industry representative on this FDA advisory committee whose name, address and telephone number you can obtain by contacting the Committee Management Staff at (301) 443-4016. CDRH believes that the industry representatives will be better prepared to participate in panel discussions if they have been provided with a copy of the Summary of Safety and Effectiveness for review prior to the panel meeting. In accordance with 21 CFR 14.86(b), all panel members are subject to all rules and regulations adopted by FDA and the committee; therefore, even though the industry representatives usually are not given access to trade secret and confidential, commercial information, they are bound to protect the confidentiality of documents that would be sent to them in preparation for panel review of a PMA. If you would like the industry representative to have access to any portion of your PMA, including the Summary of Safety and Effectiveness, please provide a copy for that purpose and notify the executive secretary of the panel at (301) 427-1205. However, review of your PMA will not be prejudiced if you elect not to provide a Summary for industry representative review.

All correspondence regarding this PMA should be submitted in 3 copies in the form of a PMA amendment. Please address all submissions to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

If you have questions, please contact Doris Terry at (301) 427-1018 or Arnold Alpert, Ph.D., at (301) 427-1186.

Sincerely yours,

Debra Y. Lewis
for Philip J. Phillips
Director
Program Operations Staff
Office of Device Evaluation
Center for Devices and
Radiological Health

DEPARTMENT OF HEALTH & HUMAN SERVICES Yellow Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

MAY 14 1992

Ms. Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576

Re: P920015
PCD Transvene System

Dear Ms. Marrone:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) is continuing to process the above named premarket approval application (PMA). Simultaneously with a review by the Office of Device Evaluation (ODE), the Office of Compliance and Surveillance (OCS) must review the manufacturing information in your PMA to determine that it is sufficiently complete and appropriately organized to permit FDA to determine whether your firm (or your contract manufacturer) has the capability of manufacturing your PMA device in accordance with (1) the conditions specified in the PMA application and (2) the requirements of the medical device GMP regulation.

The Division of Compliance Programs (DCP) of OCS has reviewed the manufacturing section of your PMA and believes that it lacks the information necessary to effectively complete a review and determine whether to initiate a PMA inspection (see enclosed). While the deficiencies outlined in the enclosure do not preclude further review of your PMA, if left uncorrected they may delay or preclude evaluation of your manufacturing process and final approval of your PMA application. We request that you respond as indicated. Please be advised that continued review by ODE of your application (including the manufacturing section) may identify additional deficiencies. Also, the OCS review of your response to this letter may identify additional deficiencies.

For your information a Guidance for Preparation of PMA Manufacturing Information was published on March 22, 1991 (a notice of availability was published in the August 20, 1991 Federal Register). It is also available as part of the PMA Manual Supplement which may be obtained from the Division of Small Manufacturer's Assistance at 1-800-638-2041.

Information supplied in response to the enclosed request should be submitted in the form of an amendment **AND BE CLEARLY IDENTIFIED AS A RESPONSE TO AN OCS REQUEST IN YOUR REFERENCE BLOCK.** FDA will consider the PMA to have been withdrawn voluntarily if you fail to respond in writing to this request for an amendment within 180 days of the date of this letter as provided under 21 CFR 814.44(g). You may, however, amend the PMA within the 180 day period to request an extension of time to respond. Any such request is subject to FDA approval and must justify the need

for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180 day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180 day period will be considered a resubmission of the PMA and will be assigned a new number. A resubmission should be complete and self-contained without reference to earlier submissions because of potential difficulties in assembling files from storage.

All correspondence regarding this PMA should be submitted in three (3) copies in the form of a PMA amendment to the address below and reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)
ATTN: MQAB
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

This letter reflects the current progress of our review of your application. Please be advised, however, that continued review of your application or questions arising from any response to this letter, may result in additional deficiencies being identified.

If you have any questions concerning this deficiency letter, please contact Frank Twardochleb at (301) 427-1128.

Sincerely yours,

for Deborah Lewis

Philip J. Phillips
Director, Program Operations Staff
Office of Device Evaluation
Center for Devices and
Radiological Health

Deficiency List

The Office of Compliance and Surveillance (OCS) in the Center for Devices and Radiological Health (CDRH) has completed an initial review of your premarket approval application (PMA), P920004, with regard to the Good Manufacturing Practice (GMP) regulations. Please address the following issues and provide the requested documentation:

1. The Design Assurance Plan, Project 6884/6996, dated 2/7/91 for the new helix electrode, part (b)(4) is not representative of the manufacturing operations. The qualification report dated 4/16/91 does not address the effects of the sterilization process on the integrity of the helical electrode. [vol.2, pp.153-156]

2. Provide the locations of the biological indicators used during the sterilization validation and routine production for the 6966 lead. [vol.2, p.207]

3. Provide the product density and configuration pattern for the 6966 sterilization cycle. [vol.2, p.207]

4. Provide the maximum parameter of the humidity specification for the sterilization cycle of the 6966 lead. [vol.2, p.211]

5. The finished device evaluation for the 6966 lead does not adress the effect of sterilization on device performance. [vol.2, p.174]

6. The validation plan for 6963 lead does not address the effects of the sterilization cycle on device performance. [vol.3, p.327]

7. The process qualification report, (b)(4) does not address the effects of the sterilization cycle on the performance of the 6999 lead. [vol.3, p.335]

8. Provide the product location of biological indicator and spore inoculation for the validation and production sterilization cycles of the 6963 and 6999 leads. [vol.3, p.372]

9. Provide the maximum parameter of the (b)(4) exposure for the 6999 lead. [vol.3, p.376]

10. Explain the difference in the sterilization (b)(4) exposure parameters of the 7217B PCD Control Device between the two manufacturing facilities. The (b)(4) exposure parameter at the Rice Creek facility is (b)(4) minutes; the (b)(4) exposure parameter at the Kerkrade facility is (b)(4) minutes minimum. The Kerkrade facility does not specify a maximum (b)(4) exposure. [vol.4, p.415 and p. 432]

11. Provide the manufacturing methods, controls, and evaluation procedures for the facility identified as Medtronic Milaca, 900 6th Ave. N.E. Milaca, MN 56353. [vol.4, p. 437]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date April 23, 1992

From Mathematical Statistician (T.C. Lu) HFZ-162
Statistical Branch, Division of Biometric Sciences, OST

Subject Statistical Review of PMA P920015, Medtronic Multiprogrammable Tachyarrhythmia Control System with Non-thoracotomy Cardioversion and Defibrillation Electrodes, Medtronic, Inc.

To Doris Terry - HFZ-450
Division of Cardiovascular, Respiratory, and Neurological Devices
Through: Director, Division of Biometric Sciences, OST
Through: Chief, Statistical Branch, DBS. OST

1. Background

The Medtronic Pacer-Cardioverter-Defibrillator (PCD) is an implantable, multiprogrammable, automatic tachyarrhythmia control device. This device is used for treatment of patients at risk of sudden cardiac death due to ventricular tachycardia (VT) and/or ventricular fibrillation (VF).

2. Reviewer's Comments

2.1 Pooling

There are a total of 319 implants in 317 patients of the PCD device. A total of 52 investigative centers participated in the clinical trials with 20 centers in the U.S. and 32 in foreign countries. In Vol 5, p 646 - p 650, a section was devoted to the justification for data pooling. Sponsor performed a comparison of U.S. and foreign patients and summarized the variables tested in Table IVA. Sponsor first combined and then compared all the data in U.S. centers and in foreign centers. However, much information was lost in these gross combinations. The initial design with centers nested within countries was reduced to a two-way classification. This is not good statistical practice.

This reviewer recomputed all the p-values listed in Table IVB and IVC; they were all found to be correct, except for the following:

Table IVC

	p-value (sponsor)	p-value (reviewer)
NYHA Classification	(b)(4)	(b)(4)
Congestive Heart Failure		
Cardiomyopathy		

2.2 Patient follow-up

Table E-2, p. 34, vol. 1, shows the follow-up time by type of data form. This is not an adequate presentation of the follow-up data. Sponsor should refer to p. 93, Table 4.6. in "Statistical Methods for Survival Data Analysis" by Elisa Lee for a more proper life-table analysis. Sponsor should also discuss the reason why some patients dropped out of the follow-up study, either withdrawn alive or lost to follow-up. For example, there are 224 patients at 1 month and only 154 patients at 3 months. Please explain the difference of 70 patients during this 2-month period.

2.3 PCD transvene system compared to AICD Epicardial System clinical experience

For the comparison of complication/observation rates for PCD vs AICD, as reported in Table IL-1, p634, vol 5, I have the following comments:

2.3.1. Please provide the numbers of complications and patients for PCD and AICD.

2.3.2. Please provide the clinical success/failure criteria used for "Failure to Cardiovert/Defibrillate and Inappropriate/Problematic VT/VF Therapy Delivery."

2.3.3. I am concerned that pocket infection is 3.5% for PCD as compared to 2.2% of AICD, even though the sponsor argues that the PCD System implant procedure requires multiple lead configurations. There are other "lead related" complications as reported on Table X1 F1 and F2, P857, Vol. 5. PCD Transvene System has more "lead related" complications than PCD Epicardial System.

2.4. One-year actuarial survival comparison of mortality between the PCD and AICD systems was discussed on p. 842, Vol. 5. Sponsor stated "there was a statistical difference in the reported (AICD) perioperative mortality ($p = 0.017$) with the PCD Transvene System having a lower reported perioperative mortality." I have the following comments concerning this statement:

2.4.1. What statistical test was used to compare survival?

2.4.2. Please provide the two survival or life tables by year of follow-up, so that this reviewer can reproduce the statistical test and the derived p-value.

2.5. Comparison to PCD Epicardial System.

P-values for one-year survival comparison of PCD Transvene System vs. PCD Epicardial System for freedom from death by "sudden cardiac", "non-sudden cardiac", "all cardiac" and "noncardiac" causes are provided in Table Xl G-2, p. 862, Vol. 5, also Table J-2, p. 54, Vol. 1. The sponsor should discuss the statistical techniques used to derive the p-values.

2.6. PCD device longevity data.

Sponsor stated in Section M.1. p. 66, Vol. 1: "Thus, the PCD device longevity, which is monitored, utilizing battery voltage and change time obtained via telemetry, was analyzed. The PCD device longevity data collected is consistent with the longevity projection." This reviewer needs to see the data and statistical test used to support the above statement.

3. Reviewer's Conclusion

The sponsor needs to adequately address the issues raised in Section 2 above before the safety and effectiveness of the PCD Transvene System can be evaluated from a statistical perspective.

T C Lu
T.C. Lu

cc: Abhijit Acharya, Ph.D. - HFZ-450
Donald F. Dahms - HFZ-450
Lynne A. Reamer - HFZ-450
PMS Group - HFZ-402
DCC - HFZ-401
Medical Device File
Board File

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date: April 7, 1992

From: Mathematical Statistician (G. Kamer) HFZ-162
Statistics Branch, Division of Biometric Sciences, OST

Subject: PMA Review Statistical Checklist Recommendations for PMA P920015, Medtronic Multiprogrammable Tachyarrhythmia Control System with Non-thoracotomy Cardioversion and Defibrillation Electrodes, Medtronic, Inc.

To: Donald F. Dahms - HFZ-450
Division of Cardiovascular, Respiratory, and Neurological Devices
Through: Director, Division of Biometric Sciences, OST
Through: Chief, Statistics Branch, DBS, OST

The Statistics Branch, DBS, OST has received the PMA referenced above and evaluated it against the attached PMA Review Statistical Checklist. The failures to provide justification for sample size or pooling of data over investigational sites were the only non-serious omissions of a statistical nature. Therefore, we recommend this PMA be filed. We will now begin an in-depth statistical review of this PMA. This review should be completed and our comments sent to you within 30 days. If you have any questions, please contact me at 227-8629 or the statistical reviewer, T. C. Lu, at 227-8627. The omissions found are from the Clinical Investigations Section of the checklist and are stated below for your information:

1. This submission does not include any acceptable justification of sample size. Please provide a complete description of your sample-size determination. This should include effect criteria, alpha and beta statistical error tolerances, anticipated variance of the response variables, and any assumptions or statistical formulae with references that are required for sample-size determination.

2. This submission does not include any justification for pooling (combining) the patient data over site. Please review and analyze your prognostic variables to provide a detailed justification why the data may or may not be pooled for evaluation. Note that an analysis by site is always necessary in any case.

Gary L. Kamer

cc: Abhijit Acharya, Ph.D. - HFZ-450
Lynne A. Reamer - HFZ-450
Doris J. Terry - HFZ-450
T. C. Lu - HFZ-162
Mel Seidman - HFZ-162
PMS Group - HFZ-402
DCC - HFZ-401
Medical Device File
Board File

PMA P920015, Medtronic Multiprog
Tachyarrhythmia Control System with Non-thoracotomy
Cardioversion + Defibrillation Electrodes, Medtronic, Inc

PMA REVIEW STATISTICAL CHECKLIST

	Yes	No	Comment
I. Organizational and Administrative Elements including Table of Contents with volume and page numbers	✓		
II. Summary of Safety and Effectiveness			
A. Indications for use	✓		
B. Claims for the device	✓		
C. Summary of studies	✓		
III. Clinical Investigations			
A. Protocol			
1. included	✓		Summary
2. adhered to	✓		
3. deviations described	✓		
B. Patient Accountability			
1. patient inclusion/ exclusion criteria	✓		
2. follow-up schedule	✓		
3. study period completed	?		
4. all patients accounted for	✓		
C. Description of Safety and Effectiveness Parameters			
1. safety			
2. effectiveness			
~~a. sensitivity~~			
~~b. specificity~~			
~~c. false positive~~			
~~d. false negative~~			
~~e. reproducibility~~			
~~f. repeatability~~			
~~g. stability~~			
D. Documentation of Statistical Analysis and Results			
1. control (comparison) group	✓		Historical - AICD + PCD Epi
2. sample size justified		✓	
3. hypothesis test stated	✓		

Not sur how stud was de Short → mean follow time (4.5 m only comple 2 yr f

	Yes	No	Comment
4. potential of bias adequately evaluated			
a. randomization or blinding techniques	—	—	NA
b. descriptive and stratified analyses			
(1) patient demographics	✓		
(2) investigator		✓	
(3) site	✓	—	US vs Foreign
(4) surgical technique		✓	NA
5. pooling of data justified	✓	✓	US vs Foreign
6. statistical test given	✓	—	Vague + Device
7. clear presentation of data	✓	—	
8. statistical results stated	✓	—	Not by site
9. statistical conclusions drawn from results	✓	—	

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DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date 4/3/92

From Chemist
Premarket Approval Staff, ODE, HFZ-402

Subject Request for PMA Filing Review

To DCRND

PMA Application No.: P920015

PMA Applicant: MEDTRONIC, INC.

Device Trade Name: MEDTRONIC® TRANVENE LEAD SYSTEM

Date of Document: 3/31/92

Date Received by DMC: 4/1/92

Date Received by PMA Staff from DMC: 4/2/92

Date letter and checklist due from ODE Division to PMA Staff: 5/11/92

Date Letter Due out of CDRH: 5/16/92

Please review the above referenced PMA for a filing/nonfiling determination. A complete checklist and "filed" or "not filed" letter should be returned to the PMA Staff by the due date specified above.

If the PMA is to be filed, please specify in the checklist special considerations or important aspects of the manufacturing process that should be included in the EDRO inspection of the manufacturing facility. A preliminary determination of whether the device is a "critical device" for purposes of the device Good Manufacturing Practice Regulations should be included (see checklist).

The biostatistics staff (HFZ-116) is notified of every PMA received and will notify the ODE Division as to the identity of the statistical reviewer. The biostatistics staff will review appropriate segments of the PMA and forward a statistical review memo to the reviewing ODE Division before the due date specified above. Please let me know if you need any further assistance.

Arnold Alpert, Ph.D.

AP
PLDB
CLRNS

0015/S000

3-Apr-1992

FROM:	LETTER DATE	LOGIN DATE	DUE DATE
MEDTRONIC INC. ATTN: JENNIFER M. MARRONE 7000 CENTRAL AVENUE, N.E. MINNEAPOLIS,, MN 554323576	03/31/92	04/01/92	/ /
	DOCUMENT: PMA	CONTROL # P920015/S000	

SUBJECT:
MEDTRONIC(R) TRANSVENE LEAD SYSTEM

	OFFICE	DATE REFERRED
8 COPIES OF VOLUME 1	~~CK~~	4/2/92
8 COPIES OF VOLUME 2	CLRNS	4/3/92
8 COPIES OF VOLUME 3		
8 COPIES OF VOLUME 4		
8 COPIES OF VOLUME 5		
8 COPIES OF VOLUME 6		
8 COPIES OF VOLUME 7		
____ COPIES OF VOLUME ____		
____ COPIES OF VOLUME ____		
____ COPIES OF VOLUME ____		

I N T E R O F F I C E M E M O R A N D U M

Date: 10-Sep-1993 09:02am DST
From: Raymond R. O'Neill
RRO
Dept: OST-DBS-PSSB
Tel No: 594-0644

TO: Lynne A. Reamer (LAR)

CC: Anita M. Rayner (ARB)

Subject: OK for Medtronic ICD lead 522 language

Anita asked me to respond to your inquiry about the language referring to section 522 in the PMA approvable letter for the Medtronic transvenous ICD leads. I am the coordinator so far for the ICD protocols for section 522. It looks fine to me.

Thanks for your interest.

Ray

Review

ROUTING AND TRANSMITTAL SLIP

Date 12/07/93

TO: (Name, office symbol, room number, building, Agency/Post)	Initials	Date
1. Annie		
2.		
3.		
4.		
5.		

	Action		File		Note and Return
	Approval		For Clearance		Per Conversation
	As Requested		For Correction		Prepare Reply
	Circulate		For Your Information		See Me
	Comment		Investigate		Signature
	Coordination		Justify		

REMARKS

I spoke to Chuck Swanson about the proposed rewording of the indication; he had no concerns. He also said that "and" will be deleted from the 6963 Manual, last sentence, P.8. Revised Indications will be sent for Changes.

DO NOT use this form as a RECORD of approvals, concurrences, disposals, clearances, and similar actions

FROM: (Name, org. symbol, Agency/Post)	Room No.—Bldg.
DCMS	Phone No.

5041-102

☆ GPO : 1983 O - 381-529 (301)

OPTIONAL FORM 41 (Rev. 7-76)
Prescribed by GSA
FPMR (41 CFR) 101-11.206

Medtronic, Inc.
7000 Central Avenue N.E.
Minneapolis, MN 55432 USA
(612) 574-3409
(612) 574-6424 fax

Charles H. Swanson, Ph.D.
Vice President, Regulatory Affairs
Cardiac Pacing Business

SENT VIA TELECOPY TO 301-594-3076

December 9, 1993

Ms. Doris Terry
Office of Device Evaluation (HFZ-450)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

RE: TRANSVENE® PMA Submission

Dear Ms. Terry:

This is to confirm our telephone conversation this morning regarding the Summary of Safety and Effectiveness for the TRANSVENE lead and the labeling for the Model 6963 lead. Regarding the Summary of Safety and Effectiveness, Medtronic agrees to the modification as you proposed that the statement regarding the patients with hemodynamically stable VT read as follows:

> "While this patient population was included in the TRANSVENE Lead clinical study, no conclusions were drawn from the data obtained on this specific patient group." The latter part of the sentence reflects a change from the earlier version and we agree to this modification. The relevant pages of our technical manuals have been modified and are attached.

With regard to the labeling for the Model 6963, the last sentence on page 8 does not make sense as written and should be modified by the deletion of the word "and" as indicated on the attachment.

If you have any questions, please call Dennis Connolly immediately at 612-574-4696.

Sincerely,

Charles H. Swanson

cs120893:sj

Attachment

6963 Reg (02088dEN/MMC 10/8/93 11:01 AM Page 8

If the electrode is to be placed in the coronary sinus, advance the lead into the right atrium and rotate the curved stylet to manipulate the tip over the tricuspid valve. Move the tip medially and posteriorly to the coronary sinus ostium and advance the lead into the coronary sinus. Continue advancing the lead through the coronary sinus to the desired position.

If the lead goes through the tricuspid valve opening, retract the lead with a gentle posterior rotation and then advance it toward the coronary sinus ostium.

The electrode for the TRANSVENE®-SVC must be as far as possible from other defibrillation electrodes. Also, the cardiac mass between the electrodes should be as large as possible. Insufficient separation between the electrodes may result in reduced defibrillation efficacy.

Proper positioning of the electrode is essential for defibrillation efficacy (Figure 7). Use fluoroscopy (P-A and lateral position) to ensure that the distal end of the electrode is properly positioned in the superior vena cava or is lodged in the coronary sinus with the proximal end of the electrode advanced beyond the coronary sinus ostium.

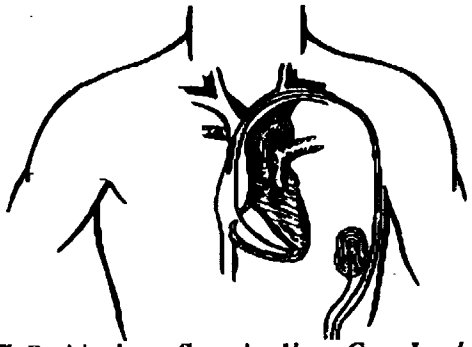


Figure 7. Positioning a Superior Vena Cava Lead

Bradycardia Pacemakers

Previously implanted bradycardia pacemakers, tachyarrhythmia devices and leads should be explanted. The output pulses of an implanted device may adversely affect the tachyarrhythmia detection capabilities of the PCD device. If leads must be abandoned rather than removed they should be capped to ensure they will not become a pathway for currents to or from the heart. If a patient requires a separate atrial or dual chamber pacemaker for hemodynamic reasons, either permanent or temporary, allow adequate space between the pacing lead electrodes and the defibrillation lead electrodes.

DEC 09 '93 12:03PM PACING REG AFFAIRS P.3/6

DESCRIPTION

The Medtronic® TRANSVENE®-SVC Model 6963 Unipolar, Endocardial, Superior Vena Cava or Coronary Sinus Lead is designed for the delivery of cardioversion and defibrillation therapies.

Silicone insulation surrounds the low resistance conductor coil and the coil electrode is a platinum alloy. The lead also has a 6.5 mm connector.

INDICATIONS FOR USE

The Medtronic® TRANSVENE®-SVC Model 6963 is intended for single long-term use in the superior vena cava or coronary sinus and is designed to be used only with a compatible Medtronic implantable tachyarrhythmia control device along with at least one other Medtronic defibrillation lead.

The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated. Current medical research indicates that such patients should:

- have survived at least one episode of a cardiac arrest, presumably due to a ventricular tachyarrhythmia as evidenced by resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; OR
- in the absence of a prior cardiac arrest, have poorly tolerated sustained VT and/or VF, which occurs spontaneously or can be induced despite the best antiarrhythmic drug therapy.

The natural history of patients with hemodynamically stable sustained VT is not well defined. While this patient population was included in the TRANSVENE® Lead clinical study, the study objectives did not include stratification of this specific patient group.

Prior to TRANSVENE® implant, it is strongly recommended that patients undergo a complete cardiac evaluation, which should include extensive electrophysiologic testing. Also, extensive electrophysiologic evaluation and testing of the safety and efficacy of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the TRANSVENE® system.

Replaced w/

no conclusions were drawn from the data obtained on this specific patient group.

DESCRIPTION

The Medtronic® TRANSVENE®-SQ Model 6999 Unipolar, Subcutaneous, Oval Patch Lead is designed for the delivery of cardioversion and defibrillation therapies.

The lead features a low resistance conductor coil and platinum alloy electrode coils for cardioversion and defibrillation therapies. The outer edge of the lead is used for suturing. The lead also has a 6.5 mm unipolar connector.

There are 3 nodes on one side of the patch, and 2 nodes at the junction of the lead body and patch electrode. These nodes are intended to mark the insulated side of the patch electrode.

INDICATIONS FOR USE

The Medtronic® TRANSVENE®-SQ Model 6999 is intended for single long-term use only with a compatible Medtronic implantable tachyarrhythmia control device along with at least one other Medtronic defibrillation lead.

~~NOTE: The Model 6999 TRANSVENE®-SQ patch lead is not intended for epicardial or pericardial placement.~~

The lead has application for patients in which implantable tachyarrhythmia cardioversion or defibrillation systems are indicated. Current medical research indicates that such patients should:

- have survived at least one episode of a cardiac arrest, presumably due to a ventricular tachyarrhythmia as evidenced by resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; OR
- in the absence of a prior cardiac arrest, have poorly tolerated sustained VT and/or VF, which occurs spontaneously or can be induced despite the best antiarrhythmic drug therapy.

The natural history of patients with hemodynamically stable sustained VT is not well defined. While this patient population was included in the TRANSVENE® Lead clinical study, the study objectives did not include stratification of this specific patient group.

Prior to TRANSVENE® implant, it is strongly recommended that patients undergo a complete cardiac evaluation, which should include extensive electrophysiologic testing. Also, extensive electrophysiologic evaluation and testing of the

modified

modified

Replaced by:

no conclusions were drawn from the data obtained on this specific patient group.

DEC 09 '93 12:09PM PACING REG AFFAIRS P.6/6

designed to be used only with a compatible Medtronic implantable tachyarrhythmia control device along with at least one other Medtronic defibrillation lead.

The coil electrode is intended to be used for delivery of cardioversion and defibrillation pulses. The helix tip electrode and the ring electrode may be used for bipolar pacing and sensing; however, when used with the standard bipolar PCD® pulse generators, pacing occurs between the tip electrode and the coil electrode.

The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated. Current medical research indicates that such patients should:

- have survived at least one episode of a cardiac arrest, presumably due to a ventricular tachyarrhythmia as evidenced by resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; OR
- in the absence of a prior cardiac arrest, have poorly tolerated sustained VT and/or VF, which occurs spontaneously or can be induced despite the best antiarrhythmic drug therapy.

The natural history of patients with hemodynamically stable sustained VT is not well defined. While this patient population was included in the TRANSVENE® Lead clinical study, the study objectives did not include stratification of this specific patient group.

Prior to TRANSVENE® implant, it is strongly recommended that patients undergo a complete cardiac evaluation, which should include extensive electrophysiologic testing. Also, extensive electrophysiologic evaluation and testing of the safety and efficacy of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the TRANSVENE® system.

CONTENTS OF PACKAGE

The leads are supplied sterile. Each package contains:

- 1 TRANSVENE®-RV lead with two non-radiopaque anchoring sleeves, stylet, and stylet guide
- 2 fixation tools
- 1 vein lifter
- Extra stylets
- End Caps
- Product literature

Replaced by:
no conclusions were drawn from the data obtained on this specific patient group.

DEC 09 '93 12:05PM PACING REG AFFAIRS P.5/6

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20850

M E M O R A N D U M

DATE: December 8, 1993

FROM: Field Programs Branch, CDRH, HFZ-331

SUBJECT: **FINAL APPROVAL - DOMESTIC AND FOREIGN FIRM**
PMA P920015

Mfrs.: Medtronic, Inc.
7000 Central Avenue NE
Fridley, MN 55432

Medtronic BV
Wenckebachstraat 10
6466 NC Kerkrade West
The Netherlands

TO: Chief, Program Operations Staff
HFZ-402

Applicant: Medtronic, Inc.
7000 Central Avenue NE
Fridley, MN 55432

Product: Transvene Lead System

This is in response to your request for final approval regarding the above PMA application. OC concurs with final approval for this PMA.

Vertleen Covington
Vertleen Covington

cc:
HFZ-331
DOE III
HFA-224
#92-79

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20850

MEMORANDUM

DATE: December 6, 1993

FROM: Field Programs Branch, CDRH, HFZ-331

SUBJECT: GMP Inspection **CLEARANCE**
PMA P920015

Mfr.: Medtronic, Inc.
7000 Central Avenue NE
Fridley, MN 55432

TO: Premarket Approval Coordinator
HFZ-402

Applicant: Same

Product: Transvene Lead System

A follow-up inspection of the above referenced manufacturer was accomplished on 10-27-93.

On the basis of the information reviewed, the firm has an acceptable GMP program.

This should complete all of the sites awaiting inspection that are currently outstanding concerning this PMA.

Vertleen Covington
Vertleen Covington

cc:
HFZ-331
HFA-224
DOE III
HFR-MW300
#92-79

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20850

MEMORANDUM

DATE: July 19, 1993

FROM: Field Programs Branch CDRH, HFZ-331

SUBJECT: GMP Inspection [redacted]
PMA P920015

TO: Premarket Approval Coordinator
HFZ-402

Mfrs.: Medtronic, Inc.
7000 Central Avenue NE
Fridley, MN 55432

Medtronic B.V.
Wenckebatchstraat 10
Kerkrade, The Netherlands

Applicant: Medtronic, Inc.
7000 Central Avenue NE
Fridley, MN 55432

Product: Transvene Lead System

An inspection of the above referenced manufacturers was accomplished on 5-27-93 and 12-18-92. On the basis of the information reviewed, Medtronic Inc., located in Fridley, MN, has an unacceptable GMP program.

Attached, please find a copy of the review performed by the Manufacturing uality Assurance Branch which details the GMP deficiencies revealed by the inspection.

On the basis of the information reviewed, Medtronic B.V., located in The Netherlands, has an acceptable GMP program.

PLEASE NOTE THAT NEITHER A COPY OF THIS EVALUATION MAY BE SENT TO THE FIRM, NOR MAY ITS CONTENTS BE DISCUSSED WITH THEM.

A follow-up inspection is being requested for the above manufacturing site. When that inspection has been completed and we have had an opportunity to review the results, you will be advised of the findings of the inspection.

This should complete all of the sites awaiting inspection that are currently outstanding concerning this PMA.

Vertleen Covington

Vertleen Covington

Attachment
cc:
HFZ-331
HFA-224
HFZ-332
HFR-MW300
#92-79

DATE: July 6, 1993

TO: Vertleen J. Covington, PMA
Coordinator, Field Programs Branch

THRU: Acting Chief, Cardiovascular Branch, DOE III 7/7/93

FROM: Consumer Safety Officer
Cardiovascular Branch, DOE III

SUBJECT: PMA P920015 Pre-Approval Inspection
May 10-14, 24, 25, 27, 1993
Manufacturer: Medtronic, Inc.
7000 Central Avenue NE
Fridley, MN 55432

CFN: 2182208

PRODUCT: Transvene Lead System

DISTRICT RECOMMENDATION: Recommend non-concurrence with the PMA approval and that the district send a non-concurrence letter to the firm.

INVESTIGATORS: Karen A. Coleman, ATL-DO
Joseph M. Edwin, MIN-D)

SITUATION: Situation 1 (In accordance with Part V of Compliance Program 7382.830, dated 9-1-91)

CDRH/OCS RECOMMENDATION: PMA Non-Approval

A review of the EIR, FDA 483, and exhibits for Medtronic, Inc. facility indicate that the criteria for a Situation 1 has been met, in accordance with the requirements of Part V of Compliance Program 7382.830, dated 9-1-91. Conditions exist whereby there is a reasonable probability that unsafe or ineffective devices will be produced and distributed.

The following is an evaluation of the EIR, exhibits, and FDA 483. The firm did not respond to the observations made by the investigator on the FDA 483.

21 CFR 820.100(a)(1)

Failure to establish procedures for specification control measures to assure that the design basis for the device is correctly translated into approved specifications, as required by 21 CFR 820.100(a)(1). For example: 1. the firm has not validated critical Tachy Lead Manufacturing Operations currently used in production including but not limited to: Welding, Crimping, and Bonding Operations. Firm does not have data showing they have run a minimum of three consecutive successful runs to provide assurance these processes are validated; 2. a review of sterilization certification (b)(4) reports dated 4/10/85 (adding Permanent Lead Introducer [PLI]) and 3/4/92 (adding 6966 Tachy RV Lead), and 3/30/93 (update certification adding a (b)(4) controller system) revealed: a) D values were determined using the samples in sterilization chambers loaded with (b)(4) (b)(4) do not contain product or simulated product). Firm's documents and SOP's do not define or describe (b)(4) (b)(4). As of 5/13/93 firm did not have a written explanation correlating product load density characteristics of a fully loaded sterilization chamber of product in packages versus a fully loaded chamber of (b)(4) (b)(4) b) Firm does not have a report correlating the results contained in the 4/10/85 and 3/4/92 certificates with conclusions that show the PLI is actually the "worst case" product for this certification group. The PLI is routinely used as the sample for requalifying products or adding new products to this group. c) D value calculations for sterilization certificate (b)(4) dated 3/4/92 and 3/30/93 only shows the D value at confidence intervals calculated at (b)(4) Firm's SOP (b)(4) requires they calculate it at (b)(4) d) Certifications dated 3/4/92 and 3/30/93 do not identify the actual Sterility Assurance Level that will be obtained; 3. Coil Part Number (b)(4) (b)(4) diameter platinum coil sputtering process has not been validated.

This charge is supported by: 1. the discussions on pages 2 & 3 of the EIR; Exhibits F1-3, L1-6, N1-4, M1-6, G1-11, O1-4, J1, K2, F1-3, G1-11, and G8; and FDA 483 #1; 2. the discussion on pages 5-7 of the EIR; Exhibits P1-14, A1-22, E1-43, D1-13, B1-10, and C1-11; and FDA 483 #4; 3. the discussion on page 7 of the EIR, Exhibits Q1-9 and S1-26, and FDA 483 #5.

21 CFR 820.181

Failure to prepare, date, and sign by a designated individual device master records, as required by 21 CFR 820.181. For example, a review of the Plans and Qualification Reports for the New Laser Source; Model 6884 Split Build; and Lead Model 6966 Connector Subassembly revealed the following: a) The plans did not require process validation. b) Sampling plans were not identified. c) Test methods or procedures are not always identified. d) They do not describe how the results will be interpreted and/or analyzed.

This charge is supported by the discussions on pages 3 & 4 of the EIR; Exhibits F1-3, G1-11, L1-6, M1-6, N1-4, and O1-4; and FDA 483 #2.

21 CFR 820.160

Failure to check and, where necessary, test for conformance with device specifications each production run, lot, or batch prior to release or distribution, as required by 21 CFR 820.160. For example, Transvene Leads have not been tested under simulated use conditions.

This charge is supported by the discussion on pages 7 and 8, of the EIR and FDA 483 #6.

21 CFR 820.162

Failure to investigate any failure of a device to meet performance specifications after it has been released for distribution, as required by 21 CFR 820.162. For example, Transvene Lead Model 6884 (b)(4) (b)(4) was returned and found to have cosmetic MIO on both the inner and middle coil insulation. The coils were not analyzed/examined to verify that the platinum sputtering process was done to specification.

This charge is supported by the discussion on page 8 of the EIR; exhibits S1-26, Q1-9, T1-4, and U1-3; and FDA 483 #7.

UNSUPPORTABLE FDA 483 OBSERVATIONS

FDA 483 #3 - There is no GMP requirement for design issues.

Kent A. Berthold

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20850

MEMORANDUM

DCND/AA

DATE: April 19, 1993

FROM: Chief, Program Development Section
Program Development and Analysis Branch
CDRH, HFZ-331

SUBJECT: Request for Assistance

TO: Chief, IPTSB
ORO, HFC-133

Mfr.: Medtronic, Inc.
Rice Creek Facility
7000 Central Avenue, N.E.
Minneapolis, MN 55432

Applicant: Same as above

Product: PMA P920015
Transvene Lead System

We are requesting that your office provide a device expert for a Premarket Approval (PMA) preclearance inspection of the above referenced manufacturer with the Minneapolis district office. We are making this request directly to your office because the subject PMA covers a complex, critical device, and several of t' firm's other sites have violative histories. During the last year and a h[illegible], the Minneapolis district has failed to complete seven of their ten PMA preapproval inspections within two months of the due date because, according to the Inspection Branch management, they do not have a sufficient number of investigators who are qualified to conduct device inspections.

It will be necessary to perform a complete PMA inspection of Medtronic per C.P. 7383.001 to determine if the firm is meeting all of its PMA commitments and GMP requirements. Emphasis should be placed upon determining whether the firm has validated all significant manufacturing processes.

We have requested that the Minneapolis district office contact you to schedule the inspection (see attached assignment). If you need any further information, please do not hesitate to call me at 427-1125.

Wes Morgenstern
Wes Morgenstern

Product Code: 74
PAC: 83001
Priority: Top
Est. Comp. Time: 45 hours
Due Date: 6-1-93
Contact Officer: Wes Morgenstern
1390 Piccard Drive
Rockville, MD 20850
Phone: 427-1125
FAX: 427-1076

4

cc:
-402
HFZ-332
HFA-224
HFR-NE1 (Beebe)
HFR-MW300 (MIN-DO)
HFZ-331 (Reading File)
#92-79

MEMORANDUM

From: Doris Terry (HFZ-450)
To: File # P920015
Subject: Medtronic Transvene System
Date: October 28, 1993
Office: DCRND/ODE

The manufacturer responded to our approvable letter of September 23, 1993. In addition, the manufacturer mentioned that a follow-up inspection is scheduled for October 18, 1993 (the PMA application might be amended to provide inspection information). The manufacturer also stated that there are no new data from the clinical study of the Medtronic Transvene System which could impact safety and effectiveness.

Deficiency # 1

The manufacturer modified the labeling to include the following: diagrams for proper insertion and the final position of the leads; defibrillation efficacy data for the different lead configurations and polarity combinations (including sequential and simultaneous discharges); information and/or recommendations regarding implantation techniques and testing methods; information regarding implanting in patients who do not have a 10 Joule safety margin; information aimed at reducing the incidence of infection; instructions stressing the importance of pausing between VF inductions; information regarding the expected change in defibrillation thresholds; guidance regarding permanent pacemaker separation from the Transvene leads (RV and SVC/CS); a statement which emphasizes the need for x-rays and pace threshold testing; information regarding techniques for placing the leads via the cephalic vein; and an explanation regarding the necessity for explant and return of the leads upon the patient's death.

The manufacturer provided the requested data. No concerns about how the data are presented in the labeling.

Deficiency # 2

The manufacturer modified the labeling to include warnings which pertain to the following: use of the Sub-Q patch lead on the pericardium or epicardium; language regarding the use of dual anchoring sleeves; and information regarding extensive inductions during implant.

No significant concerns about the warnings as written.

Deficiency # 3

We told the manufacturer that the indications and contraindications for use of the Medtronic Transvene Lead System should be identical to the PCD Epicardial System with certain exceptions. The exact language which states, "The safety and

effectiveness of the PCD...", was not used. However, the proposed language is acceptable. The indications as written are acceptable. It should be noted that the contraindication proposed by the manufacturer, "The Transvene Lead System is contraindicated for use in any system other than a Medtronic implantable tachyarrhythmia control device system for which it has been tested," will not be included in the labeling as a contraindication. The manufacturer was informed of our decision in a phone conversation. They agreed to remove the contraindication, and will send documentation confirming our agreement.

The manufacturer also satisfactorily responded to the requests which consisted of the following: placing an identifying mark to distinguish nonthoracotomy leads from thoracotomy leads; reporting warning and precautions separately and providing a copy of the Patient's Manual.

I also told the manufacturer that the Warnings and Precautions should be included in the labeling according to our Blue Book Memorandum of March, 8. 1991 (manufacturer has a copy). We reviewed the manual and found that caution statements within the context of the manuals should also be included on the list of precautions. They agreed to revise their labeling to include the referenced cautions on the list.

Recommendation

The manufacturer modified the labeling as requested. Formal documentation pertaining to the warnings and precautions and the removal of the requested contraindication will be submitted. In the interim, faxed information will be sent confirming their agreement, as we discussed, regarding those concerns.

Approval of the referenced PMA application.

MEMORANDUM

From: Doris Terry (HFZ-450)
To: File # P920015
Subject: Medtronic® Transvene® Lead System
Date: August 16, 1993
Office: DCRND/ODE

On August 2, 1993, the Circulatory System Devices Panel reviewed the PMA application for the Medtronic® Transvene® Lead System. Specific questions and labeling concerns generated from FDA's review of the PMA application are included in my memoranda of July 9, 1993 (FDA review and panel presentation).

The panel addressed all FDA's questions, and concurred with the labeling recommendations.

The panel recommended approval of the Medtronic® Transvene® PMA with modifications to the labeling. A list of FDA's and the panel's recommendations are listed below.

FDA's and the Panel's Recommendations

The labeling should be modified to include the following:

- diagrams which show proper insertion of the endocardial leads and how the patch lead should be applied to the subcutaneous tissue;
- a caution statement that the patch lead is not for use on the pericardium or epicardium;
- efficacy data of the different lead configurations via the different pathways;
- pictures or diagrams of the various electrode configurations which serve as a guide for selection;
- information and/or recommendations about implanting the leads and testing the different configurations. For example, when to use a two-lead versus a three-lead configuration and when to implant in the superior vena cava (SVC) versus the coronary sinus CS);
- information or recommendations regarding implanting in patients who do not have the 10 Joule safety margin;
- information about how the incidence of infection can be reduced;
- a reference about using 5-minute intervals between ventricular fibrillation (VF) inductions during testing;

- stronger language regarding the use of dual anchoring sleeves on the right ventricle (RV), SVC and CS leads;

- information which states that a thoracotomy after extensive testing with a nonthoracotomy lead system should be delayed at least 2 days (the clinical data showed that when a thoracotomy was performed immediately after testing, the perioperative mortality rate was increased from 0.7 to 9.3 percent);

- guidance regarding separating pacemaker leads from the Transvene leads;

- a statement which emphasizes the need for x-rays and pace/sense threshold testing at follow-up to check for lead dislodgement;

- information regarding placing the leads via the cephalic vein when possible; and

- an explanation regarding the necessity for explant and return of the leads upon the patient's death.

In addition the manufacturer should note the following:

- The indications and contraindications for use of the Medtronic® Transvene® Lead System should be the same (with certain modifications) as those for the PCD™ Epicardial System.

- The technical manuals for the Transvene® Leads should state that the leads are for use together as a system. The labeling (where appropriate) should be consistent in all of the Transvene® Lead manuals. The information regarding the Transvene® Leads in the PCD™ Manual should also be included in the Transvene® Lead manuals.

- There should be an identifying mark on the package label which distinguishes nonthoracotomy leads from thoracotomy leads.

- The Warnings and Precautions in the labeling should be identified and reported separately according to FDA's Blue Book Memorandum of March 8, 1991 (a copy of this memorandum was previously sent to you).

- Postmarket surveillance will track the explanted leads for evidence of metal ion oxidation (MIO).

The manufacturer should provide a copy of the Patient's Manual which includes a reference to use of the nonthoracotomy leads with the PCD™ models.

Recommendation

The above information will be included in an approvable letter to the manufacturer.

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 7/28/93
FROM: Doris Terry (HFZ-450)		OFFICE ODE
TO: File # P920015		DIVISION DCRND

SUBJECT: Medtronic Transvenous Lead System

SUMMARY

The following information was requested for clarification of data regarding reported complications and observations.

SIGNATURE

Doris J. Terry

DOCUMENT NUMBER

FORM FD 2034 (6/76)

modified table 7/28/93

PCD Transvene System PCD Transvene System versus PCD Epicardial System Reported Complications		
Reported Complications	PCD Transvene System (N=757)	PCD Epicardial System (N=742)
Increased Defibrillation Requirements	1.2%	0.5%
Inappropriate Therapy	-	2.2%
Pace/Sense Related	0.8%	3.5%
Infection Related - Explanted/Total	2.9%/3.2%	2.3%/2.3%
Lead Related	15.1%	3.0%
Device Related	0.5%	0.9%

Table ID2-7: Reported Complications: PCD Transvene System versus PCD Epicardial System - 2/1/93

PCD Transvene System PCD Transvene System versus PCD Epicardial System Reported Observations		
Reported Observations	PCD Transvene System (N=757)	PCD Epicardial System (N=742)
Ineffective Therapy	1.1%	1.1%
Inappropriate Therapy	9.6%	13.6%
Pace/Sense Related	9.0%	14.0%
Pocket Related	5.3%	2.6%
Lead Related	2.3%	1.2%
Device Related	-	-

Table ID2-8: Reported Observations: PCD Transvene System versus PCD Epicardial System - 2/1/93

includes hematomas & seromas

e. Survival Analysis

Despite their excellent clinical performance, epicardial defibrillation lead system have important limitations. The requirement for direct thoracic access contributes significantly to patient morbidity and mortality, patient discomfort and prolonged hospitalization. The availability of reliable

PCD Transvene System Dislodgement Complications and Observations By Investigator - CONTINUED PAGE 4/4			
	Number of Implants out of 762 (%)	# Dislodgement Complications (% of own pts)	# Dislodgement Observations (% of own pts)
(b)(4)	(b)(4)		

total: 91

PCD Transvene System Dislodgement Complications and Observations By Investigator			
	Number of Implants out of 762 (%)	# Dislodgement Complications (% of own pts)	# Dislodgement Observations (% of own pts)
(b)(4)			

(b)(4)

PCD Transvene System Dislodgement Complications and Observations By Investigator - CONTINUED PAGE 2/4			
	Number of Implants out of 762 (%)	# Dislodgement Complications (% of own pts)	# Dislodgement Observations (% of own pts)
(b)(4)			

(b)(4)

PCD Transvene System Dislodgement Complications and Observations By Investigator - CONTINUED PAGE 3/4			
	Number of Implants out of 762 (%)	# Dislodgement Complications (% of own pts)	# Dislodgement Observations (% of own pts)
(b)(4)			

(b)(4)

PCD Transvene System Dislodgement Complications and Observations By Investigator - CONTINUED PAGE 4/4			
	Number of Implants out of 762 (%)	# Dislodgement Complications (% of own pts)	# Dislodgement Observations (% of own pts)
(b)(4)			

(b)(4)

total: 91

PCD Transvene System Infection Complications and Observations By Investigator			
	Number of Implants out of 762 (%)	# Infection Complications (% of own pts)	# Infection Observations (% of own pts)
(b)(4)			

(b)(4)

PCD Transvene System Infection Complications and Observations By Investigator - CONTINUED PAGE 2/4			
	Number of Implants out of 762 (%)	Number of Complications (% of own pts)	Number of Observations (% of own pts)
(b)(4)			

(b)(4)

PCD Transvene System
Infection Complications and Observations
By Investigator - CONTINUED PAGE 3/4

	Number of Implants out of 762 (%)	Number of Complications (% of own pts)	Number of Observations (% of own pts)
(b)(4)			

(b)(4)

PCD Transvene System Infection Complications and Observations By Investigator - CONTINUED PAGE 4/4			
	Number of Implants out of 762 (%)	Number of Complications (% of own pts)	Number of Observations (% of own pts)
(b)(4)	(b)(4)		

total: 24 total: 10

PCD Transvene System
Dislodgement Complications and Observations
By Investigator - CONTINUED PAGE 3/4

	Number of Implants out of 762 (%)	# Dislodgement Complications (% of own pts)	# Dislodgement Observations (% of own pts)
(b)(4)			

(b)(4)

PCD Transvene System Dislodgement Complications and Observations By Investigator - CONTINUED PAGE 4/4			
	Number of Implants out of 762 (%)	# Dislodgement Complications (% of own pts)	# Dislodgement Observations (% of own pts)
(b)(4)			

(b)(4)

total: 91

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20850

MEMORANDUM

DCRND/AA

DATE: July 19, 1993

FROM: Field Programs Branch CDRH, HFZ-331

SUBJECT: GMP Inspection **NONCLEARANCE**
PMA P920015

TO: Premarket Approval Coordinator
HFZ-402

Mfrs.: Medtronic, Inc.
7000 Central Avenue NE
Fridley, MN 55432

Medtronic B.V.
Wenckebatchstraat 10
Kerkrade, The Netherlands

Applicant: Medtronic, Inc.
7000 Central Avenue NE
Fridley, MN 55432

Product: Transvene Lead System

An inspection of the above referenced manufacturers was accomplished on 5-27-93 and 12-18-92. On the basis of the information reviewed, Medtronic Inc., located in Fridley, MN, has an unacceptable GMP program.

Attached, please find a copy of the review performed by the Manufacturing Quality Assurance Branch which details the GMP deficiencies revealed by the inspection.

On the basis of the information reviewed, Medtronic B.V., located in The Netherlands, has an acceptable GMP program.

PLEASE NOTE THAT NEITHER A COPY OF THIS EVALUATION MAY BE SENT TO THE FIRM, NOR MAY ITS CONTENTS BE DISCUSSED WITH THEM.

A follow-up inspection is being requested for the above manufacturing site. When that inspection has been completed and we have had an opportunity to review the results, you will be advised of the findings of the inspection.

This should complete all of the sites awaiting inspection that are currently outstanding concerning this PMA.

Vertleen Covington

Vertleen Covington

Attachment
cc:
HFZ-331
HFA-224
HFZ-332
HFR-MW300
#92-79

DATE: July 6, 1993

TO: Vertleen J. Covington, PMA
Coordinator, Field Programs Branch

THRU: Acting Chief, Cardiovascular Branch, DOE III 7/7/93

FROM: Consumer Safety Officer
Cardiovascular Branch, DOE III

SUBJECT: PMA P920015 Pre-Approval Inspection
May 10-14, 24, 25, 27, 1993
Manufacturer: Medtronic, Inc.
7000 Central Avenue NE
Fridley, MN 55432

CFN: 2182208

PRODUCT: Transvene Lead System

DISTRICT RECOMMENDATION: Recommend non-concurrence with the PMA approval and that the district send a non-concurrence letter to the firm.

INVESTIGATORS: Karen A. Coleman, ATL-DO
Joseph M. Edwin, MIN-D)

SITUATION: Situation 1 (In accordance with Part V of Compliance Program 7382.830, dated 9-1-91)

CDRH/OCS RECOMMENDATION: PMA Non-Approval

A review of the EIR, FDA 483, and exhibits for Medtronic, Inc. facility indicate that the criteria for a Situation 1 has been met, in accordance with the requirements of Part V of Compliance Program 7382.830, dated 9-1-91. Conditions exist whereby there is a reasonable probability that unsafe or ineffective devices will be produced and distributed.

The following is an evaluation of the EIR, exhibits, and FDA 483. The firm did not respond to the observations made by the investigator on the FDA 483.

21 CFR 820.100(a)(1)

Failure to establish procedures for specification control measures to assure that the design basis for the device is correctly translated into approved specifications, as required by 21 CFR 820.100(a)(1). For example: 1. the firm has not validated critical Tachy Lead Manufacturing Operations currently used in production including but not limited to: Welding, Crimping, and Bonding Operations. Firm does not have data showing they have run a minimum of three consecutive successful runs to provide assurance these processes are validated; 2. a review of sterilization certification (b)(4) reports dated 4/10/85 (adding Permanent Lead Introducer [PLI]) and 3/4/92 (adding 6966 Tachy RV Lead), and 3/30/93 (update certification adding a (b)(4) controller system) revealed: a) D values were determined using the samples in sterilization chambers loaded with (b)(4) (b)(4). (b)(4) (b)(4) do not contain product or simulated product). Firm's documents and SOP's do not define or describe (b)(4) (b)(4). As of 5/13/93 firm did not have a written explanation correlating product load density characteristics of a fully loaded sterilization chamber of product in packages versus a fully loaded chamber of (b)(4) (b)(4). b) Firm does not have a report correlating the results contained in the 4/10/85 and 3/4/92 certificates with conclusions that show the PLI is actually the "worst case" product for this certification group. The PLI is routinely used as the sample for requalifying products or adding new products to this group. c) D value calculations for sterilization certificate (b)(4) dated 3/4/92 and 3/30/93 only shows the D value at confidence intervals calculated at (b)(4) Firm's SOP (b)(4) requires they calculate it at (b)(4) d) Certifications dated 3/4/92 and 3/30/93 do not identify the actual Sterility Assurance Level that will be obtained; 3. Coil Part Number (b)(4) (b)(4) diameter platinum coil sputtering process has not been validated.

This charge is supported by: 1. the discussions on pages 2 & 3 of the EIR; Exhibits F1-3, L1-6, N1-4, M1-6, G1-11, O1-4, J1, K2, F1-3, G1-11, and G8; and FDA 483 #1; 2. the discussion on pages 5-7 of the EIR; Exhibits P1-14, A1-22, E1-43, D1-13, B1-10, and C1-11; and FDA 483 #4; 3. the discussion on page 7 of the EIR, Exhibits Q1-9 and S1-26, and FDA 483 #5.

21 CFR 820.181

Failure to prepare, date, and sign by a designated individual device master records, as required by 21 CFR 820.181. For example, a review of the Plans and Qualification Reports for the (b)(4) (b)(4) Model 6884 Split Build; and Lead Model 6966 Connector Subassembly revealed the following: a) The plans did not require process validation. b) Sampling plans were not identified. c) Test methods or procedures are not always identified. d) They do not describe how the results will be interpreted and/or analyzed.

This charge is supported by the discussions on pages 3 & 4 of the EIR; Exhibits F1-3, G1-11, L1-6, M1-6, N1-4, and O1-4; and FDA 483 #2.

21 CFR 820.160

Failure to check and, where necessary, test for conformance with device specifications each production run, lot, or batch prior to release for distribution, as required by 21 CFR 820.160. For example, Transvene Leads have not been tested under simulated use conditions.

This charge is supported by the discussion on pages 7 and 8, of the EIR and FDA 483 #6.

21 CFR 820.162

Failure to investigate any failure of a device to meet performance specifications after it has been released for distribution, as required by 21 CFR 820.162. For example, Transvene Lead Model 6884 (b)(4) (b)(4) was returned and found to have cosmetic MIO on both the inner and middle coil insulation. The coils were not analyzed/examined to verify that the platinum sputtering process was done to specification.

This charge is supported by the discussion on page 8 of the EIR; exhibits S1-26, Q1-9, T1-4, and U1-3; and FDA 483 #7.

UNSUPPORTABLE FDA 483 OBSERVATIONS

FDA 483 #3 - There is no GMP requirement for design issues.

Kent A. Berthold

MEMORANDUM

From: Doris Terry (HFZ-450)
To: File # P920015
Subject: Review - Transvene PMA
Date: July 9, 1993
Office: DCRND/ODE

Description of the System

The PCD Transvene System consists of the Model 7217B PCD pulse generator, programmer, external accessories and leads (Model 6966 RV lead, Model 6966 CS/SVC lead and the Model 6999 patch lead, see description of leads and summary of testing in attached memo and in Volume 3, Section A, Bench Testing). The leads may be implanted in 3 configurations: RV/CS/SQ, RV/SVC/SQ and RV/CS/SVC via a single, simultaneous or sequential pathway.

Study Design and Objectives

(b)(4)

(b)(4)

Patient Population

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Clinical Experience

As of February 1, 1993 (the data cutoff), the clinical experience includes data from 762 implants in 757 patients. The data (stratified as described above) were provided in support of the Transvene Lead System. The data included the following: (1) the results of testing at implant and the follow-up intervals; (2) the efficacy of the treatment of VT and VF (spontaneous and induced episodes); (3) complications and observations; (4) patient deaths; and (5) survival. A comparison of the data obtained from the patient population and the different subgroups is also included.

Defibrillation Threshold (DFT) Testing

Three hundred and sixteen patients had DFT testing at implant. The mean DFT was 14.8 Joules (J). The remaining patients had testing which involved the lowest energy to

defibrillate (LED) and/or DFT testing. The mean LED was (b)(4) (b)(4).

Twenty patients were implanted with the Transvene System without a 10 J safety margin (see Volume 2, page 42).

Spontaneous and Induced Episode Experience and Treatment Efficacy of VT and VF - Total Patient Population

- 597 (78.9 percent) patients had a spontaneous VT or VF episode or had VT or VF induced post implant.
- 458 (60.5 percent) patients had a spontaneous episode of either VT and/or VF treated by the PCD Transvene System.
- 141 (60.5 percent) patients had VT only.
- 142 (18.8 percent) patients had VF only.
- 175 patients (23.1 percent) had an episode of VT and VF.
- 90.7 percent of VT episodes were successfully treated with VT therapy # 1.
- 89.1 percent of the VF episodes were successfully treated with VF therapy # 1.
- 60 patients experienced 163 (1.6 percent) spontaneous VT episodes which the PCD Transvene System was ineffective in terminating the arrhythmia (see Volume 2, page 19).
- 16 patients experienced 31 (1.3 percent) spontaneous VF episodes which the PCD Transvene System was ineffective in terminating the arrhythmia (see Volume 2, pages 20 - 21).
- 450 (59.5 percent) patients had induced or spontaneous episodes by the 3 month follow-up.
- 532 (70.3 percent) patients had either a spontaneous or induced episode by the 6 month follow-up.
- 597 (78.9 percent) patients had a spontaneous or induced episode by the 12 month follow-up.

Device Experience - Patients Followed for 6 months or More

- Of 657 patients followed for 6 months or more, 544 (82.8 percent) patients had an induced or spontaneous episode at predischarge or later.

- 113 patients did not have a chronic episode, however pace/sense parameters were measured at the chronic follow-up intervals on all patients except one (see Appendix I).

Summary of Complications and Observations

- 176 complications (required invasive intervention) occurred in 147 patients, included pocket infection (24), lead fracture (9), patch crinkling (7), explants (4) and total lead dislodgement (91). (The 91 cases of lead dislodgement occurred in 86 patients, see Appendix I).

- 212 observations (corrected by reprogramming or antiarrhythmic drug therapy) in 178 patients included inappropriate VT delivery (57), oversensing (52), seroma (17), hematoma (17), patch crinkling (5) and total lead dislodgement (12).

The manufacturer provided tables which report the complications and observations over time (see Table IB3-2 and Table IB3-3, Volume 2, pages 24-25).

The manufacturer stratified the complications and observations by U.S. and foreign patients (see Table IB3-6 Vol. 2, page 28). The complication and observation rates were comparable for the two patient groups. However, more total lead dislodgements (complications) were reported for the U.S. patients and more cases (observations) of inappropriate delivery of VT therapy occurred in the foreign population. There was also a higher incidence of oversensing (observations) in the U.S. population. It should be noted that there should be 7 observations related to loss of capture for the foreign patients instead of 9 (Volume 2, Table IB3-6, page 28).

Because of our concerns about the complications involving lead dislodgement and infection the manufacturer responded as follows: In resolving the concern regarding lead dislodgement, the manufacturer received IDE approval (September 1992) to use dual anchoring sleeves on the Models 6963 and 6966 leads. However, it is unclear if all patients, after IDE approval, are implanted with dual sleeves. The manufacturer confirmed that all patients are receiving dual sleeves. In support of the dual anchoring

sleeves in reducing the rate of lead dislodgement, a report of the clinical experience of additional patients was provided. Data from 439 patients (not a part of the PMA cohort) implanted with dual anchoring sleeves were submitted. Of the 439 patients, 292 were followed for 1 month, 195 were followed for 3 months and 17 were followed for 6 months. Thirteen dislodgements in 10 patients were reported (incidence of dislodgement of 2.3 percent (10/439). Regarding the cases of infection, the manufacturer stated that the incidence of infection in the Transvene study is not significantly different from that reported for the Ventak P Epi study. Therefore, the applicant feels that there is no substantial increase, and that labeling to address this concern is not warranted.

Patient Deaths

There have been 51 deaths (sudden cardiac (5), nonsudden cardiac (31), noncardiac (15). Five perioperative deaths (sudden cardiac (2), nonsudden (2) and noncardiac (1)) are counted within the 51 deaths. None of the deaths were attributed to the PCD Transvene System.

Explants

Sixty-three PCD Transvene Systems were explanted (N=762), patient death (22), infection (22), heart transplant (9), low battery voltage (1), PCD performance issues (4), integrated circuit problem (1) and lead problems (4). The results of analyses on 42 units returned indicated that the devices were performing within specifications.

Of the 42 PCD Transvene Systems returned, 23 lead systems or portions of systems were returned and analyzed. Of these the helix of one Model 6966 lead was damaged. The remaining leads were found to be within specification. The analyses on 19 lead systems are still outstanding. (It should be noted that one of the Model 6884 leads (implanted for 27 months) which was explanted due to heart transplant, exhibited metal ion oxidation (MIO) upon analysis. Metal ion oxidation can cause the polyurethane of the leads to degrade (see Volume 2, Section on Explants, page 296 or Appendix I).

Survival Analysis

The survival analyses encompassed all patients (screened and implanted). The projected one year actuarial survival rates for the PMA cohort (N=757) are as follows: sudden cardiac death (99.5 percent); nonsudden cardiac (96.2 percent); all cardiac (95.8 percent); noncardiac (98.1 percent); and overall (93.3 percent). The perioperative mortality is 0.7 percent.

The survival rates for 854 patients are included in Volume 2, Table IB4-2, page 31. The survival data were updated to include the 897 patients screened for the Transvene System. The one year actuarial survival rates for these patients are as follows: sudden cardiac death (99.5 percent); nonsudden cardiac (96.6 percent); all cardiac (96.1 percent); noncardiac (98.4 percent); and overall (92.9 percent). The perioperative mortality rate is 1.6 percent (see Appendix I).

Comparison Between the Patients Who Met the Implant Criteria and Patients Who Did Not Meet the Implant Criteria

A comparison of the clinical outcome between the patients who met the implant criteria and those patients who did not meet the implant criteria was included. The comparison was made to determine if there was a greater risk of morbidity and mortality among the patients who did not meet the implant criteria and received the Transvene System. The data showed the following: The efficacy of the patient groups in the treatment of spontaneous episodes of VT and VF was similar. There was no significant difference in the one year sudden cardiac death survival and the overall survival reported for the two groups. Ninety-one per cent of the patients who did not met the implant criteria had at least one successful termination of an induced ventricular comparison at 24 joules or less. In addition, there were 170 patients who had successful defibrillation of VF at less than or equal to 24 Joules. As a result the manufacturer requested and received IDE approval for a change in the implant criteria. Instead of 3 of 4 successes at 18 Joules or less, the manufacturer can implant with successful defibrillation at 24 Joules (referenced in Volume 2, page 53).

Labeling

The manufacturer has included information about the Transvene leads in the PCD Manual as well as in the technical manual for each Transvene lead model.

The technical manuals of the Transvene Models 6966, 6963 and 6999 leads should be modified to included additional information. The following modifications are included for the Panel's consideration:

- The indications and contraindications for use of the Transvene lead system should be identical to those of the PCD (with certain modifications).

- The technical manuals for the Models 6966, 6963 and 6999 leads should state that the leads are intended for use together as a system. The labeling (where appropriate) should be consistent throughout the manuals. The

information in the PCD Manual regarding the Transvene leads should also be included in the technical manuals for the leads.

- There should be more explicit diagrams in the technical manuals which show the proper insertion of the endocardial leads and the various positions for placement of the patch lead.

- Efficacy data of the different lead configurations via the different pathways should be included.

- The labeling should recommend and/or provide some direction about implanting the leads and testing the different configurations. For example, when to use a two lead versus a three lead configuration and when to implant in the SVC versus the coronary sinus.

- Information or recommendations regarding implanting in patients who do not have the 10 J safety margin should be addressed.

- There should be stronger language regarding the use of 2 anchoring sleeves.

- The labeling should address how the incidence of infection can be reduced.

Questions

1. One hundred and thirteen patients within the PMA population did not have a spontaneous or induced episode of VT or VF after predischarge. Therefore, the performance of the system in the treatment of VT and VF was not assessed. However, the pace/sense parameters of these patients were measured at the different follow-up intervals. Are these measurements sufficient in assessing the chronic performance and integrity of the lead system in these patients?

2. In light of the differences between the U.S. and foreign patients within the PMA population, are there any concerns about the poolability of the data?

3. A statistically significant decrease in the perioperative mortality was demonstrated for the PCD Transvene System versus the PCD Epicardial System. However, there was a statistically insignificant decrease in perioperative mortality for the PCD Transvene Lead System (when calculated from the intention to treat) as compared to the historical control. Are there specific concerns regarding the perioperative mortality rates reported for the PCD Transvene System versus the historical control?

4. Are there concerns regarding the potential risks of dislodgement of the leads, and the reported incidence of infection?

5. The results of analyses of an explant of the Transvene lead Model 6884 (earlier version of the Model 6966) have raised questions about the lead's chronic structural integrity. Are there significant concerns which could question the reliability of the lead? Do the benefits of the Transvene Lead Model 6966 outweigh the risks which might be associated with its potential for MIO?

In addition, the labeling modifications as referenced on pages 6 and 7 should be considered.

MEMO

To: Doris Terry
From: Quynh Hoang
Date: 7/9/93

Regarding: Descriptions of the Transvene leads from Medtronic - P920015

Parameter	Model 6963	Model 6966	Model 6999
(b)(4)			

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Electrical testing

(b)(4)

(b)(4)

Environmental testing

(b)(4)

(b)(4)

Mechanical testing

flexing

(b)(4)

(b)(4)

	(b)(4) (b)(4)
composite pull test	(b)(4) (b)(4)
crimp/weld pull test	(b)(4) (b)(4)
anchoring sleeve test (Models 6963 and 6966)	(b)(4) (b)(4)
leak test (applicable to only Model 6966 lead)	(b)(4) (b)(4)

	(b)(4) (b)(4)
lead tip stiffness (Models 6963 and 6966)	(b)(4) (b)(4)
anchoring sleeve sliding force	(b)(4) (b)(4)
connector test	(b)(4) (b)(4)
Biocompatibility testing	(b)(4) (b)(4)
Biostability testing	
Models 6963 and 6999	(b)(4) (b)(4)

(b)(4)

(b)(4)

Model 6966
MIO testing

(b)(4)

(b)(4)

ESC testing

(b)(4)

(b)(4)

Life testing

	(b)(4) (b)(4)
Crush testing (Models 6963 and 6966)	(b)(4) (b)(4)
Animal Studies	(b)(4) (b)(4)

MEMORANDUM

From: Doris Terry (HFZ-450)
To: File # P920015
Subject: Panel Presentation - Transvene Lead System
Date: July 8, 1993
Office: DCRND/ODE

The manufacturer, Medtronic, Inc. is seeking approval of the PCD Transvene Lead System.

STUDY DESIGN

The primary objectives of the PCD Transvene Lead System study include the following: (1) evaluating and monitoring the system in the detection and treatment of VT and VF; and (2) estimating the survival from sudden cardiac death and the overall survival. These data lend support to the endpoints of the study, conversion efficacy and survival from sudden cardiac death and total death.

The PMA population consists of 757 patients implanted with the Transvene Lead System and either of 2 PCD Models, the 7217B or the 7216A. The performance of the PMA population was compared to the historical control, Ventak P AICD population and a concurrent control, the PCD Epicardial System.

CLINICAL EXPERIENCE

As of February 1, 1993, the clinical experience includes data from 762 implants (447 U.S. and 315 foreign) in 757 patients. Data from the PMA population (stratified according to different subgroups) included the following: (1) results of testing at implant, predischarge and the follow-up intervals; (2) efficacy of the treatment of induced and spontaneous episodes of VT and VF; (3) complications and observations; (4) patient deaths; and (5) survival.

Defibrillation Threshold (DFT) Testing

300 patients had DFT testing at implant. The mean DFT was 14.8 Joules (J).

702 patients had lowest energy to defibrillate (LED) testing at implant. The mean LED was 16 J.

Spontaneous and Induced Treatment Efficacy

- 597 (78.9 percent) patients had a spontaneous VT or VF episode or had VT or VF induced post implant.
- 458 (60.5 percent) patients had a spontaneous episode

of either VT and/or VF.

- 90.7 percent of the VT episodes were successfully treated with VT therapy # 1.

- 89.1 percent of the VF episodes were successfully treated with VF therapy # 1.

- 60 patients experienced 163 (1.6 percent) spontaneous VT episodes which the PCD Transvene System was ineffective in terminating the arrhythmia.

- 16 patients experienced 31 (1.3 percent) spontaneous VF episodes which the PCD Transvene System was ineffective in terminating the arrhythmia.

- Of the 657 patients followed for 6 months or more, 544 (82.8 percent) patients had an induced or spontaneous episode at predischarge or later.

- 113 patients did not have a chronic episode however, pace/sense parameters were measured at the different follow-up intervals.

Complications and Observations

- 176 complications occurred in 147 patients. The complications included pocket infection (24), lead fracture (9), patch crinkling (7), explants (4) and total lead dislodgement (91).

- 212 observations occurred in 178 patients. The observations included inappropriate VT delivery (57), oversensing (52), patch crinkling (5) and total lead dislodgement (12).

Explants

Sixty-three PCD Transvene Systems were explanted: patient death (22), infection (22), heart transplant (9), low battery voltage (1), PCD performance issues (4), integrated circuit problem (1) and lead problems (4). The results of analyses on 42 PCDs returned indicated that the devices were performing within specifications.

Of the 42 PCD Transvene Systems returned, 23 lead systems or portions of lead systems were returned and analyzed. Of these the helix of one Model 6966 lead was damaged. The remaining leads were found to be within specifications. The results of analyses of 19 lead systems are outstanding. It should be noted that one Model 6884 (an earlier version of the Model 6966 lead) implanted for 27 months, which was explanted due to heart transplant, exhibited metal ion oxidation (MIO) upon analysis.

SURVIVAL ANALYSIS

There have been 51 deaths (sudden cardiac (5), nonsudden cardiac (31), noncardiac (15). Five perioperative deaths (sudden cardiac (2), nonsudden (2) and noncardiac (1) are counted within the 51 deaths.

The survival rates for the patients who were implanted with the Transvene leads are as follows: sudden cardiac death (99.5 percent); nonsudden cardiac (96.2 percent); all cardiac (95.8 percent); noncardiac (98.1 percent); and overall (93.3 percent). The perioperative mortality rate is 0.7 percent.

QUESTIONS

1. One hundred and thirteen patients did not have a spontaneous or induced episode of VT or VF after predischarge testing. Therefore, the performance of the system in the treatment of VT and VF was not assessed. However, the pace/sense parameters of these patients were measured at the different follow-up intervals. Are these measurements sufficient in assessing the chronic performance and integrity of the lead system in these patients?

2. In light of the differences between the U.S. and foreign patients within the PMA population, are there any concerns about the poolability of the data?

3. A statistically significant decrease in the perioperative mortality was demonstrated for the PCD Transvene System versus the PCD Epicardial System. However, there was a statistically insignificant decrease in the perioperative mortality for the PCD Transvene System (when calculated from the intention to treat) as compared to the historical control. Are there specific concerns regarding the perioperative mortality rates reported for the PCD Transvene System versus the historical control?

4. Are there concerns regarding the potential risks of dislodgement of the leads and the reported incidence of infection? What are considered as acceptable rates of lead dislodgement and infection as they relate to complications and observations?

5. The results of analyses of an explant of the Transvene lead Model 6884 (an earlier version of the Model 6966) have raised questions about the lead's chronic structural integrity. Are there significant concerns which would question the reliability of the lead? Do the benefits of the Transvene lead Model 6966 outweigh the risks which might be associated with its potential for MIO?

In addition, the labeling modifications as referenced in my review memo should be considered. The modifications include the following: (1) diagrams which show proper insertion of the endocardial leads and the various positions for placing the patch lead; (2) efficacy data of the lead configuration via the different pathways; (3) stronger language regarding the use of dual anchoring sleeves; (4) information about how the incidence of infection might be reduced; and (5) recommendations regarding the use of the different lead configurations.

MEMORANDUM

From: Doris Terry (HFZ-450)
To: File # P920015
To: Dr. Subramanian
Subject: Transvene Lead System - Consulting Review
Date: July 6, 1993
Office: DCRND/ODE

Please review the death summaries included in the referenced file (Volume 2, Section III, Death Summaries). The review should evaluate the accuracy in classifying the deaths. In addition, please look at the causes of death to determine if any of the deaths could be possibly linked to device performance.

Please note the following: A definition of the different death classifications can be found in Volume 2, page 293. Medtronic, Inc. has reported 51 deaths (sudden cardiac (5), nonsudden cardiac (31), noncardiac (15) in the PCD Transvene population (N=757). The perioperative deaths (5) are counted within the following classifications: sudden cardiac (2) nonsudden (2) and noncardiac (1).

Please let me know if you can review the data. If so, when do you think you will be done? Hopefully, by the first of next week? Your assistance is greatly appreciated.

MEMORANDUM

From: Doris Terry (HFZ-450)
To: File # P920015/Amendment
Subject: Transvene Lead System
Date: June 3, 1993
Office: DCRND/ODE

The manufacturer submitted the referenced amendment to inform us of a case of "cosmetic" metal ion oxidation (MIO). The MIO was found on the Model 6884 (comparable to Model 6966) Transvene RV lead explanted from a patient who underwent a heart transplant.

According to the manufacturer, the presence of MIO on the middle insulation is not entirely unexpected. It was stated that if the middle insulation completely degrades (shorting the sensing ring), then an integrated bipolar sensing system would result (sensing would occur between the unipolar pacing tip and the common defibrillation electrode instead of true bipolar (sensing between the pace/sense tip and the ring electrodes). However, if the innermost insulation degrades and the pacing tip electrode is shorted, intermittent sensing could result. This type of behavior such as intermittent sensing, oversensing, undersensing, etc. could be detected at the follow-up intervals.

Consultation and the review of the issue in the referenced amendment, as well as previous IDE supplements, have taken place with (b)(6) Due to the failure of the Medtronic, Inc. brady leads which employ the platinum sputtering process as the Model 6966 and 6884 leads, she is very concerned. In past reviews, we have requested that the manufacturer institute long term testing to asses the MIO problem.

The monthly report of all observations and complications, as referenced in our letter regarding the IDE expansion, was requested. In addition, the following concerns were conveyed to the manufacturer:

1. The differences between the Model 6884 and the Model 6966 Transvene leads. (The Model 6884 (3.2 connector size and the Model 6966 - 6.5 connector size). The number of leads explanted to date and the MIO and environmental stress cracking (ESC) noted. (As of 150 explants, there was no evidence of MIO).

2. To date, how many patients have received the Transvene lead System? How many patients have been implanted for 2 years and greater? (at least 50) What is the compliance to follow-up of these patients. (Compliance to follow-up 98 to 99 percent). Update on clinical experience: lead related complications, first shock VT/VF efficacy, survival rates,

etc. Are there patients with a dilated RV counted in the group followed for 2 years or more? At what intervals were the complications noted?

3. A description of the expected failure mechanism of the leads. In the referenced case, evidence of MIO was noted at 2 years (MIO visible on the innermost insulation and the middle insulation). What is considered the life expectancy of the leads void of signs of MIO? What is the projected rate of progression. Are their studies to confirm these speculations?

4. Based upon the review of the requested data, the protocol and testing at follow-up might need to be modified to include the following: x-rays or fluoroscopy when there are recurring and/or suspect lead complications or observations and periodically at preset intervals.

5. Regarding the patient whose lead was explanted:

   a. When were the 6 spontaneous VT/VF shocks delivered? Was the system interrogated after explant? [This was the implant history].

   b. Was there more damage noted on the innermost or middle insulation?

   c. What were the lead impedance and threshold measurements?

   d. Explain how the patient's dilated RV contributed to the MIO noted.

The occurrence of MIO noted upon explant of the Model 6966 leads and its significance will be brought to the attention of the Panel.

The manufacturer agreed to provide answers to the above questions and additional supporting data in the Panel volumes.

DOCU#: P920015/A **DATE:** 6/93
TO: Record, PEDB
FROM: Albert E. Moyal, PEDB **COMP:** Medtronic, Inc.
DEVICE: Transvene NTL System
SUBJECT: Phone MEMO, re: Questions on Amendment

I phoned and spoke with Ms. Jennifer Marrone, Regulatory Affairs Manager, regarding several questions that I had concerning the file P920015/A.

The first question concerned the use of a two-lead Transvene system. The amendment stated the use of an RV/SQ or RV/SVC configurations. Ms. Marrone stated that there were several of these configurations present within the group of patients implanted in the non-standard configuration. A total of 37 patients were implanted in this group. Most of the implant population, about 80-90% were implanted with a three-lead configuration.

I asked if these configurations would be included in the final labeling. Ms. Marrone responded by stating that they would be included in the final labeling under "Alternate Configurations". Data on those implanted with a two-lead configuration will be needed before the final review is completed on this device.

Regarding question 1b, the disparity was explained as being 24 couldn't be induced into VF/VFlutter and those patients who couldn't get an LED were also excluded.

Regarding question two, the peri-operative deaths are not included in the overall death calculations. They are stated to be reflected in the duration.

Concerning question number three, the entry sites for the SQ patch are between the first and fifth intercostal muscles.

DOCU#: P920015 DATE: 5/17/93

TO: Record, PEDB

FROM: Biomedical Engineer, PEDB
Albert E. Moyal

COMP: Medtronic, Inc.

DEVICE: Transvene NTL System

SUBJECT: Review of Amendment: Response to FDA Questions.

Medtronic has responded to the questions asked in the FDA Letter March 17, 1993. They have responded to the various concerns raised in the evaluation of the Transvene Non-Thoracotomy Lead System.

A total of 1330 patient have been implanted with the Transvene NTL System. The PMA total number of Transvene patients followed up until February 1993 is 757 patients. Out of this number, 657 have been followed for greater than six months, with 393 patients followed for greater than one year.

The one year survival rate for SCD is 99.3%. There were 458 spontaneous episodes of VT that occurred. Sixty (60) patients experienced 163 episodes that were ineffectively treated terminated. This represents a company claim of 1.6%, although 60 patients out of 757 represents 7.9% of the population.

Other information provided included patients meeting, and not meeting implant criteria, clinical experience, survival rates, clinical complications and observations, and comparisons between the PCD Transvene with the PCD Epicardial and AICD Ventak P historical data.

The concerns that I have with this amendment are as follows:

1. On page S12, the company describes the lead configurations that may be done with the leads making up the transvene system. In the first paragraph, they mentioned a three lead system that includes the RV/CS/SQ, RV/SVC/SQ, RV/SQ, and RV/SVC.

   Does Medtronic plan on including the use of a one lead/patch (RV/SQ) and/or a two lead (RV/SVC, RV/CS) system as a recommended implant technique? Have they tested this type of two lead system? Does the use of the RV/CS/SVC configuration in only 37 out of 702 lead system preclude the use of this configuration, in comparison the configurations using the SQ patch?

   It is stated on page S21, table IF-3, the breakdown of the of the lead systems used. The total is 702, yet, there are 757 patients implanted with the PCD Transvene system. Please explain the disparity, and describe what, if any, other implant configurations used with the Transvene Leads.

2. Table IK-5 on page S45 lists the Survival Analysis for patients not meeting the implant criteria for the PCD Transvene System and the patients not meeting the implant criteria for the PCD Epicardial System.

   Please explain the breakdown of survival rates for those patients not meeting the PCD Epicardial Implant Criteria when there is a total of 92 patients, of which there are 17 patient deaths (18.5%).

3. On page 105 of the amendment, the response to question 26, listed in tabular form is the breakdown of venous entry sites for the RV and CS/SVC leads. What about a breakdown of the entry sites for the SQ lead? Please provide.

These are initial concerns that I have with this amendment, that I am submitting to comply with the May 17,18 Panel decision date. I will submit further concerns if and when they arise.

SUMMARY: The company has provided the responses to the questions asked in the FDA letter sent to them regarding the review of this Non-Thoracotomy Lead System. The data provided appears to be satisfactory, although several concerns have arisen regarding the presentation of this data. The course of action to be taken is to explore any and all concerns questions that may arise from the review of the amendment prior to the panel taking place.

The recommendation for this application is to submit this to the panel at the earliest time possible.

Albert Moyal MD

Albert Moyal.

MEMORANDUM

From: Doris Terry (HFZ-450)
To: File # P920015
Subject: Transvene Lead System
Date: April 19, 1993
Office: DCRND/ODE

The manufacturer responded to the deficiencies listed in our letter of March 17, 1993. The data provided in the referenced amendment includes the experience of the PMA population (757 patients) as of a data cutoff of February 1, 1993. The letter contains deficiencies from a team of reviewers. The team consists of a medical officer, 3 scientific reviewers (including myself) and a statistician. The memos from the other reviewers will address specific requests.

Request # 1

We told the company to state the hypothesis and the objectives of the study. The hypothesis of the PCD Transvene clinical study is to demonstrate that the PCD Transvene System is safe and effective in treating VT and VF. We also asked the manufacturer to: (1) address the use of a control and the rationale for not using a concurrent control during the study; (2) randomization; (3) endpoints of the study; and (4) how the data will support the specified endpoints.

Objectives of the Study

The objectives are to determine the safety and effectiveness of the Transvene Lead System by:

- evaluating the sensitivity and specificity of the PCD with the Transvene lead system in detecting episodes of VT and VF. To evaluate the ability of the system to appropriately discriminate between VT and VF and other potentially nonmalignant rhythms;
- monitoring the efficacy of the PCD with the Transvene leads in treating VT and VF episodes;
- evaluating the performance of the Transvene leads;
- estimating one year sudden cardiac death survival and overall survival; and
- evaluating the safety and performance of the Model 9710 Programmer and the Model 9788 (b)(4) software cartridge in terms of effective programming.

Use of a Control

In addressing the use of a control, the PCD Epicardial (Epi)

system which is used as a control is similar to the PCD Transvene system with the exception of the lead system used. The manufacturer considers the PCD Epi group as the most closely matched population to the PCD Transvene population. This is because there is concurrent enrollment of the patients in the studies. In addition, the primary indications, implant criteria and clinical data requirements are identical for the two groups. A comparison between the PCD Transvene and Ventak P Epicardial lead system was also made. This was done essentially for comparison of the desired endpoints (overall survival and sudden cardiac death survival).

Randomization

In addressing the issue of randomization, the manufacturer identified patients who may not be able to withstand a thoracotomy. Therefore, randomization would not be feasible or clinically appropriate for these patients. These patients include: (1) those where there is no indication for concomitant surgery at the time of ICD implant; (2) those with pulmonary disease; (3) those with severe congestive heart failure; and (4) those who may require open chest procedures for treatment of their CAD or cardiac transplant. In these cases, the non-thoracotomy lead system is considered as the only therapy available for the ICD candidates.

Randomization was not employed, nor considered during the design of this study. This was due to: the investigators' preference; the known risks to the patient which are associated with a thoracotomy; and the urgency regarding the public health need for the product. A study such as the PCD Transvene will aid in determining, and/or making a case for or against a randomized trial involving nonthoracotomy and thoracotomy leads. The study could generate certain questions or concerns which could be answered through a randomized trial.

Endpoints of the Study

- freedom from sudden cardiac death and all causes of mortality shown through the 1 year survival; and

- treatment efficacy of spontaneous episodes of VT and VF episodes.

The data which will be used in the support of the endpoints will include data from the following: (1) patient deaths (sudden cardiac death survival and overall survival at 1 year); (2) complications and observations; (3) patient indications; (4) VT and VF detection and therapy performance; and (4) PCD Transvene System performance.

Request # 2

We asked that the manufacturer provide a side-by-side comparison between the PCD Transvene and the PCD Epi populations, and the PCD Transvene and the Ventak P AICD populations. The comparison between the named groups included: patient demographics; implant data (DFTs); programmed parameters; spontaneous VT and VF efficacy; complications an observations; and 1 year actuarial survival.

Comparison - PCD Transvene and Ventak P Epi

There were more patients with the indication of sudden cardiac death in the PCD Transvene group than in the Ventak P Epi group. The results of the Cox regression analysis showed that primary indication had no influence on the probability of survival. Therefore, it was considered that the two groups could be compared. Basically, the two groups were found to be comparable. The sudden cardiac death survival rates for the two patient groups were also comparable (99.7 percent for the PCD Transvene and 98.6% for the Ventak P Epi.

Comparison - PCD Transvene and PCD Epi

It was noted that there are more patients with the primary indication of sudden cardiac death in the PCD Transvene than in the PCD Epi population. As with the Ventak P analysis, the results showed that primary indication did not have an impact on patient outcome. The spontaneous VT episode efficacy for the PCD Transvene System was 98.4% which is comparable to that of the PCD Epi System of 98.3 percent. The spontaneous VF episode efficacy for the PCD Transvene System was 98.4 percent which is comparable to 98.7 percent reported for the PCD Epi System. The incidence of lead related complications is somewhat higher in the PCD Transvene population versus the PCD Epi population (15.1 percent versus 2.8 percent). The incidence of observations was statistically lower in the PCD Transvene group. The sudden cardiac death survival rate for the PCD Transvene was 99.5 percent and 98.9% for the PCD Epi group. The overall one year actuarial survival (including death from all causes for patients receiving the PCD Transvene System was 93.3 percent. A marked improvement of the overall one year survival for the PCD Epi of 88.6 percent. It is believed that the improvement is primarily due to the improvement in perioperative mortality of the PCD Transvene System (0.7 percent for the Transvene and 5.3 percent for the PCD Epi).

The implant pace/sense parameters (pacing threshold, R wave amplitude, slew rate and resistance) were found to be statistically significant. The mean implant DFT for the PCD Transvene System and PCD Epi System was 14.8 Joules (J) and 9.8 J respectively.

The majority (574 (75.3 percent)) of the patients in the PCD Transvene study had defibrillation programmed in the sequential pathway. Two hundred and fifty-one (33 percent) patients in the PCD Epi study were programmed in the sequential pathway. Four hundred and ninety-six (65.2 percent of the PCD Epi population were programmed with single defibrillation with only 10 (1.3 percent) patients in the PCD Transvene group with single.

Overall, the two groups were considered as closely matched as possible. The inherent difference being the design of the lead system.

Request # 3

The manufacturer provided an update of the PMA population (757 patients with a mean implant duration of 11.7 months) as of February 1, 1993.

Experience of Patients with the Dual Anchoring Sleeves

Two hundred and thirty-four patients (not included in the PMA population of 757 patients) were implanted with two anchoring sleeves. These patients received an additional sleeve due to the reported cases of lead dislodgement. This group of patients was similar to the PMA population with a slightly higher percentage of VT patients. Of the 234 patients, 186 have been followed for one month and 49 patients have been followed for 3 months. Only one lead dislodgement was reported in these patients.

Clinical Experience - Patients Followed for One Year or Greater

- 393 patients followed for one year or greater
- mean follow-up time 16.3 months
- primary indication: SCD - 150 (38.2 percent), VT - 191 (48.6 percent) and SCD/VT (52 (13.2 percent)
- defibrillation pathway: sequential - 296 (74.9 percent), simultaneous - 93 (23.6 percent) and single - 6 (1.5 percent)
- mean LED - 15.6 J (N= 365), mean DFT - 14.3 J (N=184)
- spontaneous VT success (99.0 percent)
- spontaneous VF success (98.6 percent)
- patient deaths - 7 (0 sudden cardiac, 4 nonsudden cardiac and 3 (noncardiac)

- complications - 89 in 76 patients (19.3 percent)

- observations - 122 in 99 patients (25.2 percent), forty of the observations involved inappropriate VT therapy delivery and 29 observations associated with oversensing

- none of the complications and observations resulted in patient death

Lead Dislodgements

Twenty-nine lead dislodgements occurred at greater than 30 days. None of these dislodgements resulted in ineffective therapy for the treatment of spontaneous episodes of VT or VF or patient death. The dislodgements were found during fluoroscopy at EP evaluation, chest x-ray or during pacing/sensing threshold evaluation during follow-up testing. In 29 cases, reoperation was necessary to reposition the lead.

Request # 4

A discussion of the implant criteria and how the implant testing attempted to satisfy the protocol requirements was provided.

The manufacturer described the patients who did not meet the implant criteria. These patients are among those patients referenced above who are at risk with a thoracotomy procedure. In these cases the investigators felt that if the patients had a lowest energy to defibrillate (LED) of 24 J, then they could be implanted with a 10 J safety margin (34 J max output of the device).

Request # 5

We requested that an update of the clinical experience of the patients who did not meet the implant criteria be provided. Also, a discussion regarding how the proposed labeling will address the deviation was requested.

One hundred and seventy patients did not meet the implant criteria, but had successful defibrillation at 24 J, were implanted with the PCD Transvene System. In determining if the patient's not meeting the implant criteria had a higher risk for morbidity and mortality, a comparison of their survival was made. There were no statistically or clinically significant differences in outcome between the patients who met the implant criteria and those who did not (one year survival - overall 93.8 percent for the patients not meeting the implant criteria and 93.2 percent for the patients who met the criteria).

Of the 170 patients, 41 complications were reported in 33 (19.4 percent) patients and 34 observations were reported in 31 (18.2 percent) patients. None of the complications and observations resulted in patient death.

Lead Dislodgements - Patients who did not Meet the Implant Criteria

There have been 14 lead dislodgements which occurred at greater than 30 days. The dislodgements were discovered and documented as described in the PMA application. In all 14 cases reoperation was required to reposition the lead.

There were no clinically significant differences in the characteristics and patient outcome of the patients who did not meet the implant criteria versus those who did. Based on these data, the manufacturer plans to recommend revising the defibrillation efficacy requirements to include the following: (1) two consecutive successful defibrillations with the final lead configuration with a stored output energy of 24 J or less; or (2) three successful defibrillations in four attempts with the final configuration at a stored output energy of 24 J or less.

Request # 6

Twenty patients who did not meet the implant criteria were implanted without the 10 J safety margin. We asked that an update of the clinical experience of these patients be provided. The mean ejection fraction of these patients was 26.9 percent. It is believed that the patient's condition was responsible for the termination of the implant procedure which resulted in the patients not meeting the implant criteria. Of these 20 patients, VT was induced at chronic follow-up in 16 patients and in all cases successful treatment was documented. The overall spontaneous VT episode efficacy was 98.9 percent. The spontaneous VF efficacy was 96 percent. There have been 2 deaths, both classified as nonsudden cardiac secondary to end stage heart failure. The one year sudden cardiac death survival in this population is 100 percent. The overall one year survival was 85.5 percent.

Request # 7

The manufacturer provided a table with percentages and the numerical support where appropriate.

Request # 8

An update of the patients who were implanted with the Transvene Lead system and were not counted in the PMA population was provided. The data covers a total of 1335 implants in 1330 patients with the PCD Transvene Lead System (757 patients in the PMA population and 573 additional patients). Of the 1330

patients, the primary indication was VT in 725 (54.5 percent). The spontaneous efficacy for VT and VF was 98.1 percent and 98.1 percent respectively. The overall survival was reported as 93 percent.

As of February 1, 1993, there have been 225 complications reported in 195 patients and 275 observations reported in 228 patients implanted with the PCD Transvene Lead System. How many of the complications and observations were from the additional 573 patients? According to the manufacturer, the percentage of patients with a complication or observation has decreased compared to the original PMA population of 757. Also, according to the applicant, the percentage of patients with lead dislodgements was reported to have also decreased from 12 percent of the population with a complication to 8.8 percent, and from 1.60 percent of the population with an observation to 0.9 percent.

Of the 1330 patients, there have been 30 (2.3 percent) complications involving pocket infection, and a total of 117 (8.8 percent) lead dislodgements. Included in the lead dislodgements, there were 36 cases which involved the SVC lead. (The manufacturer should discuss this information to clarify that every attempt has been made to address the complications. There should be evidence that the frequency of the complications has decreased.) There have been a total of 68 deaths (10 sudden cardiac, 37 nonsudden cardiac and 21 noncardiac) of the population of 1330 patients. The patients in whom the PCD was programmed OFF were included in the survival analysis. The perioperative death rate was 0.8% (10/1330). The one year actuarial survival rates were reported as follows: sudden cardiac death - 99.3 percent; nonsudden cardiac - 96.3 percent; all cardiac - 95.6 percent; noncardiac - 98.1 percent; perioperative - 0.8%; and overall - 93 percent.

Request # 9

We asked that the manufacturer differentiate between DFT testing and lowest energy to defibrillate (LED) testing. Also, we asked that samples of patient report forms which show the scheme of testing which was used in determining DFT and LED be provided. DFT testing was described as 3 out of 4 successes at 18 Joules. The protocol which included step down testing was included. The investigators were allowed to waive the step down testing if the patients could not tolerate the additional VF inductions. In these cases, the LED which is the lowest energy that successfully defibrillated the heart was programmed.

Request # 10

There was a statistically significant difference between the mean DFT obtained with the RV-CS-SQ lead configuration and other configurations. We asked the manufacturer to discuss the difference and the intended ramifications. The manufacturer

stated that the tests demonstrated that the RV-CS-SQ configuration had a lower DFT than the other configurations. This was simply due to the energy being better distributed throughout the myocardium with this configuration. It was pointed out that the intent of the study was not to show that lower DFTs result in better patient outcome. The primary emphasis was to demonstrate that the patient could be reliably defibrillated over time, and that there is a high probability of survival from sudden cardiac death regardless of the lead configuration or pathway chosen.

In terms of comparison of the PCD Transvene and PCD Epi groups, it was stated that the defibrillation efficacy protocol was identical for both groups.

Request # 11

The manufacturer provided a discussion of the DFTs or energy requirements obtained with the use of the single versus the sequential and simultaneous pathways. Essentially, even though the majority of the patients in both PCD populations were programmed with different defibrillation pathways, the DFTs were comparable (single - mean DFT 10.5 J and for sequential/simultaneous - mean DFT 8.8 J). It was reported that there was no difference in outcome for the patients with either of the systems.

Request # 12

According to the manufacturer, the time between detection and delivery of therapy of the PCD Transvene System is dependent upon the programmable VT and VF detection parameters. (The manufacturer should respond to the effect that an increase in lead impedance could have on the time from detection to delivery of therapy). In both of the PCD populations (Transvene and Epi), the majority (90 percent) of the spontaneous episodes of VT and VF were converted with the first shock. The most frequently programmed VT detection and therapy parameters were: VT number of intervals to detect (NID) (b)(4) VT tachycardia detection interval (TDI) (b)(4) VT therapy # 1 type - (b)(4) VT therapy # 1 parameters (b)(4) percent rate adaption, (b)(4) (b)(4) sequences, (b)(4) ms decrements; VT therapy # 2 type - cardioversion; and VT therapy # 2 parameters (b)(4) The most frequently programmed parameters for VF detection and therapy included: VF number of intervals to detect (NID) (b)(4) VF tachycardia detection interval (TDI) (b)(4) VF therapy #1 type/parameter - defibrillation/(b)(4) J; charge time for VF therapy # 1 -(b)(4) seconds; VF therapy # 2 type/parameter - defibrillation/(b)(4) and charge time for VF therapy # 2 -(b)(4) seconds.

Request # 13

In response to the deficiency regarding the 2:1 VF sensing margin, the manufacturer provided the following information. The

recommendations for programming include a programmed sensitivity value of 0.3 mV for the PCD. During defibrillation testing, the ETCD is programmed with a nominal sensitivity value of 1.2 mV which is four times the nominal sensitivity setting (0.3 mV) of the PCD. When the PCD is programmed at 0.3 mV, it provides a four step safety margin (because sensing was evaluated at a value four times less sensitive than the programmed value). When the device is programmed at 0.6 mV, there would be a 2:1 VF sensing margin. It was stated that all of the patients who received the PCD Transvene System had a 2:1 VF sensing margin. At the last known follow-up, the manufacturer mentioned that 76.6 percent of the patients were programmed to 0.3 mV and 22.3 percent were programmed to 0.6 mV. There have been no reports of undersensing during induced VF episodes and no deaths due to the nondetection of a spontaneous VF episode.

Request # 14

As of the June 24, 1992 data cutoff, 130 of the 329 patients followed for 6 months or greater had a spontaneous VT episode with a mean of 28.9 (3752/130) episodes per patient. One hundred and twenty patients had a spontaneous VF episode with a mean of 5.6 (667/120) episodes per patient. A total of 179 patients had either spontaneous VT or VF episodes with a mean of 24.7 (4419/179) episodes per patient.

Of the 115 patients followed for 12 months or greater, 60 patients had a spontaneous VT episode with a mean of 29.5 (1770/60) episodes per patient. Thirty-seven patients had a spontaneous VF episode with a mean of 6.7 (248/37) episodes per patient. A total of 67 patients had either spontaneous VT or VF episodes with a mean of 30.1 (2018/67) spontaneous episodes per patient (will be updated).

Request # 15

We asked that clarifications be provided regarding how the treated episodes, designated as success or failure, were categorized. The manufacturer reiterated that spontaneous episodes (VT and VF) are defined as those which satisfy the detection criteria for VT and VF. A table which included the spontaneous VT and VF experience was provided. The table clearly outlined the experience which included a breakdown of the number of episodes and patients and the ineffective episode experience.

It was noted that 60 patients had 163 VT episodes in which the PCD was ineffective in terminating the spontaneous episode of VT despite the delivery of all four therapies. No patient deaths occurred as a result of the ineffective VT therapy. Reprogramming and an adjustment of the patient's drug regimen resolved the problems. There are no concerns regarding the data as presented.

Sixteen patients experienced 31 episodes of VF in which the PCD

was ineffective in terminating the episodes despite the delivery of all four programmed VF therapies. Three of the patients experienced ineffective therapy of a spontaneous VF episode due to lead performance or "secondary to a terminal event." One patient had an episode of ineffective VF therapy due to lead dislodgement. A second patient had an episode of ineffective VF therapy due to lead fracture which generated "noise" which was detected as VF by the PCD. The third patient had two episodes of ineffective therapy at the time of his "monitored" death. Pharmacologic intervention and reprogramming was used in resolving the events associated with the majority of the 16 patients.

Request # 16

The Table IM-6 was modified to include the episodes which were unsuccessfully terminated due to atrial fibrillation or sinus tachycardia. The percent of unsuccessful termination (ineffective in terminating the arrhythmias despite the delivery of all four therapies) is also included for VT and VF. There was a higher incidence (0.9 - Epi and 0.4 Transvene) of unsuccessful termination of VT with the PCD Epi System versus the PCD Transvene System. The information in the Table is as of the June 24, 1992 cutoff date. It is unclear if the data on the proceeding pages are as of the updated cutoff (February 1, 1993). These data state that 30 patients out of 757 had 68 spontaneous VT episodes where the PCD was ineffective in terminating the episode despite delivery of all four therapies. Twenty-five of the patients experienced 45 (0.9%) episodes which were due to sinus tachycardia or atrial fibrillation/flutter with a rapid ventricular response which were detected as VT. Five patients in the Transvene population had 9 spontaneous VF episodes where the device was ineffective in terminating the episode despite the delivery of all four VF therapies. This was due to the detection of sinus tachycardia and atrial fibrillation with a rapid for The device responded appropriately as programmed. However, the rhythms were not VF as seen by the device. Reprogramming and pharmacologic intervention resolved these problems and those mentioned regarding the detection of the spontaneous episodes of VT.

Request # 17

We asked for a clarification regarding the category "Failure to Cardiovert/Defibrillate" and how an episode of an inappropriate therapy is categorized. The manufacturer reported that the incidence of "Fail to Cardiovert/Defibrillate" was 0.8 percent is now 1.2 percent due to the increased follow-up time. The manufacturer stated that the instances of failure to cardiovert and/or defibrillate were due to increased defibrillation requirements during induced episodes of VF. It was stated that the failures reported in the article by Winkle, et. al, (AICD patient population used for comparison to the PCD Transvene population) were associated with patch dislodgement, patch

crinkling, lead conductor fracture and elevated defibrillation thresholds due to changing patient condition. The comparison between the complications/observations of the PCD Transvene and the AICD showed a somewhat greater incidence of pocket infection within the PCD Transvene population.

Request # 18

We asked the manufacturer to differentiate between the 38 inactive patients reported in Table IH-1 (previous amendment) and the 34 patients who were reported as no longer active. The manufacturer stated that the amendment contained an error. According to the manufacturer, the text preceding the Table should have read, "there are a total of 38 patients who had received a PCD System and are no longer active in the study as of 6/24/92." As of the data cutoff, it was reported that 82 patients (patient deaths - 51, infection (explant) - 22 and heart transplant - 9) who received a PCD system are no longer active in the study.

Request # 19

This request had to do with how the sudden cardiac death survival was calculated and if all patients who had a prior cardiac arrest were included in the analysis. The manufacturer adequately responded to the request. It was mentioned that additional data regarding the statistics would be available upon request if there was a need to verify the survival probability. It was mentioned that all patients in the Transvene study were included in the analysis regardless of the indication or prior cardiac arrest status.

Request # 20

At our request the manufacturer included the number of patients in the referenced Table with the percentage and calculated p-values. It was again referenced that verification of the percentages and p-values are available upon request.

Request # 21

As requested, the manufacturer stated that the null hypothesis was that the patient characteristics are equivalent for the three lead configurations: RV/SVC/SQ, RV/CS/SQ and RV/CS/SVC. The Chi-Square test was used to test for association between variables (the Pearson chi-square statistic was used). The commercial statistical software package was used in calculating the statistical information presented in Table IV-C. The validity of the statistical analyses performed along with statistical methods employed will be reviewed by FDA's statistician.

Request # 22

In order to justify data pooling and data analysis, the FDA

statistician questioned the statistical procedure which was used. The manufacturer responded by saying that there is no reason to adjust the significance level below 0.05 to eliminate type 1 errors because none of the comparisons are significant at a 0.05 significance level. However, the adequacy of the response will be addressed by the statistician.

Request # 23

The manufacturer discussed how the confidence interval was calculated. According to the manufacturer, the interval was calculated by taking the survival probability (b)(4) the (b)(4) (survival standard error). It was stated that the survival standard error was (b)(4) therefore the confidence interval for Transvene survival at 1 year was 95.3 ± 2.2 or [93.1, 97.5]. The statistician should review this response. provided.

Request # 24

Clarifications regarding the information presented in Table XB-1, page 378 of Volume 2 were requested. The response involved the use of the (b)(4) computer software in analyzing whether there were significant differences between the PCD and Ventak P populations. The FDA statistician should also address the adequacy of this response.

Request # 25

The manufacturer discussed the instances of inappropriate therapies. The majority of the cases involved atrial fibrillation with a rapid ventricular response or sinus tachycardia. In these cases the rhythms overlapped the programmed detection criteria. In cases like these, the investigator either reprogram the device or modifies the patient's drug regimen. The manufacturer stated that the labeling for the PCD contains programming recommendations and warnings for potential programming problems.

The Manual also contains explicit recommendations for programming the Onset Criterion and the Stability Criterion. It was reported that as of February 1, 1993, 33 of the 757 Transvene patients had the Onset Criterion enabled and 55 patients had the Stability Criterion enabled. Eleven of the patients had both the Onset and the Stability algorithms enabled. The majority of the patients with the Onset and Stability enabled had the algorithms programmed ON within 30 days of implant. However, many patients had the algorithms programmed ON for the first time very late in the follow-up period. The efficacies for the treatment of VT and VF (induced and spontaneous episodes) when the algorithms are programmed ON were provided. In the cases of induced episodes, it was reported that the PCD performed appropriately. Specifically, the spontaneous experience includes the following:

The efficacies for VT and VF of the patients with the Stability Criterion programmed ON was 94.8 percent and 100 percent respectively. The efficacy for VT and VF in patients with the Onset Criterion programmed ON was 97 percent and 100 percent respectively.

Request # 26

We asked the manufacturer to provide a discussion of the "device related" complications reported for the Transvene and the PCD epicardial populations. The manufacturer stated that "device related" complications have reference to the complications which resulted in explantation of the device for reasons other than death, infection or transplant.

There were 4 patients within the Transvene population who were explanted due to reasons other than those named above. Reasons for explant included: (1) low battery voltage due to leakage at the input of one of the integrated circuits; (2) failure to appropriately synchronize and deliver cardioversion therapy for an induced VT episode; (3) Power on Reset condition which was not related to the delivery of external defibrillation or cautery; and (4) inappropriate delivery of VF therapy during manual capacitor charge time. In all cases, it was reported that the devices were safely replaced with no adverse consequences to the patient.

There were 7 patients in the PCD Epi population in whom the PCD was explanted due to reasons other than death. The reason for explant in all 7 cases was because of lower than expected battery voltage. The causes for low battery voltage included the following: (1) failure of the integrated circuit; (2) leakage at the input of one of the integrated circuits; and (3) tantalum capacitor leakage. In all of these cases, the devices were also safely removed with no adverse effects on the patients.

There were 4 patients in whom the PCD was explanted due to reasons other than those mentioned above. In these cases the events were classified as complications. These cases involved: low battery voltage (1); inappropriate VF therapy (1); failure to synchronize and delivery therapy (1);and Power On Reset condition due to electrocautery or external defibrillation (1). (The results of all pending analyses should be provided.

Request # 27

The manufacturer discussed complications reported in the patients followed for one year or greater. As of February 1, 1993, there have been 393 patients implanted for one year or greater. There have been 89 complications reported in 76 patients and 122 observations reported in 99 patients. Therefore, 19.3 percent (76/393) of the patients had an event categorized as a

complication and 25.2 percent (99/393) had an event categorized as an observation. The observations included 40 cases of inappropriate VT therapy and 29 cases of oversensing.

The complications included 5 cases of pocket infection, 6 cases of lead fracture and 56 cases of total lead dislodgement. Of these there were 29 dislodgements which occurred at greater than 30 days. Reoperation was required in all cases to reposition the lead.

None of the complications and observations have resulted in a patient death.

Request # 28

We questioned the infection rate reported for the Transvene study. The manufacturer stated that the incidence of infection in the Transvene study is not significantly different form that reported for the Ventak P epicardial lead system (2.3 percent for the Transvene and 2.4 for the Ventak P). The manufacturer feels that there is no substantial increase in the infection rate. Therefore, the current labeling is appropriate.

Request # 29

The manufacturer discussed the experience in the use of the different entry sites. We wanted to know whether the labeling would aid in the selection of an entry site. The manufacturer stated that the left subclavian vein was the most frequently used entry site regardless of the lead and location. It was stated that the physician makes the decision about the specific entry site. However, the technical manuals contain information about the selection of a entry site, and cautions regarding the different entry sites. There are no specific concerns regarding this information.

Request # 30

This deficiency asked about the Transvene Systems that were explanted, returned and analyzed. Of the 762 implants in 757 patients, 41 units were explanted. Fifteen systems were explanted due to patient death, infection (17), cardiac transplant (5) low battery voltage measurement (1) and PCD performance issues (3). Fifteen systems of the 22 deaths were explanted and returned to the company for analysis (five systems were interred with the patients). Of the 15 systems which were returned, ten were analyzed and found to be performing to specifications. Of the 41 devices explanted, final analysis on 19 systems showed that the systems were performing to specifications. It was reported that final analysis is pending on 17 units. The report of the analyses of these units should be provided. The manufacturer mentioned that of the 41 lead

systems, 21 lead systems or portions of the systems were returned. Of these 21 lead systems, the helix of one 6966 lead was damaged (explant data will be updated in requested volumes).

Request # 31

The manufacturing discussed the death of the patient who died 22.5 months post implant. The manufacturer stated that the patients was admitted to the hospital for heart failure and increased episodes of VT and VF. In addition, the patient was reported to have digitalis toxicity. The patients later expired, described as secondary to heart failure due to LV dysfunction. The death was categorized as nonsudden cardiac and not related tot e PCD Transvene System. Interrogation of the device at the explant revealed a normal battery voltage and charge time. Therefore, the patient had experienced no new episodes of VT or VF since the last follow-up visit. The analysis showed that the PCD was performing to specifications. Were the leads returned and analyzed?

The manufacturer provided all relevant data (implant and follow-up data, programmed status of the PCD, etc.) pertaining to the patient (PCD Serial Number (b)(4) implanted for 22.5 months.

Request # 32

We asked about the number of perioperative deaths, and if in these cases there were devices programmed OFF. As of February 1, 1993, there have been 51 deaths in the Transvene PMA population. Five (0.7 percent) of the deaths were perioperative (sudden cardiac (2, nonsudden cardiac (2) and noncardiac (1)). The patient death in which the PCD was programmed OFF, was classified as non-sudden cardiac not related to the tachyarrhythmia episode. A copy of the death summaries was provided for our review.

Request # 33

This deficiency deals with the 1 year sudden cardiac death survival and overall actuarial survival of the patients followed for a year. According to the manufacturer, the survival calculations took in to account the following: all of the patients were alive at one year post implant so their survival from all causes of death was 100 percent. Patients who died within 30 days are not counted within this group. There are no concerns about how the manufacturer addressed this deficiency.

Data (treatment efficacy, lead orientation, complications and survival rates, etc.) of the patients who have been followed for 1 year or more were provided. Of the 115 patients followed for one year or more, the majority (94.7 percent), the primary indication was recurrent, sustained VT without an episode of sudden cardiac death. The treatment efficacy for the patient

population was 98.9 percent for spontaneous VT and 98.8 percent for VF. The treatment efficacy is equivalent to the overall patient population. Twenty-four of the patients followed for 1 year or more had a complication. There are no specific concerns regarding the data submitted.

Request # 34

The manufacturer provided an engineering drawing of the Transvene lead models and a description of the testing of each segment and the full lead body. These data have been reviewed in the IDE application. However the adequacy of the response will be assessed by one of the reviewers on the team.

Request # 35

We asked that the manufacturer discuss the adequacy of the flexing procedures employed (b)(4) cycles at a bend radius of (b)(4) inch per lead model over a (b)(4) month period). The manufacturer discussed the life testing protocol and how the leads were tested. These data were also reviewed in the IDE application. We asked that the manufacturer document, for clarity, all relevant testing of the Transvene leads. The response will be reviewed further by one of the reviewers on the team.

Request # 36

The manufacturer provided documentation regarding the potential for failure of the platinum sputtered Transvene Model 6966. A side-by-side comparison of the Model 6966 and the 4,000 series bradycardia leads (platinum sputtered leads where failure was noted) was included. The review of other team members will specifically address the specifics of the response.

Request # 37

The manufacturer provided a copy of the Summary of Safety and Effectiveness with the updated clinical data.

The manufacturer submitted copies of the technical manuals for our review. Data as referenced in the review will be considered for incorporation into the labeling. At this time there are no specific concerns. The Transvene Lead System will be labeled for use with the pulse generator with which it has been tested. Namely the Medtronic Model 7217B PCD.

It should be noted that as a condition for approval of expansion (allotment of 200 patients per month), the manufacturer has agreed to submit monthly reports. The reports should include a

trend analysis of the observations and complications, returned devices and deaths. These data will be a beneficial adjunct to the data contained within the PMA application. These data will lend support and help to alleviate any concerns which might be related to the incidence of complications and observations reported for the PCD Transvene System.

Discussion of the Review of the PMA Application for the PCD Transvene System

The manufacturer has responded satisfactorily to the deficiencies listed in our letter of March 17, 1993. Several issues which are noted in the teleconference memo (attached) were discussed with the manufacturer. Namely, presentation of the data for Panel review, questions pertaining to the performance of the PCD Transvene and the reported observations and complications. The manufacturer adequately responded to our questions and/or agreed to include specific data in the Panel PMA volumes.

Teleconference

Between: Medtronic Representatives
And: Doris Terry (HFZ-450)
Date: April 29 - May 17, 1993

We discussed and/or requested the following:

1. Updated information on patients with non-standard Transvene configurations should be provided. It was stated that twenty-four patients received the Transvene leads initially (not counted in the 757). Need data on this group. Four of the patients with non-standard configurations received the leads after implant and are counted. Data are not separated out. The manufacturer will provide a "patient tree" which includes all patients.

2. Updated data on the 97 patients who were screened for the Transvene and went on to receive the Epi system should be provided.

3. How many of the patients followed for a year or greater did not meet the implant criteria? Need to know the experience of these patients.

4. The PMA Data should be arranged to include the following sections for panel review:

   Preclinical Tests (Bench, Animal, Life)

   Investigational plan (protocol, hypothesis, objectives of the study, patient report forms)

   Updated clinical report

      Patients who did not meet the implant criteria.
      Patients in the non-standard lead configuration
      Patient followed for one year and greater
      patient followed for 6 months and greater
      (spontaneous experience)
      experience by primary arrhythmia
      Foreign patients

   Observations and Complications

   Additional Transvene patients

   Pertinent Data from June 24, 1993
   Clinical Report

   Comparison Data

Explants

Deaths

Labeling

Summary of Safety and Effectiveness

Survival curves (statistics)

Pertinent Articles (when referring to an article, please include)

Patient Manual

Responses to FDA Concerns (Reviewers and Statisticians). All questions will be included an addressed. If data are incorporated into other sections of the volumes, the section and page number will be referenced.

4. A comparison table of mortality and survival data for the PCD Epi and PCD Transvene and the Ventak P should be provided.

5. Number of patients followed for one year or greater who had spontaneous episodes or were induced after 6 months. Update of Table, page 73.

6. Update of table (complications and observations by follow-up interval) as presented in Volume 2, September 21, 1992 amendment. Complications and observations for the two patient populations (PMA cohort and additional Transvene patients) should be reported separately.

7. Update on foreign experience, namely complications and observations.

8. Trend analysis of the incidence of complications observations and complications within the patient groups (patients followed for 1 year and more, patients implanted with nonstandard lead configuration, etc.) and by primary indication (VT, VF, and VT/VF). These data should be updated. Statistical methods employed should be identified.

9. The complications and observations of the 573 additional Transvene patients should be reported separately. How many have dual sleeves?

Update on experience with dual anchoring sleeves. Update on

573 patients, complications and observation by follow-up.

10. There should be a section which includes ineffective therapies. The Section should report the circumstances surrounding these patients.

11. There should be an update on the reprogrammings (Table VIIF-5, September amendment).

12. Incidence of ineffective therapies with the PCD Epi and PCD Transvene. Updated data as reported in Table IM6, page 78 of the March amendment should be provided.

13. Data obtained from interrogation of the device upon the patient's death should be provided. The data should be referenced as explant data.

14. On Page 338, it was stated that all 58 devices were returned. A Table which contains these data should be prepared.

Continued - May 12, 1993

15. Evidence to support the claim that gender, primary indication and the system implanted (PCD Epi or PCD Transvene) had no impact on survival outcome. The evidence would consist of a description of the computer program used, data input and output, and the decision criteria.

26. A statistically significant difference between the PCD Transvene and the AICD Epicardial System using the confidence interval analysis was found. How was the confidence interval computed?

27. The table on page 24 shows the actuarial survival of PCD Transvene versus PCD Epi. The statistician would like to see a Table which includes mortality data according to monthly intervals, e.g., number dead/number at risk for the Transvene and Epi systems. Then the Mantel Haenszel Chi square test should be used to compute the p-values. The manufacturer should also discuss how the p-values in Table 2-16, page 24 were derived.

28. Based on the clinical experience, will include addition to the labeling: different positions for patch placement. Majority (75 percent) of patients had patch leads placed at the mid axillary line or fourth or fifth intercostal space. Data will be provided about surgical approach.

29. In support of the chronic performance and integrity of the lead system, We asked the manufacturer to provide data regarding the induced and spontaneous activity of the

patients followed for 6 months and beyond. We reiterated that they should be able to account for the experience of each patient. Each of the patients should have been tested or should have had spontaneous episodes. The data can be presented at 90 days and beyond, 6 months and beyond, 12 months and beyond, etc.

30. Results of remaining analyses on all device explants. should be provided. Note: There was a total of 58 explants.

31. Update of the observations and complications as per the time interval. The data in Table XII-E-2 in the September amendment will be updated.

32. In response to Albert Moyal's review, I asked the company about the use of a two lead configuration. The manufacturer stated that the patients who were implanted with a two lead configuration are counted within the group of patients (43) with a non-standard configuration. Among these, 6 patients have a RV-SVC or RV-SQ; and 10 patients have three leads, programmed in a two lead configuration.

    The 702 patients counted in the table on page 289, March Amendment, include only those patients who had LED and/or DFT testing. Other concerns included in the reviewer's memo will be documented in a phone conversation by the reviewer.

The manufacturer agreed to provide the requested information.

Response to Statistician's Review

Items # 2.1 and 2.2

The statistician stated that the p-values for sex and primary indication rendered the two groups (PCD Transvene and PCD Epi) significantly different. Therefore, the statistician contends that the two groups are not "compatible." According to the manufacturer, primary indication and gender did not impact survival. However, the implanted system did influence the probability of survival. The manufacturer used the Cox Regression Analysis to support this position. The statistician asked that the manufacturer provide evidence (description of the computer program, the data input and output and the decision criteria which were used) to support the claim. The request was discussed with the manufacturer. Appropriate data will be submitted in the Panel Volumes to address this issue.

Item # 2.3

The manufacturer was asked to provide data regarding how the confidence interval (as referenced on pages 13 and 256, March Amendment) for the one year overall survival data was computed. The response will be included in the Panel volumes.

Item # 2.4

The manufacturer was asked to prepare a table which depicts the number of patients dead versus the number at risk or total patient population at the different monthly intervals, e.g. 0-3, 3-6, 6-9 and 9-12. In addition, the manufacturer was asked to use a specific Chi square test to compute the p-value for the "association" between the Transvene and Epi survival. It was unclear how the p-values were derived. The requested data will be submitted in the Panel volumes.

Item # 2.5

The similarities and differences between Table 2-12 and Table 3-3 essentially involve data presented for the entire population versus patients followed for one year.

Item # 2.6

The data set and a description of the computation procedure for calculating the survival probabilities were requested. These

data are necessary for verification purposes. A response will be included in Panel volumes. The manufacturer mentioned that the requested data consists of reams of raw data. However, a response which includes a description of the statistical procedure utilized and how the probabilities were calculated will be provided.

Item # 2.7

The similarites and differences between the one year actuarial survival in Table 1K-4, page 43 and Table 8-5, page 451 should be discussed. The numerators and denominators used to derive the one year actuarial survival shown in Table 8.5 should be provided in the requested volumes.

Item # 2.8

The data set and the computation procedure (as referenced on page 83) used in the calculation of the survival probability should be provided for verification. Same as in Item # 2.6. However, the requested data will be condensed, and included in the Panel volumes.

Item # 2.9

The manufacturer should provide the data set and the SAS procedure (statistical software package) used to derive the p-values for the data provided in Table 1M-10, page 84. Information will be included in the Panel volumes.

Item # 2.10

The manufacturer reported a p-value of (b)(4) The statistician calculated a p-value of (b)(4) The manufacturer should discuss how the p-value was calculated. The manufacturer will address the difference in the calculations.

Item # 2.11

We requested that the results of the analyses pending on the devices that underwent early explant should be provided. Data will be included in the requested volumes.

Item # 2.12

The choice of 30 days (in reporting lead dislodgement) can be justified because of its use historically on an acute basis. Acute is described as within the first 6 weeks.

Item # 2.13

The concern deals with justifying pooling the data from all 78 centers which participated in the PCD Transvene clinical trial. It should be noted that all centers used the same protocol or investigational plan (patient selection criteria, follow-up plan, data collection procedures, etc.) for the PCD Transvene study. The manufacturer will also address this issue in the data which will be submitted.

Item # 2.14

The statistician stated that Table E-2, page 215 does not provide an adequate presentation of the follow-up data. The statistician directed the manufacturer to Table 4.6 as published in Lee, Elisha, "Statistical Methods for Survival Data Analysis", page 93 to see how the data could be best presented. This was considered as a good reference for preparing a life table analysis. It was pointed out that the manufacturer should also discuss the reasons why some of the patients were not represented in the follow-up data. It should be noted if the patients were withdrawn alive or lost to follow-up. The statistician's request was relayed to the manufacturer. The response will be provided in the Panel volumes.

Item # 2.15

The statistician would like to see the survival table (page 231) stratified monthly as referenced in Item # 2.4. How the projected one year survival calculations were done should be explained. The manufacturer agreed to provide the data for our review.

Item # 2.16

The numerators and the denominators for the percent success (Table I-1, page 233; Table IF-2, page 287 ; and Table IF-4, page 290) for the treatments of spontaneous episodes should be provided. These data will be included in the Panel volumes.

Item # 2.17

The data collected at the designated follow-up intervals will be included in the updated report and reflected throughout the Panel volumes.

Item # 2.18

The manufacturer was asked to address the calculation of the p-values reported in Table 2.16, page 24. FDA's statistician calculated the p-values and obtained different values than those reported by the manufacturer. This will be addressed in the

Panel volumes.

Note: These data are for clarification and verification purposes. The data do not significantly impact upon the safety and effectiveness of the PCD Transvene System. Therefore, the request for these data are being made via a telephone conversation to the manufacturer.

MEMO

To: Doris Terry
From: Quynh Hoang
Date: 1/27/93

Regarding: Review of the Medtronic PCD Transvene System - P920015 amendment dated 9/18/92

SUMMARY

This amendment contains the response to the deficiencies of the original PMA. It also contains a clinical update on the PCD Transvene System.

Response to Deficiencies

The amendment have fully addressed a majority of the deficiencies. There remain, however, a few items which were not fully answered. Please refer to the Questions section below.

Clinical update

The clinical update covers 757 Transvene patients (447 US) in 78 investigational centers (35 US), as of 6/24/92. For the 757 patients, 762 Transvene systems were used since 5 systems were explanted and replaced due to infection. The 762 lead systems included 762 RV leads, 801 CS/SVC leads, and 723 SQ patches.

By indication: 37.1% of the implants were due to SCD (281/757), 49.8 % for VT (377/757), and 13.1% for SCD/VT (99/757). Coronary artery disease existed in 74.1% (561/757). The mean ejection fraction was 35.6% (688/757). Only 1.5% were of NYHA class IV (11/757). The patients were primarily male (80.6%, 610/757) with a mean age of 59.4 years.

At implant: 71.7% (543/757) met criteria, 97.4% (737/757) had at least a 10 J margin safety, and 2.6% (20/757) failed to finish the implant evaluation due to poor conditions. The most chosen Transvene configuration included: left subclavian as the entry site, RV-SVC-SQ as the lead system (65.6%, 500/762), and sequential as the shock pathway (75.3%, 574/762). The RV always served as the common (-) defibrillation electrode. The mean DFT at implant was 14.8J (316/757), and mean LED was 16.0J (702/757). Sixteen patients also have each a concomitant pacemaker.

Follow-up at one year have been performed on 113 patients, and six month follow-up on 329. Spontaneous VT occurred in 226 patients for a total of 5430 episodes. There were 68 episodes (1.3%, 68/5430) in 30 patients where all four VT therapies were unsuccessful

in terminating the problem; none resulted in a patient death. Spontaneous VF occurred in 198 patients for a total of 973 episodes. Nine episodes (0.9%, 9/973) in 2 patients could not be terminated by the four VF therapies; no patient died. At 3 month, the mean DFT was 15.9 J (54 patients), and mean LED was 19.3 J (88 patients).

There were 138 complications occurred in 138 patients (18.2%, 138/757) and 157 observations occurred in 157 patients (20.8%, 157/757). The majority of the complications were because of lead dislodgement (77 cases) and pocket related (26 cases). Most of the observations were due to inappropriate therapies (62 cases), pocket related (37 cases), and pace/sense related (31 cases). Of the 295 complications and observations, 48.1% (142/295) occurred during the perioperative period. There were 22 patient deaths with 5 in the perioperative period. Thirty-eight patients are no longer active in the study (22 deaths, 11 explants due to infection, and 5 heart transplants). Forty-one systems were explanted.

As of 6/24/92, there are also 548 patients who received the Transvene after the cutoff for the study population. These patients and the 43 who received non-standard lead systems were not included in this clinical update.

Please refer to the Questions section below, for the clarifications required of this update.

QUESTIONS

1. Please describe the similarities and differences between the 6966 and 6968 to justify the use of the 6968 lifetest results in supporting the reliability of the 6966.

2. Given their respective defibrillation thresholds, discuss the differences in battery or energy requirement of the Transvene and Epicardial systems.

3. Clearly identify the objectives, endpoints, and indicators which show that the endpoints have been met. Also, discuss the control in this study.

4. Provide data to show that the new anchoring sleeve does reduce the number of lead dislodgement.

5. Please give the time between Detection and Delivery of therapy. Compare the data from the Transvene and the patch leads.

6. Please provide a breakdown of the electrodes' polarities (cathode or anode) and pathways.

7. Provide the number of patients who died when their devices were turned off. Please breakdown the number by follow-up period.

8. Provide an update analysis of the explanted devices.

9. Provide a profile of the explanted system: how long were the leads implanted; what was found with the leads; and, explanting due to lead or device failure.

10. Document the comparability of the PCD Transvene and the PCD epicardial systems.

12. Provide the status (complications, observations, and death rate) of the "Other" patients who were not in the study population, and of the patients with the non-standard lead systems.

PHONE MEMO

On 1/26/93, Medtronic is contacted. Jennifer Marrone and colleagues responded.

1. Please explain the discoloration of the 6999 lead which occurred during lifetesting. Was it also observed in the explanted leads from human implants?

   Response: The discoloration was an anomaly induced by the lifetest procedure, because the lead was in and out of the saline solution for flexing. They attempted to dry the lead before flexing, but were not entirely successful. Analysis showed that the discoloration was not due to corrosion and there were no electrical problem. It is not expected that the lead would discolor while implanted, since the lead would not be moved in and out of the liquid environment.

2. Please identify the sections on the leads where flex testing was performed. Describe the comparability of the Transvene lead and the 6907 lead, such that the flexing criterion derived from the 6907 data may be applied to the Transvene.

   Response: A section of the defibrillation coil and a section of the cable body were flexed. The whole lead was not flexed since the flex equipment can handle a small section at a time. It is assumed that the cable body is homogeneous so that one section is identical to another. No testing on the distal tip of any of the lead was performed because that part is stiff and not expected to flex.

   There does not exist a model to predict the reliability of a lead; thus, data on the Model 6907 pacing lead were used because the lead has the worst performance of any Medtronic leads. The only determining factor for the choice is the fact that the

Model 6907 is an endocardial lead, and so are the Transvene. The Model 6907 is a silicone lead; however, this should not be a factor where the functional specification is concerned.

During benchtesting, the minimum of flex cycle to failure was (b)(4) for 6966 where (b)(4) leads were tested. Only (b)(4) 6966 underwent lifetesting because the 6968 is considered equivalent to the 6966 lead, and (b)(4) 6968 were used in the lifetest.

3. In this study, is the RV coil always serves as the common electrode.

   Response: No.

4. Please verify these tables:

   a. Tables E-2 and E-3, the number of patients followed at 6M does not match.

      Resp: 329 is the correct number.

   b. Table E-7, switch the numbers under the "attempts" and "successes" headings.

      Resp: will modify accordingly.

   c. Explain why the numbers in Table F-2 do not add up to the 18.2% rate of complications and 20.7% rate of observations.

      Resp: some data are not included. Will be more complete in the next summary

   d. Include <u>all</u> lead-related complications in Table F-3 (and not just those beyond the perioperative period), since it is intended to be a <u>summary</u> of clinical experience.

      Resp: will modify accordingly.

5. Discuss how the screening requirements (Transvene leads or epicardial patches) are different from the implant requirements. If they are the same, explain the Transvene subset that did not meet implant criteria.

   Resp: All study subjects undergo the Transvene implant evaluation (3 out of 4 at 18 J or less). Those who didn't have a 10J safety margin were screened out to receive

the epicardial patches. Of the remaining, they were divided into two groups: one which meets the implant criteria and one which didn't meet the implant criteria. The ones designated to have the epicardial patches would then undergo the patch lead implant evaluation.

6. In the cases where inappropriate VT therapy was delivered, was ONSET programmed On? If so, please explain why this algorithm fails to detect.

Resp: Refer to page 417 of the 9/18/92 submission. Out of 49 instances of inappropriate VT therapy, 21 was resolved by reprogramming, 26 by drugs, 1 with no action, and 1 by AV node ablation. In 2 patients with sinus tachycardia, the ONSET algorithm was enabled and was successful in resolving the problem. In 3 patients with atrial fib, the STABILITY algorithm was enabled and resolved the problem.

7. How are those dropped from the study (due to infection or heart transplant) classified in the survival analysis?

Those patients who were alive when they received heart transplants, a new PCD system, etc. were included in the analysis up to the day where the changes took place. After which, they were censored out of the data. Those receiving the new PCD system will be considered as new patients in the survival curve.

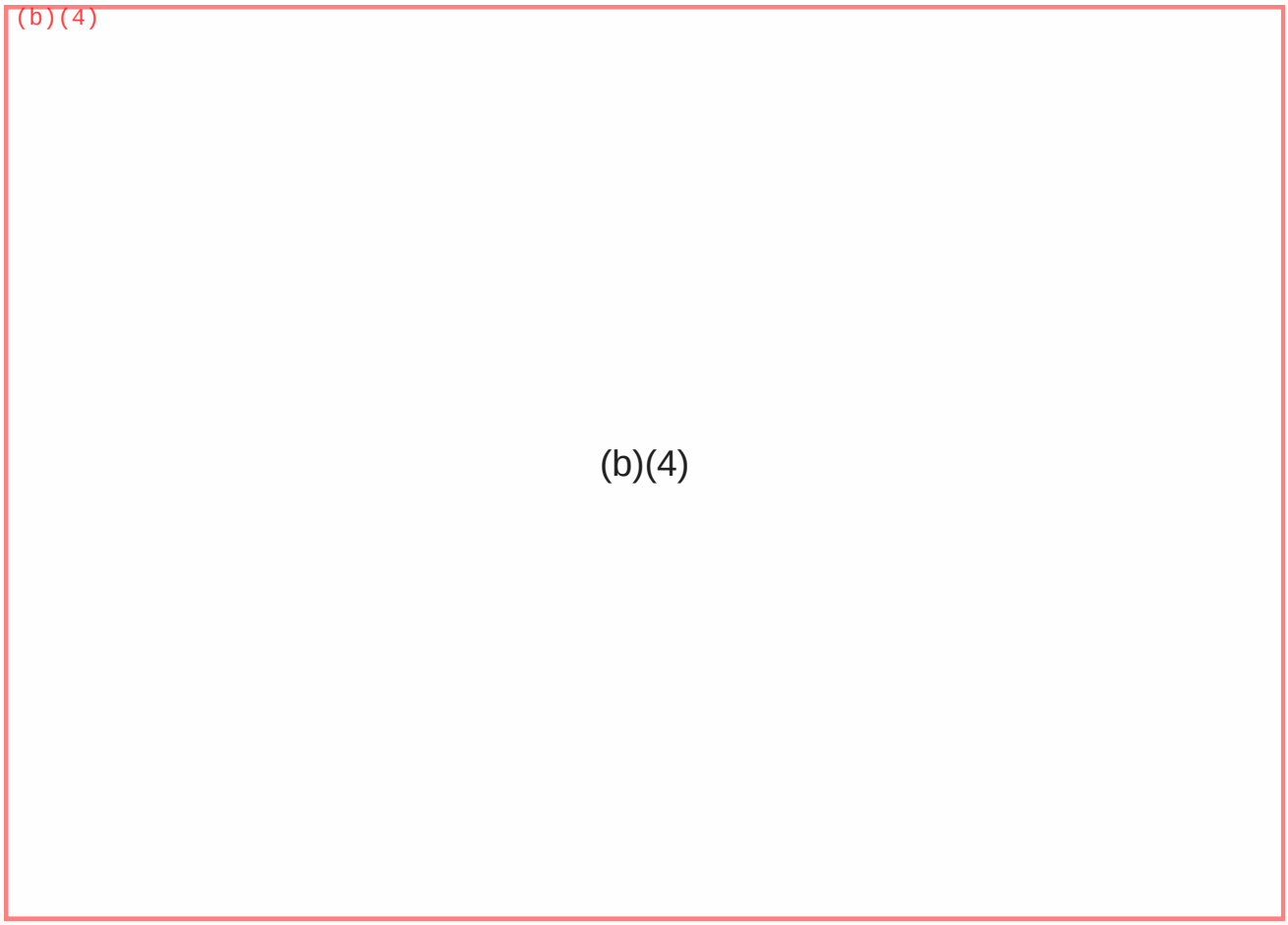
MEMO

To: Doris Terry
From: Quynh Hoang, ODE/DCRND/PEDB
Date: 1/7/93

Regarding: Descriptions of the Transvene leads from Medtronic - P920015

Parameter	Model 6963	Model 6966	Model 6999
Intended Use	cardioversion defibrillation	cardioversion defibrillation pacing sensing	cardioversion defibrillation

(b)(4)



(b)(4)

(b)(4)

(b)(4)

(b)(4)

Electrical testing

(b)(4)

(b)(4)

Environmental testing

(b)(4)

(b)(4)

Mechanical tests' passing criteria

flexing

(b)(4)

(b)(4)

median flexing failure cycle	(b)(4) (b)(4)
composite pull test	(b)(4) (b)(4)
crimp/weld pull test	(b)(4) (b)(4)
anchoring sleeve test (Models 6963 and 6966)	(b)(4) (b)(4)
leak test (Model 6966)	(b)(4) (b)(4)
connector test	(b)(4) (b)(4)

Biocompatibility testing

(b)(4)

(b)(4)

Biostability testing

Models 6963 and 6999

(b)(4)

(b)(4)

Model 6966

(b)(4)

(b)(4)

Life testing

(b)(4)

(b)(4)

	(b)(4) (b)(4)
Crush testing (Models 6963 and 6966)	(b)(4) (b)(4)
Animal Studies	(b)(4) (b)(4)

MEMORANDUM

From: Doris Terry (HFZ-450)
To: File # P9110015
Subject: Medtronic Transvene Lead System
Date: December, 8, 1992
Office: DCRND/ODE

The sponsor has responded to our deficiency letter dated August 6, 1992.

Update of Patient Population

The update of the clinical experience of the Model 7217B and Transvene System is as of June 24, 1992. The Medtronic Models 7216A and 7217B PCD with epicardial leads underwent panel approval in February, 1992. The System presented for review in the referenced file is the Models 7216A and 7217B with non thoracotomy leads (Transvene™ System). The review will concentrate on the study of the Transvene leads in conjunction with the PCD models.

The patient population consists of 757 patients, three hundred and twenty-nine patients have implant durations greater than or equal to 6 months. Identical data pertaining to the spontaneous VT and VF efficacy, overall success rate, complications and observations and deaths were reviewed in the expansion request (IDE supplement G870102/S87). To reiterate there were 22 deaths (sudden cardiac - 3, non-sudden cardiac - 15 and noncardiac - 4).

A total of 854 patients were evaluated for the Transvene System. The patients were divided into the following groups: (1) patients who received a Transvene System (757) and (2) patients screened for a Transvene System and received an epicardial lead system (97). Of the 757 patients who received the Transvene System, 543 patients (71.1%) met the implant criteria and 214 patients (28.3%) did not. Of these 214 patients, 170 had an LED of less than or equal to 24 J and 194/214 had at least one successful termination of an induced ventricular tachyarrhythmia at 24 Joules or less. In 20 patients, their condition precluded further testing. Of the 97 patients who received the epicardial system, 81 patients met the implant criteria for the epicardial system and 16 patients did not. The overall survival for patients who met the implant criteria for the Transvene System was 94.9% and for the patients who did not was 97.4%. For the patients who received the epicardial system who met the criteria, the overall survival was 92.9% and for those who did not meet the implant criteria for the epicardial system was 80.7%.

It was stated that 737/757 (97.4%) received the Transvene System with at least a 10 Joule safety margin. The cardiovascular condition of 20 patients (2.6%) precluded an adequate definition of the safety margin. The investigators in these cases felt that the benefit of the Transvene System outweighed the risks of

further inductions and a thoracotomy. In most cases, the venous entry site for the placement of the Transvene Leads was the left subclavian vein. The majority of the investigators placed the SQ patch subcutaneously and laterally near the mid axillary line. The choice of the lead system was at the physician's discretion. The RV-SVC-SQ configuration was the selection in most cases.

A comparison between the PCD Transvene Study and the PCD Epicardial Lead System and Ventak P AICD studies was made. The comparison entailed looking at patient demographics, clinical performance (DFTs, incidence of spontaneous VT and VF episodes, incidence of complications) and one year survival. Overall there were no issues that rendered the groups significantly different and could be of concern in the evaluation of the data.

The pace/sense performance of the PCD Transvene versus the PCD Epicardial System was compared. In both systems sensing is performed in a standard bipolar configuration and pacing is performed in the integrated bipolar configuration. The pace/sense implant criteria are as follows: pacing threshold - less than or equal to 1.5V at 0.5 ms; R-wave amplitude - greater than or equal to 5 mv; slew rate - greater than or equal to 0.75 volt/sec; and resistance - 200-880 ohms. There was a statistically significant difference in all of the pace/sense parameters of the Transvene versus the epicardial lead system. This was anticipated due to reportedly better endocardial pace/sense parameters. However, it was stated that the difference had no impact on the pacing and sensing performance of the PCD Transvene System. The PCD Transvene System reported a higher mean implant DFT (14.8J versus 9.8J for the PCD Epicardial System). There was a statistically significant difference between the mean DFT obtained with the RV-CS-SQ System and the mean DFT obtained with the other lead systems (RV-CS-SVC and RV-SVC-SQ).

There was also a higher incidence of lead related complications in the PCD Transvene System (6.6% versus 2.8% in the epicardial population). Observations of interest included: inappropriate therapy - 8.2% for the Transvene - 10.6% for the Epicardial System; pace/sense related - 4.1% for the Transvene and 10.2% for the epicardial.

Statistical Analysis

The applicant provided a justification for pooling the U.S. and foreign data. The patient selection criteria, investigational protocol procedures and indications for implant of the Transvene System were identical in all of the studies. Even though there were statistically significant differences in the patient groups (U.S. and foreign), they were not considered to be clinically sitgnificant enough to require stratification of the U.S. and foreign populations. This issue will be left to the discretion of the reviewing statistician.

Patient Data

The applicant provided a list of the primary indications for use which are identical to those for the PCD Epicardial System. The patient demographics of the PCD Transvene Lead System were presented and discussed in detail. A description of the implant and follow-up procedures and a discussion of the data obtained at each interval were provided. The procedures performed at implant and follow-up were identical to those for the PCD Epicardial System.

Response to Deficiencies

The deficiencies relating to the leads were adequately addressed, as per the consulting review. I have the following concerns about the life testing. I have repeatedly questioned the sequence of testing flexing - soaking - high energy pulsing - soaking - electrical and visual inspection. The testing should have involved more than (b)(4) cycles per lead. (b)(4) leads (b)(4) Model 6963, (b)(4) Model 6966 and (b)(4) Model 6968 (tined version of the Model 6966 which is not a subject of the PMA). I question the use of only (b)(4) Model 6966 leads during the life testing. How many Model 6966 leads were used during the course of bench testing and life testing? The data obtained from testing only (b)(4) leads during life testing appears to be inadequate. It was stated that the leads were placed back onto the test and flexed until failure, and that the data would be used only for improvement of the leads. It seems as if only the defibrillation segment of the leads were flexed to failure. Data from the defibrillation electrode segment of each lead model flexed at (b)(4) inch radius was reported as follows for the Model 6963 lead, the median was greater than (b)(4) cycles, for the Model 6966, the median was greater than (b)(4) cycles and for the Model 6999, median greater than (b)(4) cycles. A justification for the use of (b)(4) inch radius for flexing should be discussed. It is unclear how each segment (other than the defibrillation coil) of the Model 6966 lead was tested. The Model 6963 which has a polyurethane platinum sputtered lead body has the job of both pacing and sensing and defibrillation. In light of the recent failure of platinum sputtered brady leads, alot of concentration should be placed on how each of the segments of the Model 6966 were tested. Some background about the failure and mechanism of the failure of the brady platinum leads should be provided for our review.

An update of the animal studies which addressed the tumorigenesis issue was included. These findings were reviewed during the IDE study. There are no new findings to report.

The results of chronic animal studies which assessed chronic performance of the lead system were provided. Data, such as defibrillation thresholds, pacing thresholds, slew rates and R-wave amplitudes, the amount of energy delivered through the lead system for each shock delivered and the amount of current and

voltage across the lead system for each delivered shock were used in the chronic assessment of the Transvene Lead System. According to the manufacturer, the results of testing demonstrated the acceptable stability and performance for its intended use.

The manufacturer provided information regarding the improvement of perioperative and long term patient morbidity with use of the Transvene Lead System. The perioperative mortality of the patients implanted with the Transvene and the epicardial leads were compared and discussed. Undoubtedly, there is a decrease in perioperative mortality with use of the Transvene System. For as it was discussed, the majority of ICD patients are patients in which a thoracotomy poses an additional risk. The study has shown that the use of the Transvene Lead System which is implanted via a non-thoracotomy approach results in a decrease of perioperative death.

Treatment efficacy, complications and survival analysis on the patients followed for 6 months were provided for our review. There were 329 patients followed for 6 months. The primary indication for this group was recurrent sustained VT without an episode of sudden cardiac death. Sixty-six percent of the patients were implanted with the RV-SQ-SVC lead orientation. The mean LED was 15.4J (n=306) and the mean DFT was 13.9J (n=155). Percent success of VT spontaneous episodes was 99.0% and % success of spontaneous VF episodes was 98.7% The one year overall survival for patients followed for 6 months was 99.4% and the one year survival from sudden cardiac death was reported to be 100.0%.

There were 115 patients followed for one year. The primary indication was VT in 56 patients (48.7%). The mean LED and DFT were 15.2 J (n=105) and 13.8J (n=62) respectively. The treatment efficacy was 98.9% for spontaneous VT and 98.8% for spontaneous VF episodes. The overall and sudden cardiac death at one year was reported as 100%. It was stated that one death which was classified as non-sudden occurred 22.5 months post implant. It was reported that 24 of the 115 patients followed for a year had as complication. Specific information will be requested regarding the patient deaths.

Complications and Observations

Complications were reported in 138 patients and 157 patients experienced clinical observations. The incidence of complications was 18.2% (18/757) and 20.8% (157/757) for the observations.

Complications included: increased defibrillation requirements - 0.8%; pace/sense performance related - 0.8%; infection related-explant required - 2.0%; infection related - 1.5%; lead related 12.4%; and device related - 0.5%. The observations were increased defibrillation requirements 0.5%, inappropriate

therapy delivery- 8.2%, pace/sense performance related- 4.1%, infection related - 4.9% and lead related 2.6%. Of the observations related to inappropriate therapy delivery, there were 49 observations which involved inappropriate VT therapy delivery
and 13 observations of inappropriate VF therapy delivery. The manufacturer made a comparison of the Transvene complications and observations to those reported for the PCD Epicardial System. Of interest, the comparison showed that the lead related complications for the Transvene were 6.6% versus 2.8% for the PCD epi and pace/sense related complication which were considerably less (0.9%) for the Transvene and 3.5% for the epi. there were more infection related observations with the Transvene (5.3%) versus 2.2% for the epi and more lead related observations with the Transvene (2.2%) than with the epi (1.2%).

Lead dislodgement which has been a problem in the study, has been addressed in earlier IDE supplements. IDE approval was granted for the use of new anchoring sleeves. It was requested that the results of the experience of at least 50 patients with the new sleeves implanted for 30 days be provided in the PMA for our review According to the manufacturer the lead dislodements have occurred within the first 30 days of implant. However, the frequency of dislodgement greater than 30 days is also of interest. The majority of the dislodgements were reported as complications since reoperation was necessary.Most of the dislodgements involved the Model 6881/6963 CS/SVC lead.

Patient Deaths

As of 6/24/92, there have been 22 deaths (15 U.S. and 7 foreign). Three of the deaths were sudden cardiac, non-sudden cardiac 16 and noncardiac 3. The PCD Transvene sudden cardiac death survival at one year is 99.8% which is comparable to that of the PCD Epicardial System (98.7%) and the commercially available AICD (98.6%). There were 5 perioperative deaths out of the total deaths with a resultant perioperative mortality of 0.7% (sudden cardiac 2, non-sudden 2 and non-cardiac 1). A Table which included the clinical characteristics of the patients who expired was submitted for our review. Death classifications were also provided by primary indication. There was no difference in patient survival based on the Transvene configuration or the indication for implant. The PCD Transvene one year actuarial survival is as follows: sudden cardiac 99.8%; non-sudden cardiac 96.8%; all cardiac 96.6%; noncardiac 99.4%; and overall 95.3% (includes perioperative deaths).

My concerns regarding the referenced will be relayed in the form of deficiencies which should be fully addressed and documented in a PMA Amendment for our review.

Questions and Concerns

1. For documentation and purposes of the PMA application, please reiterate and outline the following:

    a. the hypothesis and the objectives of the study;

    b. a discussion of the use of the AICD™ as a historical control, and how your study addressed the concept of a control which is pertinent in clinical trials, and the practicality, at this time, of the use of a concurrent control during an implantable defibrillator study (ICD);

    c. the endpoints of the study; and

    d. and how the data provided in the PMA application support the specified endpoints.

2. Based on data provided in your PMA application, please prepare Tables which will include a side-by-side comparison of the PCD™ Transvene™ and the PCD™ Epicardial System and the PCD™ Transvene™ and Ventak P AICD™ populations. The data should also include inclusion and exclusion criteria which were used in each study. A discussion of how these data may or not represent a valid comparison and other comments which justify, and support the use of these groups as controls should be included.

3. An update of the PMA population should be provided. The update should include the data as presented in the PMA application. Your update should also include the clinical experience in the use of the new anchoring sleeves which are aimed at decreasing the incidence of dislodgement, and a summary of the clinical experience (spontaneous treatment efficacy of VT and VF, observations and complications, number of patient deaths and overall survival) of the patients followed for a year or more.

4. For purposes of documentation in the PMA, please clarify and reiterate how you identified the "patient who did not meet the implant criteria." Please discuss your implant criteria and how implant testing attempted to satisfy protocol requirements.

5. Of the 214 patients who did not meet the implant criteria, 170 patients had successful defibrillation with 24 Joules (J). Please provide a updated summary of the clinical experience (as referenced in item # 2) on these patients.

6. There were 20 patients among the 214 who did not meet the implant criteria who were implanted without the 10 J safety margin. An update of the spontaneous episode experience in

the treatment of VT and VF in these patients and the overall survival should be provided.

7. Table IK-4, page 151, compares the patients meeting the implant criteria to those who did not met the criteria. However, many of the percentages were presented without numerical support. Please provide the appropriate numbers.

8. Please provide an update on the patients who are implanted with the Transvene™ System and were not counted in the PMA population. The update should include a summary of the clinical experience as referenced in item # 2.

9. Based on your study protocol, please differentiate between defibrillation threshold (DFT) testing and lowest energy to defibrillate (LED) testing. Based on the individual patient report forms, of the 757 patients, how many patients underwent what is described as DFT testing and how many had LED testing? Samples of the patient report forms showing the scheme of testing which was categorized as DFT and LED testing should be provided. Please discuss how the DFT and LED data were reported and presented in the PMA application.

10. There is a statistically significant difference between the mean DFT obtained with the RV-CS-SQ lead configuration and the mean DFT obtained with the other lead configurations. How do you account for this difference? Was the DFT as reported and discussed for all lead configurations obtained using an identical or similar scheme? Please discuss. It should be documented that there were no significant differences between the scheme for performing DFT and LED testing between the PCD Transvene™ and PCD Epicardial patient populations.

11. Please elaborate on how the comparison of DFTs obtained from the PCD™ Epicardial Lead study and the Transvene™ study can be considered as a valid comparison in that the majority of the patients (574 (75.3%)) in the Transvene™ study were programmed with the sequential pathway and 178 (23.4%) were programmed via the simultaneous pathway. The majority of the patients (496 (65.2%)) in the PCD™ Epicardial study were programmed with the single pathway. Based on your PCD™ Epicardial study, please discuss the DFTs or energy requirements obtained with the use of the single defibrillation pathway versus the sequential and simultaneous pathways.

12. Please discuss the time between detection and delivery of therapy of the Transvene™ PCD™ System versus the PCD™ Epicardial System.

13. On page 125 of the application, please explain and/or discuss what is meant by "a 2:1 VF sensing margin", how it

is determined and if the patients met the criteria.

14. Of the 329 patients who were followed for 6 months, 130 patients had spontaneous episodes, what was the average number of VT and VF episodes per patient? Of the patients followed for a year, how many had spontaneous episodes of VT and VF and what was the mean number of episodes per patient in this group?

15. On page 130, Table IF-4, it was reported that there were 5362 episodes of VT successfully terminated. On page 131, paragraph 2, it was stated that 25 patients experienced 45 (0.8%) episodes of sinus tachycardia or atrial fibrillation. Are these patients included in the success or failure category? Nine hundred and sixty-four episodes of VF were reported, however, 75 episodes were not actual VF. It should be clarified how the successful and ineffective therapies and failures are discerned and categorized. Please prepare a Table which includes a category of ineffective therapies with actual patient numbers and percentages.

16. Table IM-6, page 173 should be modified to include a column on inappropriate therapy or therapies delivered as device was programmed so that the percentage can add up to 100%.

17. On page 162, Table IL-2 lists a category "Fail to Cardiovert/Defibrillate" as 0.8%, please clarify. If a patient survives an episode of an inappropriate therapy, is it categorized as a success? Please discuss. The Tables should include percentages with the representative numerical support.

18. There were 38 inactive patients reported in Table IH-1, however, 34 patients were reported to be no longer active. Please clarify.

19. Please discuss how the one year sudden cardiac death survival, as reported in Table IF-2 page 128, was calculated. The numbers and an explanation of patient classification should be included. Was every patient who had a prior cardiac arrest regardless of the arrhythmia included?

20. On page 177, the number of patients should be provided so that the percentages an calculated p-values can be confirmed.

21. Table IV-C shows a comparison of patient variables for the three lead systems. Please state the hypothesis of the study. The p-values obtained when reporting by primary indication should be discussed. The chi-square test of the data set and how it was computed should be discussed.

22. For purposes of justification of data pooling and data analysis of Table IV -C, please discuss why the multiple statistical significant difference was not adjusted at a 0.05 significance level using a more widely accepted procedure such as the Hochberg procedure (Dunnett and Tarnhoue: A Step-up Multiple Test Procedure, Journal of the American Statistical Association, March, 1992, Vol 87: pp.162-170).

23. A comparison was made between the mortality between the PCD™ and AICD™ populations. What was the confidence interval?

24. Please clarify and/or discuss the following regarding Table XB-1, page 378, Volume 2:

    a. the total number of patients in the Ventak P population (292) versus those reported by primary indication (291); and

    b. a chi-square test of primary indication, using the (b)(4) computer software, yields a p-value of nearly 0. This is statistically significant, indicating the PCD™ and Ventak P populations are significantly different.

25. Please discuss the incidence of inappropriate therapies reported as observations in the Transvene™ study. It appears as if there has only been a slight improvement over the PCD™ Epicardial study as it relates to programming and patient management (drug therapy). Please discuss the experience of both studies and how the labeling supports effective programming of the device parameters and the use of the Onset and Stability algorithms. How many patients in the Transvene™ study have the Onset and Stability algorithms programmed ON? At what interval during the study were the majority of patients programmed with the algorithms? Your experience in the treatment induced and spontaneous episodes with use the algorithms should be discussed.

26. Please discuses the "device related" complications reported for the Transvene™ and the PCD™ epicardial System.

27. Please describe in detail the complications reported in the patients followed for a year.

28. There was a substantial increase in the number of infections reported in the Transvene™ study. Even though you discussed why there was an increase, based on your experience, how will your labeling address the reduction in the number of infections?

29. A discussion of your experience in the use of the different entry sites for the placement of the Transvene™ leads and how your labeling assist in the selection of an entry site should be provided.

30. Of the 22 deaths, 15 systems were explanted and returned for analysis. The results of the analyses (PCD™ and Transvene™ leads should be provided. What did device interrogation reveal? How many of the 41 Transvene™ lead systems which were explanted were returned and analyzed? How long were the leads implanted? A description of the protocol for analysis and the results of the analyses on all leads and devices should be provided. The PMA application should document how your study has addressed the need for the return and analysis of all Transvene™ leads and the PCD™.

31. Please discuss the circumstances surrounding the death in the patient who died 22.5 months post implant. What did interrogation of the device reveal?

32. Of the perioperative deaths, how many devices were programmed OFF. Please discuss the circumstances surrounding each death. The number of perioperative deaths should be reported in a Table. The deaths should also be reported as sudden cardiac, non-sudden cardiac and cardiac non-cardiac. Were there other deaths when the device was programmed OFF?

33. It was stated that there have been no reported patient deaths in the group with a one year sudden cardiac death survival and overall actuarial survival of 100%. Does this include the patients who have been followed out for a year and the perioperative deaths?

34. An engineering drawing of each Transvene™ lead model which identifies the segments of the lead and a description of the tests that each segment and the full lead body underwent should be provided.

35. Since flex testing exerts a considerable amount of stress on the lead, and is essential to life testing, why was it considered that (b)(4) cycles at a bend radius of (b)(4) inch per lead model over a (b)(4) month period would be sufficient. Describe how the lead and different segments were flexed.

36. In light of the failure of your platinum sputtered polyurethane bradycardia pacing leads, and since the Transvene™ lead Model 6966 is also a platinum sputtered polyurethane lead, please provide documentation regarding the failure mechanism of the pacing leads and all relevant information pertaining to these cases. How can we be assured that the failure may be restricted to the bradycardia pacing leads. Based on your testing to date regarding the pacing leads and the testing of the Model 6966 lead, discuss the potential and the probability of failure of the Model 6966 lead. A side by side comparison of the Model 6966 and the 4,000 series bradycardia pacing leads should be provided. The comparison should include material,

design, dimensions, function, tests performed and a schematic drawing.

The deficiencies also include the concerns as per the consulting reviews. See memos.

MEMORANDUM

From: Doris Terry (HFZ-450)
To: File # G870102/S87
Subject: Medtronic Transvene System
Date: December 7, 1992
Office: DCRND/ODE

The sponsor is requesting expansion of the Transvene study to include an additional 150 patients.

The following is an overview of the clinical data as of June 24, 1992:

- Patient population of 757, 329 patients have implant durations equal to or greater than 6 months
- 744 PCD implants and 18 7216A implants, of these 444 Model 7217B in U.S. and 300 Model 7217B implants internationally)
- Mean implant duration - 5.6 months
- Defibrillation pathway: sequential - 574 (75.3%); simultaneous - 178 (23.4%); and single - 10 (1.3%)
- Mean DFT - 14.8J (n=316)
- Mean LED 16.0J (n=702)
- Spontaneous VT: 226 patients, 5430 episodes % success = 98.7%
- Spontaneous VF: 198 patients, 973 episodes, % success = 99.1%
- One year survival 99.8%

Of the 757 patients who received the PCD Transvene System, 443 patients (58.5%- 443/757) have either experienced a spontaneous VT or VF episode or had VT or VF induced during a post implant EP study.

There have been 138 complications identified in 138 patients (77 U.S.) and 157 observations identified in 157 patients (68 U.S.) in the Transvene patient population. None of the complications and observations resulted in patient death. Included among the complications were 33 lead dislodgements reported in 33 patients at greater than 30 days. The dislodgements were identified through fluoroscopic examinations during EP evaluation and chest x-rays and pacing/sensing threshold evaluations during routine follow-up. In all cases reoperation was performed and the leads were repositioned. Approval was obtained under IDE in September,

1992 for the use of new anchoring sleeves which will aid in eliminating lead dislodgement. In the last expansion request, we requested one month follow-up experience on at least 50 patients implanted with the new anchoring sleeves to be reported in the PMA application.

Recommendation: Approval to add 150 patients to the study. At this time, no specific plan of expansion which will allow a certain number of patients per month to be added to the study is being approved.

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date DEC 9 1992

From Engineer, DCRND, ICDB

Subject Platinum-Iridium Mesh Leads

To Doris Terry, DCRND, PEDB

This memorandum is a formal response to your question regarding the possibility that platinum-iridium could be a contributing factor in the observation of tumor growth in canines in which epicardial patch defibrillation leads were implanted. It should be noted that my comments are purely speculative and are not based upon a review of the leads in question or any data associated with such.

The toxicity of elements contained in alloys is related to the solubility of their corrosion products and the levels of the element present. Tumors can result because of one or several of the following factors:

1. Presence of a chemical carcinogen.
2. Generation of a carcinogenic chemical(s) through degradation of the material or through a chemical reaction of an ingredient in the material.
3. Cancer through physical effects (referred to as a solid state cancer).

With the defibrillation patch leads, solid-state carcinogenicity is a definite possibility. The use of platinum-iridium in the lead (versus another material) could influence this phenomenon since the mechanical/physical properties of the patch will be influenced by the materials of construction, i.e., stiffness, thickness, etc.

With respect to the presence of a chemical carcinogen in the (b)(4) (b)(4) it is doubtful that the metal itself would produce a toxic effect. However, the use of platinum-iridium in defibrillation leads could present new safety concerns. One obvious problem would be the fatigue resistance of the (b)(4) (b)(4) This material is not used as a coil material in permanent pacing leads so I am unsure of its fatigue properties for this application. Given the large amount of current used in defibrillation leads, (b)(4) (b)(4) could be the cause of the burning/degradation observed in some studies. Also if (b)(4) (b)(4) (b)(4) (b)(4) the metal is subject to accelerated corrosive attack. Products of corrosion will diffuse out and local tissues can suffer from both metallic toxicity and electrochemical changes at the implant surface.

The issue of electrochemical reaction at the stimulation electrode-physiological saline interface is significant and the possibility of dangerous electrochemical reactions should be eliminated. A conservative requirement

for any "safe" electrical stimulation is the absence of chemical changes adjacent to the stimulating electrode. In electrochemical terms, this means that charge transfer processes producing dissolved species or gaseous products must be avoided. Possible dissolved species resulting from reactions at the Pt/saline interface include (b)(4) (b)(4) (b)(4) (b)(4) and (b)(4) Little information is available about the body's tolerance for the species produced at the Pt/saline interface and I cannot provide any estimate of a "safe level". Possible damage resulting from the flow of electric current through the physiologic solution produced at the interface presents another layer of complexity which may need to be considered.

In summary then, it may be advisable to have the manufacturers of these devices explore these areas in more detail to ensure safety and effectiveness, particularly long-term. If you have any questions please let me know.

Tara A. Ryan

cc: Nancy Teague
Christopher B. Sloan

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20850

MEMORANDUM

AA/DCRH

DATE: September 28, 1992

FROM: Program Development and Analysis Branch
CDRH, HFZ-331

SUBJECT: Request for **Follow-up**
Pre-Approval Inspection
PMA P920015

TO: Madalyn Sheldon
PDAB, HFZ-331

Mfr.: Medtronic, B.V.
Wenchebachstraat 10
6466 N. Kerkrade West
The Netherlands

Applicant: Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432

Product: PVD Transvene System

A Premarket Approval application is still pending for the above referenced product due to the previous violative inspection completed on 1-9-92 for the manufacturer identified above. Our records indicate that the firm is currently on Automatic Detention.

Please arrange to have a follow-up inspection conducted which should be scheduled as soon as possible after the manufacturer has indicated that the necessary corrections have been made and a satisfactory response to the Warning Letter has been received.

Please have the finished report (EIR) submitted to HFZ-331 and mark the coversheet **"PMA PRE-APPROVAL FOLLOW-UP INSPECTION"**.

Mary Ann Fitzgerald

Product Code: 74
PAC: 83001
Priority: Top
Est. Comp. Time: 30 Hours
Contact Officer: Mary Ann Fitzgerald
1390 Piccard Drive
Rockville, Maryland 20850
Phone: 8-301-427-1125
FAX: 8-301-427-1076

cc:
HFZ-402
HFZ-332
HFA-224
HFZ-331
HFR-NE1 (Beebe)
#92-79

MEMORANDUM

From: Doris Terry (HFZ-450)
To: File # P920015
Subject: Medtronic Transvene System
Date: June 5, 1992
Office: DCRND/ODE

On the basis of a further review of the referenced file, the following concerns have been identified. These deficiencies should be included in a major amendment letter for the manufacturer's response.

Questions and Concerns

1. An update of the clinical experience of the Transvene Lead System should be provided. The update should include all additional patients and the clinical experience to date. The data should be presented as done in your original PMA application, and should include, e.g., implant and follow-up data, spontaneous episode experience, analyses by different groups, complications/observations, and survival analysis. All remaining deficiencies listed below which pertain to your patient population should be addressed using the updated patient group.

2. What is the mean time of device activation for the patient population?

3. Please discuss your clinical data which support the claim which states that the Transvene Lead System improves both perioperative and long term patient morbidity.

4. A discussion of the data or past performance of similar marketed leads which support the adequacy of (b)(4) flex cycles in support of lead performance should be provided.

5. Please discuss how patient treatment is affected if one or two of the electrode coils of the Model 6999 patch lead becomes damaged.

6. Please specify the section of each lead assembly that was flexed during life testing. the results of the tests should be included.

7. Please provide a detailed discussion of all cases of crinkling and curling of the patch leads and dislodgement of the coronary sinus lead.

8. An update of the chronic animal studies should be provided.

9. Are there patients currently implanted with the Model 6895

and 10317 patch leads? If so, please provide a breakdown of the clinical data, e.g., complications, survival, etc. for each lead.

10. A side-by-side comparison of the Model 6897 epicardial patch lead and the Model 6999 patch lead should be provided.

11. Please discuss the results of tests performed with the Transvene System and the Model 2394.

12. Data such as treatment efficacy, complications and survival analysis on the patients followed for 6 months should be provided.

13. Please list the reasons for not performing pre-hospital discharge testing.

14. The number of spontaneous episodes of the patients followed for six months and beyond should be provided.

15. Based on your experience and on the data as reported in the literature, what is the percentage of patients who have been found unable to withstand a thoracotomy?

16. Provide a detailed discussion of the clinical experience (implant duration, spontaneous episodes, treatment efficacy, survival analysis, complications, etc.) of the patients who did not meet the implant criteria and were implanted with the Transvene System. Also discuss the experience of the patients who were implanted without the 10 Joule safety margin.

17. Please discuss your clinical experience (treatment efficacy, complications and survival rates) of the patients who have been followed for one year and more.

18. Based upon your clinical experience, the Physician's Manual should recommend the sequence of testing with the different lead configurations during implant.

19. A breakdown of the different lead configurations within the patient population, and the treatment efficacy reported for each configuration should be included.

20. An update of the life tests on the leads should be provided.

21. A discussion of the energy requirements of the Transvene versus the epicardial lead system should be provided.

22. A copy of the Summary of Safety and Effectiveness with the updated clinical data should be submitted.

MEMO

TO: Doris Terry

FR: Quynh Hoang

RE: Questions concerning the benchtest/prior investigations performed on the Transvene leads from Medtronic - P920015

DA: 6/5/92

SUMMARY

Medtronic requests market approval for the Transvene lead system. The Transvene leads are used with the Model 7217B PCD for pacing, sensing, cardioversion, and defibrillation of the heart. They require non-thoracotomy means for implantation. For a detailed summary of the prior investigations, please refer to the 5/7/92 memo.

Based on my review and the comments given at the working group and filing meetings, the questions for Medtronic include:

1. Discuss the use of a silicone adhesive to prevent tissue in-growth in the Model 6963 lead. Where is the adhesive placed? From experience, discuss the use of polyurethane and silicone in leads to prevent tissue in-growth.

2. Provide a description of the helix electrode fixation tool and of the tests to verify the torsional force for implanting the helix electrode.

3. From experience, identify the minimum number of flex cycles that a lead should withstand. Also, give the stress level exerted on the Model 6907 lead (from which the median failure time of (b)(4) cycles was observed).

4. Since the electrode coil is flexed separately from the insulated conductor, discuss the reliability of the section where the electrode is coaxial to the conductor. Is there friction between the electrode and the conductor, when the section is flexed?

5. Model 6999's (b)(4) electrode coil fails at a much lower flex cycle than the (b)(4) electrode coil. Discuss the reliability of the (b)(4) electrode coil, and the effects of its failure on the performance of the lead.

6. Discuss the properties of polyurethane which make it the ideal insulation material for the 6966 lead. Why was silicone not chosen?

7. Discuss the biostability tests (stress cracking, MIO, etc.) performed on the two types of polyurethane. Why chose a

different polyurethane for the inner coil?

8. Discuss why the (b)(4) and the (b)(4) (b)(4) (anchor sleeve) have not undergone the mutagenicity test.

9. Based on the results of the lifetest, what is the life expectancy of the leads. Please include your assumptions.

10. What section of each lead was flexed in the lifetest? Does this section include the electrode coil?

11. Provide an update of the (b)(4) month lifetest.

12. The Transvene leads seem to tolerate crush testing better than the pacing leads. Please discuss the properties of the Tranvene leads which take them better.

13. The provided data indicate that a new lead is used for each (temperature tolerance, crush load, or life) test, correlate the results from those tests to the worst case condition where the same lead has to face temperature differences, crushing, and flexing. Why was sequential testing not performed?

14. Compare the 6999 against the epicardial patch leads.

15. Discuss any differences in battery life, between the epi-lead

system and the Transvene system.

16. Some Transvene subjects were also evaluated with the Model 10388 hollow can electrode. Please compare the infection rate of these subjects to the ones who did not undergo the hollow can evaluation.

17. Discuss any possible interaction between the pacemaker leads and the Transvene leads. Also, discuss the effects of these leads on the tricuspic valve and the host vein.

MEMO

TO: Doris Terry
FR: Quynh Hoang
RE: Review of the benchtest/prior investigations performed on the Transvene leads from Medtronic - P920015
DA: 5/7/92

SUMMARY

Medtronic requests market approval for the Transvene lead system. The Transvene leads are used with the Model 7217B PCD for pacing, sensing, cardioversion, and defibrillation of the heart. They require non-thoracotomy means for implantation.

Device Descriptions

The Transvene lead system consists of three leads, Models 6963, 6966, and 6999. The leads contain conductor coils made of a (b)(4) (b)(4) and a (b)(4) (b)(4) shell. Their electrodes are made of a (b)(4) (b)(4)

Model 6963 is a unipolar, transvenous, coronary sinus/superior vena cava (CS/SVC) lead. It serves as an anode for cardioversion and defibrillation. It consists of a (b)(4) connector (b)(4) (b)(4) connector pin and (b)(4) (b)(4) sleeve); a conductor coil insulated by (b)(4) (b)(4) and, a coil electrode of (b)(4) inches in length (b)(4) (b)(4). To prevent tissue in-growth, a silicone adhesive is used with the lead.

Model 6966 is a tripolar, transvenous, right ventricular (RV), screw-in lead. It serves as the pacing/sensing, as well as a cathode (common) for cardioversion and defibrillation. It consists of a bipolar (b)(4) connector (b)(4) (b)(4) connector ring and rotatable pin, and (b)(4) (b)(4) for the ring and helix electrodes; an unipolar (b)(4) connector (b)(4) (b)(4) connector pin and (b)(4) (b)(4) sleeve) for the coil electrode; a tri-layer conductor coil coated with (b)(4) (b)(4) and insulated by (b)(4) (b)(4) rubber; a coil electrode of (b)(4) inches in length (b)(4) (b)(4); a ring electrode with (b)(4) surface area; and, a helix electrode of (b)(4) surface area. Correlating the functions of the lead and its three electrodes: pacing takes place between the coil and helix electrodes; sensing takes place between the ring and helix electrodes; and, cardioversion/defibrillation takes place between the coil electrode and the other leads. (b)(4) (b)(4) tubing prevents tissue in-growth in the lead.

Model 6999 is a unipolar, sub-cutaneous (SQ), patch lead. It serves as an anode for cardioversion and defibrillation. It consists of a (b)(4) (b)(4) connector (b)(4) (b)(4) pin and (b)(4) (b)(4) sleeve); a conductor coil insulated by (b)(4) (b)(4) rubber; and a (b)(4) (b)(4) rubber patch embedded with a (b)(4) (b)(4) and (b)(4) electrode coils. The

inside of the electrode coils is filled with (b)(4) rubber to prevent tissue in-growth in the patch.

Components for use with the leads are: a (b)(4) anchoring sleeve for stationing the lead body at the insertion site; a (b)(4) for stiffening the lead during insertion; and, an (b)(4) tool for entrenching the helix. Descriptions of the (b)(4) tool have not been provided.

Performance Data

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

RECOMMENDATION

Based on the above review of the Transvene lead system, filing is recommended. A major amendment, regarding the concerns raised here, is expected.

MEMORANDUM

From: Doris Terry (HFZ-450)
To: File # P920015
Subject: Medtronic Transvene System
Date: April 13, 1992
Office: ODE/DCRND

The applicant seeks approval of its non-thoracotomy leads, the PCD Transvene System. The system is composed of the Model 6963 Unipolar Coronary Sinus or Superior Vena Cava lead for cardioversion and defibrillation; the Model 6966 Tripolar, Endocardial, Screw-In Lead for pacing, sensing and cardioversion and defibrillation and the Model 6999 unipolar, subcutaneous patch lead for cardioversion and defibrillation.

The indications for use of the Transvene System are similar to those of the Medtronic PCD models. The applicant contends that due to the less invasive nature of the non-thoracotomy leads, the system can be implanted in patients who may not be able to undergo a thoracotomy.

Description of the System

The Model 6963 is a silicone, unipolar, coronary sinus or superior vena cava lead with (b)(4) connector and platinum alloy electrode for delivery of cardioversion and defibrillation therapies.

The Model 6966 is a (b)(4) tripolar extendable/retractable, screw-in lead with a (b)(4) connector and platinum alloy electrode for cardioversion and defibrillation. The lead also has a (b)(4) connector for pacing and sensing.

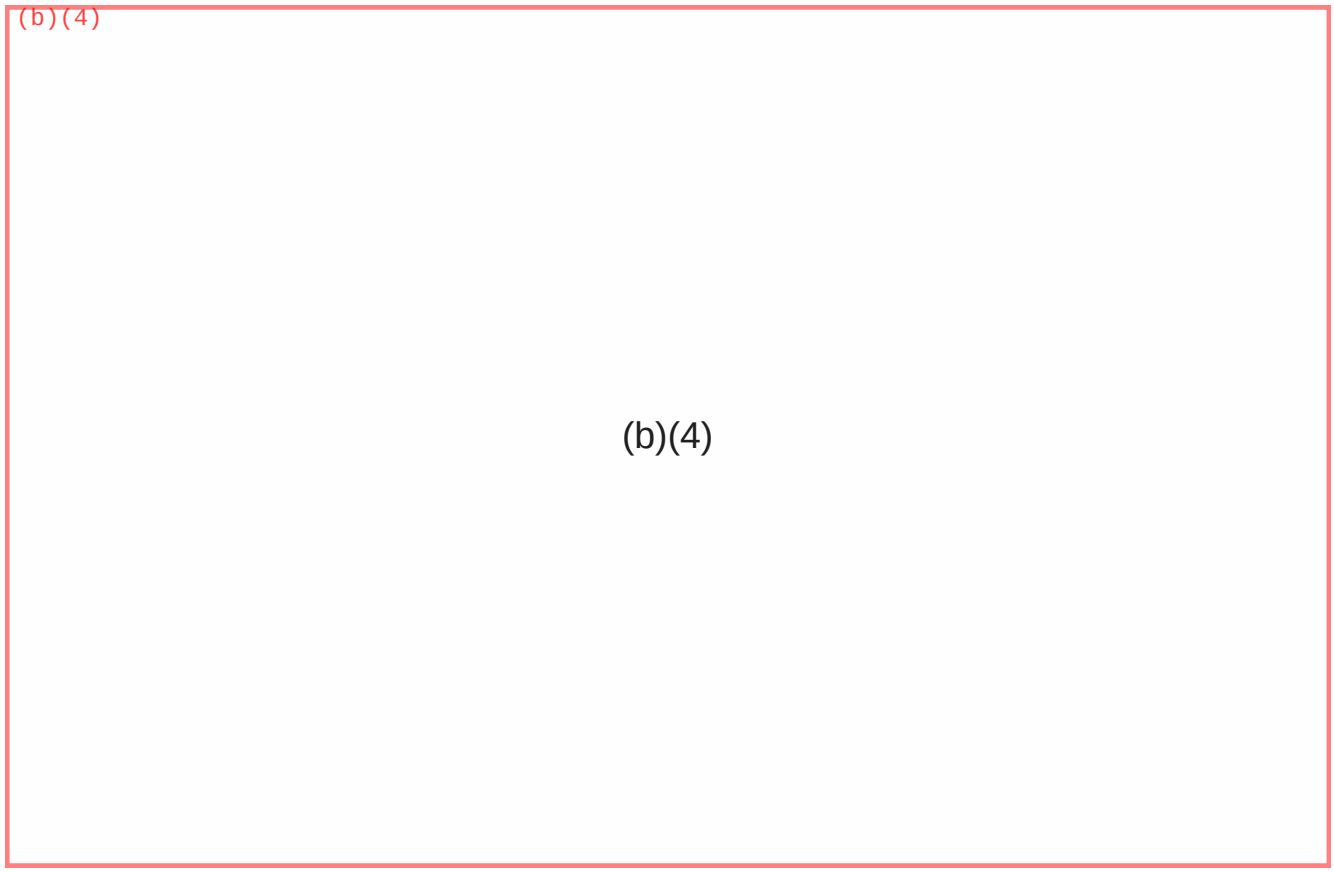
The Model 6999 is a (b)(4) unipolar, oval subcutaneous patch with a (b)(4) connector and platinum alloy electrode coils embedded in the (b)(4) patch. The lead is intended for cardioversion and defibrillation.

Lead System Life Testing

(b)(4)

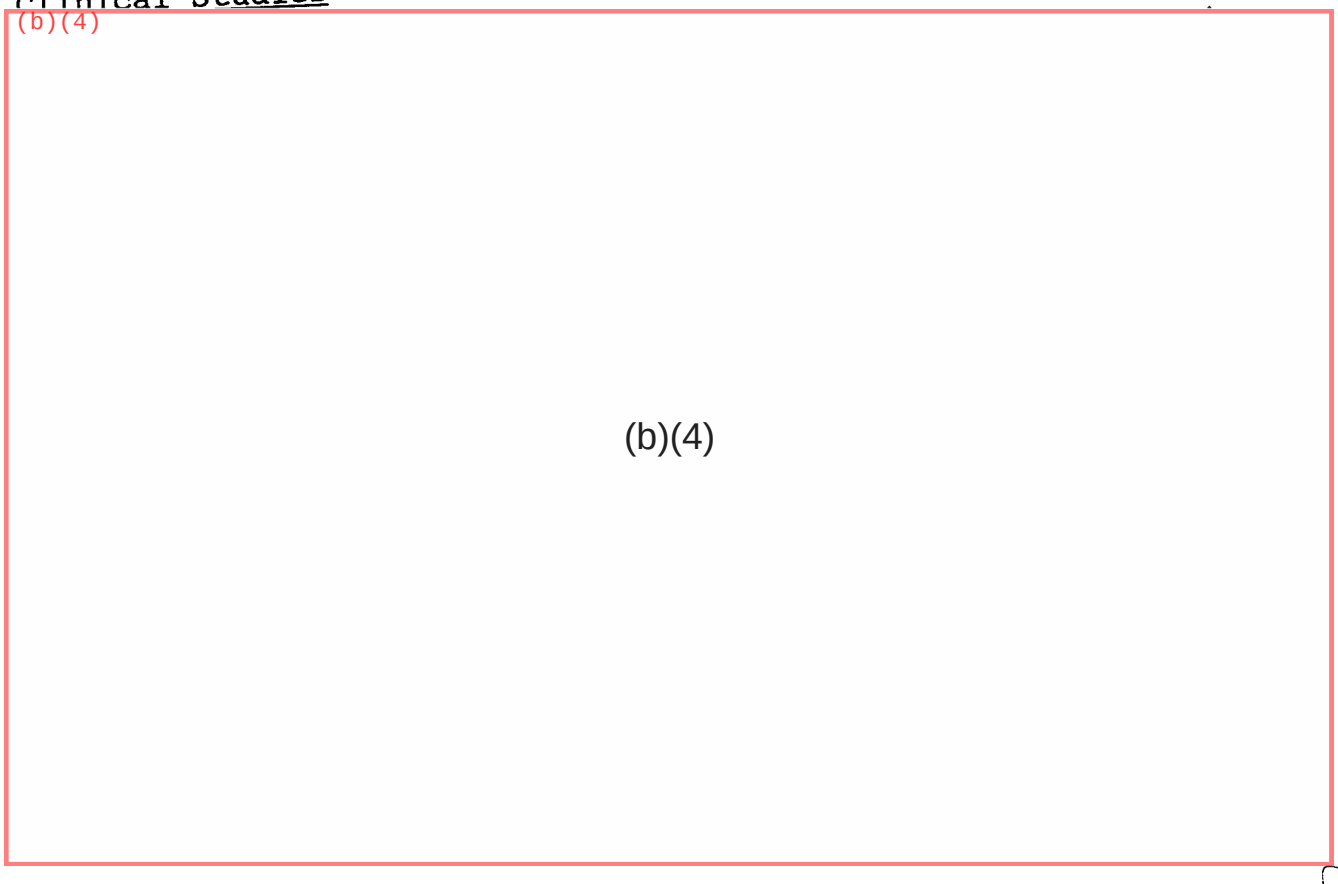
(b)(4)

(b)(4)



Clinical Studies

(b)(4)



(b)(4)

(b)(4)

Recommendation: There are no concerns regarding the data as submitted. Based on our review, to date. the determination has been made that the application is suitable for filing.

Medical Officer

MEMORANDUM TO THE RECORD

From: R. Subramanian, M.D., DCRND

Subj: Addendum to review of death summaries, Medtronic Transvene Lead - P920015

Date: October 1, 1993

::

The death summaries were rereviewed to determine if the infections noted:
a) were related to the device, and to
b) obtain further details regarding time and sites of infection.
This rereview does not include "pocket infections" which have been listed separately in the submission and have been addressed previously (see memo from Dr. J. Jones).

1. A total of 68 deaths were reported in the PCD Transvene System population of 1330.

2. Eleven (11) of these patients had clinical evidence of (or were clinically suspected to have had) infections as follows:

#	Patient #	Infection	Autopsy
1.	(b)(6)	Staph sepsis, ? prosthetic valve infection.	No
2.		Sputum and blood positive for enterobacteriaceae	NA
3.		Pneumonia	NA
4.		Pneumonia, sepsis (83 year old with metastatic lung CA)	NA
5.	(b)(6)	"pt. diagnosed with sepsis"	NA
6.		? Pneumonia, pleural effusion of unknown cause	NA
7.		Pneumonia vs. amiodarone toxicity	No
8.		Sepsis, no source noted	No
9.		"Pneumonia with subsequent sepsis"	NA
10.		Sepsis due intestinal perforation	No
11.		Sepsis secondary to pneumonia	NA

NA = Not available

Conclusion: Although the information provided in the death summaries is limited, there does not appear to be any evidence of device related infection causing death in this group of patients.

CC Ms. Doris Terry, reviewer, DCRND
a:\deathsum.rcs

MEMORANDUM

To: Doris Terry, DCRND

From: R. Subramanian, DCRND

Subj: Review of death summaries, Medtronic Transvene lead - P920015

Date: August 4, 1993

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I have reviewed the death summaries provide with the amendment to the above application. As we have discussed previously:

1. The classification of deaths appears to be reasonable.

2. It is not possible, with the information provided in the death summaries, to state categorically, whether or not any of the deaths could be possibly linked to device performance.

3. As indicated by the sponsor, there appears to be only one death (Patient (b)(6) vol 2, page 134) that is clearly device related.

Recommendation: In future studies, instances where the cause of death is considered unknown, and no autopsy is performed, such death should classified as device related.

a:transvene. rcs

Memorandum

June 11, 1993

To: Doris Terry, B.S., M.S., Medical Reviewer, DCRND

From: Jeffrey D. Jones, M.D., F.A.C.C., Medical Officer, DCRND

RE: Medtronic PCD Transvene Lead System, PMA Amendment P920015

At your request I have reviewed the relevant clinical aspects of the Medtronic PCD Transvene PMA amendment. The clinical study involved 757 patients followed for a mean of 11.7 months. 657 patients were followed for 6 months or greater and 393 patients were followed for 1 year or greater. Inclusion criteria were as follows:

1. Those patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction.

2. Those patients who have recurrent sustained ventricular tachycardia that remains inducible via programmed electrical stimuli or exercise, or occurs spontaneously despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

The 757 patient population was compared to three (3) different historical controls in a retrospective fashion. The three historical controls were 1) the Ventak-P Epicardial system PMA (which was obtained through the freedom of information act), the published AICD clinical experience published from Winkle et al, in the May 1989 JACC (copy attached to this consult for reasons described below) and the PCD Epicardial System clinical experience.

This retrospective picking and choosing of historical controls is not only **not** scientifically sound but it gives the impression that Medtronic is attempting to maximize any demonstrable benefit or minimize less desirable qualities by inappropriate manipulation of historical data. For example, the JACC article by Winkle which was referenced by Medtronic was conducted over a seven (7) year period. It is inappropriate to use these total complication rates as a comparison. To do so markedly minimizes the "complication and observation" rates presented in this study of lesser duration than the control. Specifically, it minimizes the significance of the incidence to failure to cardiovert or defibrillate, of inappropriate VT/VF therapy delivery, pocket

infection (explant) and erosion rates. Approximately half of the infection in the control was due to generator replacement at end of life. It clearly is misleading to compare this to the incidence of primary infection in the study population. In addition, I was unable to determine how the 4.1% failure to cardiovert or defibrillate that is presented by Medtronic was calculated from this article.

Regardless of their flawed scientific approach and manipulation of the historical data several important clinically relevant statements can be made based on the data provided by the company.

1. The patient population of the Ventak-P is likely similar enough to the PCD Transvene study population to allow the comparison of carefully selected endpoints.

2. The one year actuarial survival from SCD in probably comparable between the PCD Transvene and the Ventak-P Epicardial system. Regardless of the fact that survival distributions were not compared by an acceptable statistical method (eg: Mentel-Haenszel), the conclusion is probably a reasonable one.

3. The perioperative mortality of the PCD Transvene is **comparable** to the Ventak-P patient population but **not** statistically lower. When all patients screened for a PCD Transvene are included into the study group (as is clinically appropriate) the perioperative mortality increases from 0.7% to 1.6% and is no longer statistically significantly different than the 2.7% in the Ventak-P population which Medtronic chose as their comparison.

4. The PCD Transvene and the PCD Epicardial patient populations are likely similar enough to allow the comparison of carefully selected endpoints.

5. The one year actuarial survival from SCD is probably comparable between the PCD Transvene and the PCD Epicardial system. Again however, survival distributions were not compared.

The comparison of spontaneous VT/VF episode efficacy is so inconsistently performed and contradictory that no definite conclusions can be drawn from this analysis in my opinion. In addition, R-R interval analysis is not accurate enough to make the bold claims of the high success rates of appropriate therapy that are made by the company. My overall impression is that this device delivers inappropriate therapy much more frequently than the 9.6% that the current method of analysis suggests. In other words, the device is over sensitive to avoid under detection. Medtronic recognizes this and states that "the philosophy behind Medtronic's labeling recommendations and the practice of PCD

investigators is to accept some over detection of non-VT/VF rather than risk under detection of a life threatening tachycardia." At this stage in the development of these devices this is a very reasonable approach. Therefore, the PCD Transvene is probably no more oversensitive than currently available devices but this has not been clearly established from the data in the PMA.

Of continued concern is the very high incidence of lead dislodgment (15.7% total, 9.7% for SVC, 10% for CS) with a reported lead related complication rate of 15.1%. Recall that Medtronic defines complications as requiring invasive interventions to correct. This explains the 5.3% infection rate in the PCD Transvene patient population compared to the 2.5% in the PCD Epicardial system population. Re-operation and repositioning of the lead contributes to the iatrogenic infection rate. This absolute difference is even more alarming when one considers that the mean follow-up in the epicardial group was 16.3 months compared to the lesser 11.7 months is the Transvene. The infection related explant was 2.9% in the PCD Transvene patient population compared to 2.3% in the PCD Epicardial study and 2.4% in the Ventak-P study. No statistical analysis was provided by Medtronic between these comparisons.

In response to FDA's deficiency letter, Medtronic has submitted data in an additional 234 patients which have been implanted with two (2) separate anchoring sleeves. These patients were not included in the 757 patients in the study population. 186 patients completed their one (1) month follow-up and 49 completed a 3 month follow-up. Reportedly, there has been only a single documented dislodgment. Additional follow-up on these patients is needed. If prior to panel review, the follow-up data appears favorable, changing the labeling to emphasize the need for the use of 2 anchoring sleeves should be adequate. FDA should inquire as to the recruitment method used to obtain these additional 234 patients. It could be phrased in the following question:

In reference to the 234 patients who received 2 anchoring sleeves, please explain how these patients were chosen. For example, were they consecutive patients from selected institutions or were consecutive patients from all institutions represented? Are all patients currently undergoing implantation implanted with 2 anchoring sleeves? If not, why not and how are you assured that alternative methods are as effective as the two anchoring sleeve method?

In summary, this collection of clinical data presented by Medtronic in support of their PMA has demonstrated the following:

1. In a similar patient population the PCD Transvene had an equivalent 1 year SCD survivorship when compared to the PCD epicardial system and the Ventak-P systems.

2. A higher incidence of lead dislodgment and infection and probably infection related explant is present in the PCD Transvene PMA patient population when compared to controls.

3. No definite improvement in perioperative mortality has been demonstrated in the PMA population when compared to the Ventak-P study population.

4. No definite conclusions can be drawn about the appropriateness or "efficacy" of spontaneously delivered VT or VF therapy.

The above conclusions can be summarized in the following question which can be posed to the panel:

Has Medtronic demonstrated in its clinical study that the increased risk of lead dislodgment and potential iatrogenic infection justifies a small but statistically insignificant decrease in perioperative mortality?

Lastly, I have a continued concern regarding the perioperative death of patient (b)(6) This death was classified as Sudden Cardiac and rightfully so; however, even though the device was interrogated, we have not been told of the results of that interrogation. This information was to be provided to us with this submission but as with the last update Medtronic states, "The results of this analysis are not available as of this submission but will be provided to the FDA." I suggest we require this information before the device is allowed to be reviewed by the panel.

If I may be of further assistance please do not hesitate to ask.

Pages removed for the following reason: Copyright Material

Memorandum

January 25, 1993

To: Doris Terry, Reviewer, DCRND

From: Jeffrey D. Jones, M.D., F.A.C.C., Medical Officer

RE: Medtronic PCD Transvene, Clinical Review

At your request I have reviewed the clinical data found in the PMA Amendment to the Medtronic PCD Transvene System. I will first answer your specific questions but will then expand to a more general evaluation with specific comments.

In response to your questions regarding the data presented by the company concerning the patients that did not met the recommended defibrillation implant criteria but who received a device anyway. Apparently each individual investigator who implanted such a device was given the latitude to make such a decision if he/she felt it was clinically appropriate. Reportedly, when the implant criteria could not be met but the patient was felt to be at increased risk for an arrhythmic death the device was subsequently implanted. Medtronic claims that regardless of the implant criteria that almost all of the patients had a 10 j safety margin. This "safety margin" has not been established in the literature by a well controlled prospective study. The reference sited by Medtronic on page 145 of the PMA does not discuss safety margins at all. It was however discussed in a subsequent reference of theirs. In addition, 20 patients had no DFT trial performed because they were judged to be in "poor condition". One could argue that if their general medical status was so poor that they could not undergo testing of the device then perhaps their short term survival was such that they should not have received the device at all. However, with such a high risk group of patients with a high likelihood of cardiac death perhaps it is acceptable to proceed in this fashion. It does unfortunately give the impression that Medtronic has little control over its investigators. Regardless, the reported overall survival in this group is 97.4% This is presented on pg. 153. We are not informed as to the average time of follow-up and maximum time of follow-up in these patients.

Therefore, my recommendations are as follows. We insist that Medtronic restrain investigators from implanting devices in patients that do not meet the implant criteria. This is not only bad science but it will decrease the actual patient population cohort that will be available and potentially prolong their study and subsequent approval. If Medtronic wishes to change their implant criteria they should provide data to support their position. I spoke to (b)(6) (b)(6) M.D. who was recently appointed Chief of Cardiovascular Electrophysiology at Baylor College of Medicine in Houston. He claims that no standard for defibrillation threshold exists but that the recommendations that he

recently presented at the NASPE Board Review Course in Cardiac Electrophysiology are based on his experience in electrophysiology. We need a more scientific approach. This burden should be placed on the manufacturer. I would also like to see up to date data on the overall survival between those meeting implant criteria and those patients not meeting implant criteria along with statistical analysis of those data. They should include the average and total time of follow-up.

Medtronic uses three historical control study populations in evaluating the safety and effectiveness of the PCD Transvene. They utilize the Ventak-P data, obtained through the freedom of information act, for comparison of patient characterists, clinical performance, and survival analysis (to include perioperative death).

The comparison is acceptable and favors the PCD Transvene in several ways. 92% of VT's were successfully treated with anti-tachycardia pacing and did not require further therapy. This represents an advantage with translates into better tolerance by the patient. My concern as explained below is that this figure may be artificially inflated. It requires that we assume that the attending physician is correct 100% of the time when he reports the device functioned properly after treatment. All that is available to the physician is the R-R interval and it would be relatively easy to misinterpret SVT as VT. For this reason we should refrain Medtronic from boldly proclaiming 99+% success rate (also see #4 and #5 below).

Perioperative mortality was lower in the PCD Transvene population at 0.7% compared to 2.7% with P = (b)(4) DFT's were reported as similar although we are not told how Ventex-P determined the DFT's, this is necessary to make an accurate comparison.

In addition to the specific questions you asked I would like to take this opportunity to comment in general on the presentation of the clinical data. A recurring difficulty I encountered was the presentation in table form of percentages when comparing two or more variables. It is very frequently unclear how these percentages are calculated. For example, in the table on pg. 128 it is unclear how the "One Year SCD Survival" percentages presented are calculated. They repeatedly place the burden on us to manipulate the numbers to achieve their percentages. In addition, an accompanying P value is often presented and again, it is unclear how this number is calculated. Frequently the number of patients is very small and representing this information as a percentage is misleading (eg; the number of patients in several categories followed for one year). In future submissions, all data presented as percentages should be accompanied by the number of patients so that the numbers can be easily verified and all P values can be easily confirmed by our statisticians. This would also allow us to easily add up all patients at a glance to confirm that all patients are accounted for and appropriately classified.

The general presentation of the data is also disorganized and very often redundant. I would suggest that for future submissions we insist on a clinical study mainframe for presentation of their data. For example, all the clinical data is presented in a section called "Clinical Data" in

table form where all the information can be easily review and compared and all calculations confirmed. They should save their comments and conclusions for those specific sections. This would greatly reduce our review time. There were also several occasions in which I came upon a term that had not yet been defined and I had to "stumble" through the data until I eventually came upon a definition (eg: DFT and LED). A section entitled, "Definitions" would have been helpful. We should insist on the same standards that a peer review journal would insist upon prior to publishing a manuscript.

In addition, when a manufacturer sites a specific reference and/or author to support their position they should not only provide a copy of the reference but also highlight the pertinent portion of the document. This would greatly reduce our reviewing time and speed up the review process in general. I spent approximately 6 hours looking up references cited by the authors in this current clinical section. The librarian had to call several other libraries to find one particular reference which was subsequently faxxed to me.

To continue, I have several additional recommendations to make and specific questions to pose.

1) Pg. 125, #2 near the bottom of the page. It is unclear to me what "a 2:1 VF sensing safety margin" is. This is not defined. How is it determined and did the patients meet the criteria.

2) Pg. 128, at the bottom of the table. How was "One year SCD Survival" calculated ? We need the specific numbers and an explanation of patient classification. Was every patient that had a prior cardiac arrest regardless of the arrhythmia included ?

3) Pg. 129, end of paragraph 2. Do we know what the manufactures recommendations are that they reportedly give to institutions "that prefer to obtain DFT,s during the implant procedure ?"

4) Pg. 130, table. The manufacturer claims that there were 5362 successful episodes of VT termination. On pg. 131, paragraph 2, they claim that 25 patients experienced 45 (0.8%) episodes of sinus tachycardia or atrial fibrillation. Are these patients included in the success or failure category. They should not only clarify this but restructure the table to include a category of ineffective therapy with actual patient numbers and percentages.

5) As in #4 above, 964 successful episodes of VF are reported but on pg. 131 at the bottom they claim that 75 episodes were not VF. It appears to me that they count these episodes as successes when they should place them in the category of ineffective therapy. I would also like to know how they definitively confirm that an episode of VT or VF was definitely an episode. Is there a blinded third party interpreter of the interrogated retrieved events or is this based solely on the opinion of the attending physician ?

6) Pg. 136, Table H. There are a total of 38 patients who are inactive according to the chart but this does not correlate with the 34

patients as listed in the paragraph above the table.

7) There should be a similar table for periopeative deaths as the one shown on pg. 138. Perioperative deaths should be classified in chart form with numbers and percentages into sudden cardiac, non-sudden cardiac and non-cardiac deaths. I realize this is done in sentence form on page 451 but it would lend itself to more efficient review and comparison if it was present with the rest of the clinical data.

8) Pg. 139, The table at the top of the page relates a value for overall one year actuarial survival and again it is unclear how many patients actually were followed for a year. As I mentioned previously, every percentage should have an associated number of patients so we may verify the calculations immediately and not spend unnecessary time trying to confirm their calculations.

9) Pg. 151, The table compares the patients meeting and those not meeting implant criteria but again many percentages are presented without numerical support.

10) Pg. 156, They claim that there have been no reported patients deaths in the patient group with a resultant one year sudden cardiac death survival and overall actuarial survival of 100%. The real important data is the number of patients followed out this far. Does this also include perioperative deaths ?

11) Pg. 160, The DFT of the Ventak-P is compared to the DFT of the Transvene but we are never told how the DFT of the Ventak-P is determined. This is a worthless comparison without that knowledge. This mistake is repeated when the PCD-Transvene is compared to the PCD Epicardial device in chart form on pg. 171.

12) Pg. 162, The chart lists a "Fail to Cardiovert/Defibrillate" as 0.8% but for the reasons I provided above this is a gross misrepresentation. If a patient survives an episode of inappropriate therapy it should not be classified as a success. Again, tables of percentages are not acceptable without the numbers of patients in an adjacent column.

13) Pg. 173, The chart lists efficacy of termination of spontaneous episodes of VT and VF. The chart should be modified to include the total number of episodes out of the total and a column on inappropriate therapy so that the percentages all add up to 100% in each column.

14) Pg 177, Again, the number of patients should be provided so that the percentages and calculated P-Value can be confirmed.

In general, the comparison of the Transvene clinical data to data collected from three different historical sources gives the impression of manipulation to selectively compare in a manner aimed at maximizing the advantage of the Transvene. In the future, a single historical source should be used unless the manufacturer can convincingly argue to the contrary. Lastly, I would suggest that you obtain statistical input from our statistician in those areas that I have suggested above.

STATISTICIANS' REVIEWS

RB90-B

REVIEW OF STATISTICIAN

PMA #P 920015

	YES	NO
Has this PMA been reviewed by a statistician?	✓	
Have all the concerns of the statistician been addressed?	✓	
If not, is there a memo in the file explaining why each of the statistician's concerns are not germane to this PMA?		

Branch Chief

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date October 29, 1993

From Mathematical Statistician (T. C. Lu) HFZ-162
Statistics Branch, Division of Biometric Sciences, OSB

Subject Statistical Review of PMA P920015 Panel Package, Medtronic Multiprogrammable Tachyarrhythmia Control System with Non-thoracotomy Cardioversion and Defibrillation Electrodes, Medtronic, Inc.

To

Doris Terry - HFZ-450
Division of Cardiovascular, Respiratory, and Neurological Devices, ODE
Through: Director, Division of Biometric Sciences, OSB
Through: Chief, Statistics Branch, DBS, OSB

In my July 9, 1993 memo to you, I asked for the numerators and denominators used for the percent success (Table I-1, page 233, Table 1F-2, page 287 and Table 1F-4, page 290, PMA Amendment, March 26, 1993) for the treatment of spontaneous episodes. After thorough investigation, I have the following results:

Spontaneous VT % success 98.4% of Table I-1, p. 233 can be obtained from Table 8-1, p. 110, June 11, 1993. (9864/10027 = 98.4%)

Spontaneous VF % success 98.4% of Table I-1, p. 233 can be obtained from Table ID2-6, p.98, June 11, 1993. (1951/1982 = 98.4%)

Spontaneous VT % success 99.0% after 12 months of follow-up of Table 1F-2, p. 287 can be obtained from Table ID3-1, p.78, Vol. 2, June 11, 1993. (6273/6338 = 99.0%)

Spontaneous VF % success 98.6% after 12 months of follow-up of Table IF-2, p. 287 can be obtained from ID3-1, p. 78, Vol. 2, June 11, 1993. (1090/1105 = 98.6%)

I couldn't locate the section or table to address 6 months of follow-up for spontaneous VT and VF % success.

Table IF-4, p. 290, March 26, 1993 agrees with the table in the June 11, 1993 panel package.

If you have any questions concerning this memorandum, please contact me at 594-0627.

T. C. Lu

cc: Thomas J. Callahan, Ph.D. HFZ-450 — PMS Group HFZ-402
Donald F. Dahms HFZ-450 — Medical Device File
Lynne A. Reamer HFZ-450 — Board File

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date .July 9, 1993

From Mathematical Statistician (T. C. Lu) HFZ-162
Statistics Branch, Division of Biometric Sciences, OSB

Subject Statistical Review of PMA P920015 Panel Package, Medtronic Multiprogrammable Tachyarrhythmia Control System with Non-thoracotomy Cardioversion and Defibrillation Electrodes, Medtronic, Inc.

To Doris Terry - HFZ-450
Division of Cardiovascular, Respiratory, and Neurological Devices, ODE
Through: Director, Division of Biometric Sciences, OSB
Through: Chief, Statistical Branch, DBS, OSB

1. Background

The original PMA was submitted in April 1992. Amendment two was submitted for review in March 1993. The purpose of this memo is to review the response from the sponsor to the deficiencies stated in the FDA letter and in the telephone conference call held on July 7, 1993. Information provided in this panel package includes clinical experience of 757 patients through February 1, 1993.

2. Reviewer's Comments

2.1. Cox Regression

This reviewer wants the sponsor to provide a description of the computer program, including data input and output, and the decision criteria used to support the sponsor's claim that primary indication and gender do not impact survival. Sponsor stated that "Appropriate data will be submitted in the panel volumes to address this issue" in response to statistician's review. In the telephone conversation, the sponsor stated that (b)(4) was used for survival curve comparison, but the (b)(4) test was used for testing the equality of survival curves. (Table 1D2-10, page 76).

2.2. Actuarial Survival

In my March 10, 1993 memo to you, I asked for the number of deaths, number at risk for transvene and epicardial by month intervals (0-3, 3-6, 6-9 and 9-12). Sponsor claims that Table 1B1-5, page 17 "Patient Compliance" will serve this purpose. The compliance rate is very high, according to this table. However, to use this patient compliance table for survival analysis would be misleading, because it does not give survival probability. Sponsor said they will fax a copy of their survival curve graphical comparison.

2.3. Percentage Success

This reviewer needs to review the numerators and the denominators used for the percent success (Table I-1, page 233, Table 1F-2, page 287 and Table IF-4, page 290) for the treatment of spontaneous episodes. Sponsor pointed out that those numbers are located in other sections of the panel package.

2.4. P-values

The sponsor was asked to address the calculation of the p-values reported in Table 2.165, page 24. I calculated the p-values and obtained different values than those reported by the sponsor. Sponsor claimed that (b)(4) Life-test was used for the calculation. Subsequently, a computer output was faxed to me by the sponsor for review.

3. Conclusion

In my previous memos to you, I raised questions about the safety and effectiveness of the device. My telephone conversation with the sponsor certainly helped to answer some of these questions. The safety and effectiveness of the device should be evaluated from a clinical perspective.

T. C. Lu

cc: Thomas J. Callahan, Ph.D. HFZ-450
Donald F. Dahms HFZ-450
Lynne A. Reamer HFZ-450
Medical Device File
Board File

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date May 10, 1993

From Mathematical Statistician (T. C. Lu) HFZ-162
Statistical Branch, Division of Biometric Sciences, OST

Subject Statistical Review of PMA P920015 Amendment, Medtronic Multiprogrammable Tachyarrhythmia Control System with Non-thoracotomy Cardioversion and Defibrillation Electrodes, Medtronic, Inc.

To Doris Terry - HFZ-450
Division of Cardiovascular, Respiratory, and Neurological Devices, ODE
Through: Director, Division of Biometric Sciences, OST
Through: Chief, Statistical Branch, DBS, OST

1. Background

The Medtronic Pacer-Cardioverter-Defibrillator (PCD) is an implantable, multiprogrammable, automatic tachyarrhythmia control device. This device is used for treatment of patients at risk of sudden cardiac death due to ventricular tachycardia (VT) and/or ventricular fibrillation (VF). The original PMA was submitted in April 1992. Amendment One was submitted in September 1992. Amendment Two was submitted for review in March 1993. The purpose of this memo is to review the response from the sponsor for the deficiencies stated in the FDA letter. Information provided in this amendment includes clinical experience of 757 patients through February 1, 1993.

2. Reviewer's Comments

2.1. Historical Control

Sponsor compared the PCD transvene system (treatment group) clinical experience to the reported PCD epicardial system (control group) clinical experience. Sponsor argued that patients were enrolled in the two studies concurrently and patients' indications, implant criteria and clinical data requirements were identical for the two patient groups. But, in Table 2-7, comparison of patient characteristics, PCD transvene system versus PCD epicardial system, as of February 1, 1993, page 19, gives different information. The p-values for sex and primary indication, (b)(4) and (b)(4) respectively, are statistically significantly different. Therefore, the sponsor's argument that the two groups are compatible is not correct.

2.2. Cox Regression

Sponsor stated, on pages 12 and 90, that: "Cox regression analysis was performed to see what effect gender, primary indication and system implanted (PCD transvene or PCD epicardial) had on survival outcome. This analysis showed that for overall survival at one year, the system implanted had an influence on the probability of survival but gender and primary indication had no influence". This reviewer would like to see the detailed evidence to support this claim, including the computer program, input, output and decision criteria.

2.3. Confidence Interval Analysis

Sponsor compared the PCD transvene system and Ventak-P epicardial system and claimed a statistically significant difference in one-year overall survival between the PCD transvene and AICD epicardial system, using confidence interval analysis, pages 13 and 256. This reviewer asked for this information in my December 16, 1992 memo to you and I would like to ask again for the computation of this confidence interval.

2.4. Actuarial Survival Comparison I

Table 2-16, page 24, depicts the actuarial survival of PCD transvene vs. PCD epicardial. This reviewer would like to see a more detailed Table such as this:

Month	Transvene	Epicardial
0-3	No.dead/No.at risk	No.dead/No.at risk
3-6	No.dead/No.at risk	No.dead/No.at risk
6-9	No.dead/No.at risk	No.dead/No.at risk
9-12	No.dead/No.at risk	No.dead/No.at risk

Then use the Mantel-Haenszel Chi-square test to compute the p-value for association between transvene and epicardial survival. Sponsor didn't discuss how the p-values in Table 2-16 were derived; it looks as if the binomial distribution was used for the computation. Sponsor should address this issue.

2.5. Please discuss the similarities/differences between Table 2-12 (page 22) and Table 3-3 (page 27).

2.6. Survival Probability I

Sponsor stated, on page 43, that the survival probabilities are calculated using a life-table survival analysis. For verification of survival probabilities, the data necessary to do calculations are available upon request. This reviewer would like to see this data set and the computation procedure.

2.7. Please discuss the similarities/differences between "one-year actuarial survival" of Table 1K-4 (page 43) and Table 8-5 (page 51). This reviewer would like to see the numerators and denominators actually used to derive the one-year actuarial survival shown in Table 8.5.

2.8. Survival Probability II

Sponsor stated, on page 83, that: "Presentation of the number of patients does not allow calculation of the survival probability. Therefore, a data set will be available upon request if you desire to verify the survival probability". This reviewer would like to see this data set and the computation procedure.

2.9. Actuarial Survival Comparison II

Table 1M-10 (page 84) depicts the comparison of actuarial survival: transvene vs epicardial as of June 24, 1992. Again, this reviewer would like to see the data set and the (b)(4) procedure actually used to derive the p-values.

2.10. NYHA Classification

The p-value for the NYHA classification in Table IV-C (page 88) is (b)(4), as computed by the sponsor. Based on the data provided in this table, the reviewer calculated a p-value of (b)(4) Sponsor should address this difference in p-values.

2.11. Early Device Explant

There were four patients in whom the PCD device was explanted due to reasons other than death, infection or heart transplant. Analysis of one explanted PCD device indicated a random device failure in the microprocessor and low power hybrid. Another patient experienced a power on reset (POR) condition, see page 100. Please submit the other two results for review as soon as the results are available.

2.12. Lead Dislodgement

Lead dislodgements are reported as complications/observations in Table 27-2 (page 103). The sponsor should justify his choice of thirty (30) days as a cutoff.

2.13. Pooling

There are seventy eight (78) investigative centers participating in the clinical trial with thirty five (35) domestic centers and forty three (43) foreign centers. Please justify pooling all seventy eight centers together.

2.14. Follow-up Presentation

Table E-2, page 215, depicts the PCD transvene system follow-up. This is not an adequate presentation of the follow-up data. As I requested in my April 23, 1992 memo, the sponsor should refer to page 93, Table 4.6, in "Statistical Methods for Survival Data Analysis" by Elisa Lee for a more proper life-table analysis. Sponsor should also discuss the reasons why some patients dropped out of the follow-up study, i.e., either withdrawn alive or lost to follow-up.

2.15. Actuarial Survival Comparison III

Table 11-2 (page 231) depicts the PCD transvene system one-year actuarial survival as of 2/1/93. Again, this reviewer would like to see the actuarial survival table stratified by every month, similar to that in Section 2.4 above. Sponsor also stated "this table included the projected one year survival calculations for patients who ultimately received a PCD transvene system....". Please explain in detail the projected one-year survival calculations.

2.16. Data Summary by Primary Indication

Sponsor provided PCD transvene system data summary by primary indication as of 2/1/93 in Table I-1 (page 233). This reviewer would like to see the numerators and denominators for percent success from treating spontaneous VT and spontaneous VF. Sponsor provided similar information in Table IF-2 (page 287) and Table IF-4 (page 290).

2.17. Follow-up Evaluations

Sponsor indicated, on page 284, that clinical data were collected for follow-up evaluations at 1 and 3 months post-implant and at 3-month intervals. Please provide all of this information

2.18. P-values for Actuarial Survival

This reviewer calculated the p-values in Table 2-16 (page 24) as follows:

Cause of Death	P-Values Sponsor	Reviewer
Sudden Cardiac	(b)(4)	(b)(4)
Non-Sudden Cardiac		
All Cardiac		
Non-Cardiac		
Overall		

3. Conclusion

The sponsor needs to adequately address all issues raised in Section 2 above, mainly actuarial survival and follow-up, before the safety or effectiveness of the PCD transvene system relative to the PCD epicardial system can be evaluated from a statistical perspective.

T. C. Lu

cc: Abhijit Acharya, Ph.D. HFZ-450
Donald F. Dahms HFZ-450
Lynne A. Reamer HFZ-450
Medical Device File
Board File

L. Kramer

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date December 16, 1992

From Mathematical Statistician (T. C. Lu) HFZ-162
Statistical Branch, Division of Biometric Sciences, OST

Subject Statistical Review of PMA P920015 Amendment, Medtronic Multiprogrammable Tachyarrhythmia Control System with Non-thoracotomy Cardvioversion and Defibrillation Electrodes, Medtronic, Inc.

To Doris Terry - HFZ-450
Division of Cardiovascular, Respiratory, and Neurological Devices
Through: Director, Division of Biometric Sciences, OST MKB for RPC
Through: Chief, Statistics Branch, DBS, OST CSL for HFB

1. Background

Per our telephone conversation on December 7, 1992, you requested a statistical review of this PMA amendment. This amendment was received at FDA on September 21, 1992. I wasn't notified of any action until December 7. This amendment was sent to me on December 8, 1992. You indicate that you would like to receive my comments before December 18, 1992. With the limited time frame, I can only concentrate on the sponsor's response to the deficiency letter dated August 6 from FDA to the sponsor.

2. Reviewer's Comments

2.1. Item 21. Sponsor provided the p-values for Tables IV-B and IV-C of the original PMA. This reviewer recomputed the p-values and found them identical to those of the sponsor's. However, there is a problem, sample sizes are (b)(4) for 7216A and (b)(4) for 7217B. With such a large difference in sample size, this will cause very low statistical power, then the small difference is very difficult to detect.

2.2. Table IV-C shows comparisons of patient variables for the three lead systems. All the p-values computed by this reviewer is identical to those of the sponsor's. The total numbers of patients of primary indication are 329 for RV/SVC/SQ (of which 187 for SCD, 114 for VT, and 28 for SCDlVT), which are not in agreement with a total sample size of (b)(4) (b)(4) The sponsor provided p-values for variables tested in Table IV-C. The hypothesis was not clearly stated. After recomputing the p-values listed in the table, all are in agreement except primary indication. The chi-square test of this data set, computed using (b)(4) computer software, yield a p-value of nearly 0, which is also different from that of sponsor's computed p-value of (b)(4)

2.3. The sponsor, for the purpose of justification of data pooling and data analysis of Table IV-C, adjust the multiple statistical significant difference at 0.05 significance level using Hochberg procedure (Dunnett & Tarnhoue: A Step-up Multiple Test Procedure, Journal of the American Statistical Association, March 1992, 87:162-170). Although this is a published, peer reviewed article, the sponsor's multiple test adjustment procedure is not widely accepted by the biostatistical and clinical community.

2.4. Comparison of Mortality Between One PCD and the AICD

Item 25. The sponsor compared the end points of the two devices. Sponsor claimed that confidence interval analysis was performed but that confidence interval was not given. Confidence interval should be computed by the sponsor to support this claim.

Sponsor provided a table for the comparison of patient characteristics, PCD versus ventak-P. I have two questions about Table XB-1, Page 378, Vol. 2:

(i) The total numbers of patients of primary indication, 291 for Ventak-P (49 for SCD, 169 for VT, and 73 for SCD/VT) are not equal to the total number of patients of Ventak-P of 292.

(ii) A chi-square test of primary indication, using (b)(4) computer software, yield a p-value of nearly 0. This is statistically significant, indicating that PCD and Ventak-P are significantly different.

The inclusion and exclusion criteria for patients of PCD and AICD studies are not discussed by the sponsor.

Conclusion

The sponsor needs to adequately address the issues raised in Section 2 above before the safety and effectiveness of the PCD transvene system can be evaluated from a statistical perspective.

T. C. Lu

cc: Abhijit Acharya, Ph.D. - HFZ-450
Donald F. Dahms - HFZ-450
Lynne A. Reamer - HFZ-450
PMS Group - HFZ-402
DCC - HFZ-401
Medical Device File
Board File

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date: April 23, 1992

From: Mathematical Statistician (T.C. Lu) HFZ-162
Statistical Branch, Division of Biometric Sciences, OST

Subject: Statistical Review of PMA P920015, Medtronic Multiprogrammable Tachyarrhythmia Control System with Non-thoracotomy Cardioversion and Defibrillation Electrodes, Medtronic, Inc.

To: Doris Terry - HFZ-450
Division of Cardiovascular, Respiratory, and Neurological Devices
Through: Director, Division of Biometric Sciences, OST
Through: Chief, Statistical Branch, DBS, OST

1. Background

The Medtronic Pacer-Cardioverter-Defibrillator (PCD) is an implantable. multiprogrammable, automatic tachyarrhythmia control device. This device is used for treatment of patients at risk of sudden cardiac death due to ventricular tachycardia (VT) and/or ventricular fibrillation (VF).

2. Reviewer's Comments

2.1 Pooling

There are a total of 319 implants in 317 patients of the PCD device. A total of 52 investigative centers participated in the clinical trials with 20 centers in the U.S. and 32 in foreign countries. In Vol 5, p 646 - p 650, a section was devoted to the justification for data pooling. Sponsor performed a comparison of U.S. and foreign patients and summarized the variables tested in Table IVA. Sponsor first combined and then compared all the data in U.S. centers and in foreign centers. However, much information was lost in these gross combinations. The initial design with centers nested within countries was reduced to a two-way classification. This is not good statistical practice.

This reviewer recomputed all the p-values listed in Table IVB and IVC; they were all found to be correct, except for the following:

Table IVC

	p-value (sponsor)	p-value (reviewer)
NYHA Classification	(b)(4) (b)(4)	(b)(4) (b)(4)
Congestive Heart Failure		
Cardiomyopathy		

2.2 Patient follow-up

Table E-2, p. 34, vol. 1, shows the follow-up time by type of data form. This is not an adequate presentation of the follow-up data. Sponsor should refer to p. 93, Table 4.6. in "Statistical Methods for Survival Data Analysis" by Elisa Lee for a more proper life-table analysis. Sponsor should also discuss the reason why some patients dropped out of the follow-up study, either withdrawn alive or lost to follow-up. For example, there are 224 patients at 1 month and only 154 patients at 3 months. Please explain the difference of 70 patients during this 2-month period.

2.3 PCD transvene system compared to AICD Epicardial System clinical experience

For the comparison of complication/observation rates for PCD vs AICD, as reported in Table IL-1, p634, vol 5, I have the following comments:

2.3.1. Please provide the numbers of complications and patients for PCD and AICD.

2.3.2. Please provide the clinical success/failure criteria used for "Failure to Cardiovert/Defibrillate and Inappropriate/Problematic VT/VF Therapy Delivery."

2.3.3. I am concerned that pocket infection is 3.5% for PCD as compared to 2.2% of AICD, even though the sponsor argues that the PCD System implant procedure requires multiple lead configurations. There are other "lead related" complications as reported on Table X1 F1 and F2, P857, Vol. 5. PCD Transvene System has more "lead related" complications than PCD Epicardial System.

2.4. One-year actuarial survival comparison of mortality between the PCD and AICD systems was discussed on p. 842, Vol. 5. Sponsor stated "there was a statistical difference in the reported (AICD) perioperative mortality (p = (b)(4) with the PCD Transvene System having a lower reported perioperative mortality." I have the following comments concerning this statement:

2.4.1. What statistical test was used to compare survival?

2.4.2. Please provide the two survival or life tables by year of follow-up, so that this reviewer can reproduce the statistical test and the derived p-value.

2.5. Comparison to PCD Epicardial System.

P-values for one-year survival comparison of PCD Transvene System vs. PCD Epicardial System for freedom from death by "sudden cardiac", "non-sudden cardiac", "all cardiac" and "noncardiac" causes are provided in Table X1 G-2, p. 862, Vol. 5, also Table J-2, p. 54, Vol. 1. The sponsor should discuss the statistical techniques used to derive the p-values.

2.6. PCD device longevity data.

Sponsor stated in Section M.1. p. 66, Vol. 1: "Thus, the PCD device longevity, which is monitored, utilizing battery voltage and change time obtained via telemetry, was analyzed. The PCD device longevity data collected is consistent with the longevity projection." This reviewer needs to see the data and statistical test used to support the above statement.

3. Reviewer's Conclusion

The sponsor needs to adequately address the issues raised in Section 2 above before the safety and effectiveness of the PCD Transvene System can be evaluated from a statistical perspective.

T. C. Lu
T.C. Lu

cc: Abhijit Acharya, Ph.D. - HFZ-450
Donald F. Dahms - HFZ-450
Lynne A. Reamer - HFZ-450
PMS Group - HFZ-402
DCC - HFZ-401
Medical Device File
Board File

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date: April 7, 1992

From: Mathematical Statistician (G. Kamer) HFZ-162
Statistics Branch, Division of Biometric Sciences, OST

Subject: PMA Review Statistical Checklist Recommendations for PMA P920015, Medtronic Multiprogrammable Tachyarrhythmia Control System with Non-thoracotomy Cardioversion and Defibrillation Electrodes, Medtronic, Inc.

To: Donald F. Dahms - HFZ-450
Division of Cardiovascular, Respiratory, and Neurological Devices
Through: Director, Division of Biometric Sciences, OST
Through: Chief, Statistics Branch, DBS, OST

The Statistics Branch, DBS, OST has received the PMA referenced above and evaluated it against the attached PMA Review Statistical Checklist. The failures to provide justification for sample size or pooling of data over investigational sites were the only non-serious omissions of a statistical nature. Therefore, we recommend this PMA be filed. We will now begin an in-depth statistical review of this PMA. This review should be completed and our comments sent to you within 30 days. If you have any questions, please contact me at 227-8629 or the statistical reviewer, T. C. Lu, at 227-8627. The omissions found are from the Clinical Investigations Section of the checklist and are stated below for your information:

1. This submission does not include any acceptable justification of sample size. Please provide a complete description of your sample-size determination. This should include effect criteria, alpha and beta statistical error tolerances, anticipated variance of the response variables, and any assumptions or statistical formulae with references that are required for sample-size determination.

2. This submission does not include any justification for pooling (combining) the patient data over site. Please review and analyze your prognostic variables to provide a detailed justification why the data may or may not be pooled for evaluation. Note that an analysis by site is always necessary in any case.

Gary L. Kamer

cc: Abhijit Acharya, Ph.D. - HFZ-450
Lynne A. Reamer - HFZ-450
Doris J. Terry - HFZ-450
T. C. Lu - HFZ-162
Mel Seidman - HFZ-162
PMS Group - HFZ-402
DCC - HFZ-401
Medical Device File
Board File

PMA P920015, Medtronic Multiprog Tachyarrhythmia Control System with Non-thoracotomy Cardioversion + Defibrillation Electrodes, Medtronic, Inc

PMA REVIEW STATISTICAL CHECKLIST

	Yes	No	Comment
I. Organizational and Administrative Elements including Table of Contents with volume and page numbers	✓		
II. Summary of Safety and Effectiveness			
A. Indications for use	✓		
B. Claims for the device	✓		
C. Summary of studies	✓		
III. Clinical Investigations			
A. Protocol			
1. included	✓		Summary
2. adhered to	✓	✓	
3. deviations described	✓	✓	
B. Patient Accountability			
1. patient inclusion/ exclusion criteria	✓		Not su how stu was de
2. follow-up schedule	✓		Short
3. study period completed	?		→ mean follow
4. all patients accounted for	✓		time (4.5
C. Description of Safety and Effectiveness Parameters			
1. safety			only
2. effectiveness			comple
a. sensitivity			2 yr f
b. specificity			
c. false positive			
d. false negative			
e. reproducibility			
f. repeatability			
g. stability			
D. Documentation of Statistical Analysis and Results			
1. control (comparison) group	✓	✓	Historical - AICD + PCD Epi
2. sample size justified	✓		
3. hypothesis test stated	✓		

	Yes	No	Comment
4. potential of bias adequately evaluated			
a. randomization or blinding techniques	—	—	NA
b. descriptive and stratified analyses			
(1) patient demographics	✓		
(2) investigator		✓	
(3) site	✓	—	US vs Foreign
(4) surgical technique		—	NA
5. pooling of data justified		✓	US vs Foreign
6. statistical test given	✓	—	Vague + Device
7. clear presentation of data	✓	—	
8. statistical results stated	✓	—	Not by site
9. statistical conclusions drawn from results	✓	—	

Correspondance

CORRESPONDANCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

Ms. Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

SEP 23 1993

RE: P920015
Medtronic® Transvene® Lead System
Filed: April 1, 1992
Amended: August 27, September 21, October 27 and November 5, 1992, March 29, June 2, 14, and July 9, 1993

Dear Ms. Marrone:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA). The Circulatory System Devices Panel which also reviewed your PMA, recommended to CDRH at the August 2, 1993, panel meeting that the PMA be considered approvable. CDRH is pleased to inform you that the PMA is approvable subject to your submission of the following:

1. The labeling should be modified to include the following directions for use:

   a. diagrams which demonstrate the proper insertion technique and final anatomic position of the intravascular leads and the Sub-Q patch;

   b. defibrillation efficacy data on the different lead configurations, various polarity combinations and sequential versus simultaneous discharges;

   c. information and/or recommendations regarding specific implantation techniques and methods of testing the different configurations. For example, when is it recommended to use a two-lead configuration versus a three-lead configuration, when to implant in the superior vena cava (SVC) versus the coronary sinus (CS), and how the most advantageous position of the Sub-Q patch is determined;

   d. information or recommendations, based on your experience, regarding implantation in patients who do not have at least a 10 Joule safety margin;

   e. information aimed at reducing the incidence of infection;

   f. instructions stressing the importance of pausing between inductions of ventricular fibrillation (VF) at the time of implantation for at least a specified period of time in order to

decrease morbidity and mortality. The comments and the pause duration suggested should be based on the experience of the primary investigators in your study;

g. information regarding the change in defibrillation thresholds that one may expect with time as based on the experience of your investigators in your study;

h. guidance and techniques for separating permanent pacemaker leads from the Transvene® leads to minimize the interaction between the two devices, and diagnostic methods which can be employed at implant or predischarge to confirm the absence of adverse interaction;

i. a statement which emphasizes the need for x-rays and pace/sense threshold testing at follow-up to check for lead dislodgement (x-rays should be done at 3-month intervals for 1 year);

j. information regarding techniques for placing the leads via the cephalic vein when possible; and

k. an explanation regarding the necessity for explant and return of the leads upon the patient's death.

2. The labeling should be modified to include the following warnings:

a. a statement that the Sub-Q patch lead is not for use on the pericardium or epicardium, because it is too inflexible to be used as such;

b. stronger and more specific language regarding the use of dual anchoring sleeves on the right ventricle (RV), SVC, and CS leads. Based on the experience of your investigators, please describe the techniques used to fixate the lead at the insertion into the vein to minimize dislodgment; and

c. information which states that after extensive VF inductions at implant testing with the nonthoracotomy lead system, serious consideration should be given to delaying the thoracotomy for at least 2 days. Please include a statement which states that the clinical data showed that when a thoracotomy was performed immediately after testing, the perioperative mortality rate was increased from 0.7 to 9.3 percent.

3. In addition you should note the following:

a. The indications and contraindications for use of the Medtronic® Transvene® Lead System must be identical (except for certain modifications which pertain to the Transvene® Leads and those described below) to those for the PCD™ Epicardial System. Please change your second indication to read: Poorly tolerated,

sustained ventricular tachycardia and/or fibrillation which recurs spontaneously or can be induced despite the best antiarrhythmic drug therapy. Please also include the following statement in your indications section:

Note: The clinical outcome of hemodynamically stable, sustained VT patients is not fully known. The safety and effectiveness of the PCD® Transvene System in this subgroup of VT patients has not been determined.

b. The technical manuals for the Transvene® Leads must state that the leads are for use together as a system. The labeling (where appropriate) must be consistent in all of the Transvene® Lead manuals. The information regarding the Transvene® Leads in the PCD® Manual must also be included in the Transvene® Lead manuals.

c. There should be an identifying mark on the package label which distinguishes nonthoracotomy leads from thoracotomy leads.

d. The Warnings and Precautions in the labeling must be identified and reported separately according to FDA's Blue Book Memorandum of March 8, 1991, (a copy of this memorandum was previously sent to you).

4. Provide a copy of the Patient's Manual which includes a reference to use of the non-thoracotomy leads with the PCD® models.

The PMA must be amended to include your concurrence with, or suggested revision of, the enclosed "Conditions of Approval for Implantable Defibrillators and Programmers."

The condition that the sale, distribution and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act.

The device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the approved labeling specifies the requirements that apply to the training of physicians who may use the device.

In addition to the above, an FDA inspection must find that the manufacturing facilities, methods and controls comply with applicable device Good Manufacturing Practice Regulations (21 CFR Part 820). If applicable, amend the PMA to include required manufacturing information not previously submitted.

This is to advise you that, following receipt of an approvable letter, an applicant is required by 21 CFR 814.20(e) to update its pending PMA with new safety and effectiveness information learned about the device from ongoing or completed studies that may reasonably affect an evaluation of the safety or effectiveness of the device or that may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling. This updated reporting is limited to studies sponsored by the applicant or to which the applicant has reasonable access. The update report shall be consistent with the data reporting provisions of the protocol. Any update report shall be submitted in three copies as an amendment to the PMA and shall include the FDA reference number assigned to the PMA.

CDRH will issue an approval order after the requested information has been reviewed and determined to be acceptable. You may not begin commercial distribution of the device until you have received an approval order.

As provided by 21 CFR 814.44(e)(2), you may amend your PMA as requested, or withdraw it, or you may treat this letter as a formal denial of approval. If you choose the latter, you may request administrative review, either through a hearing or review by an independent advisory committee, under section 515(d)(3) and 515(g) of the act by filing a petition with the Food and Drug Administration, Dockets Management Branch (HFA-305), Room 1-23, 12420 Parklawn Drive, Rockville, Maryland 20857, within 30 days of the date you receive this letter. A petition for administrative review must be submitted in accordance with general administrative procedures for submission of documents to the Dockets Management Branch (21 CFR 10.20) and in the form of a petition for reconsideration (21 CFR 10.33). After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issues to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

The above requested information must be submitted in the form of an amendment (3 copies). Unless you amend this PMA to request an extension, and the extension is approved, FDA will consider the PMA to have been withdrawn voluntarily if you fail to respond in writing to this request for an amendment within 180 days of the date of this letter as provided under 21 CFR 814.44(g). Any request for an extension must be submitted within the 180-day period, justify the need for the extension, and provide a reasonable estimate as to when the requested information will be submitted.

All amendments to the PMA must be submitted in triplicate to the address below and shall reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

In addition, under Section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under Section 522(a)(1)(A) the above noted device as requiring postmarket surveillance.

Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study to include the evaluation of the explanted leads for evidence of metal ion oxidation (MIO), and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

Postmarket Studies Document Center
Room 408 (HFZ-107)
12720 Twinbrook Parkway
Rockville, Maryland 20852

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will cause your product to be misbranded and could lead to the imposition of civil money penalties or other regulatory actions. Any distribution of a misbranded device is a violation of the act and may result in a number of FDA enforcement actions, including (but not limited to) withdrawal of your PMA.

If you have questions concerning postmarket surveillance study requirements, contact Postmarket Surveillance Studies Branch at (301) 594-0639.

Finally, on August 16, 1993, the Final Rule for Device Tracking was published in the FEDERAL REGISTER, pages 43442-43455 (enclosed). FDA is required to provide notice to PMA applicants in an approvable letter that their device is

subject to the regulation. Therefore, be advised that under Section 519(e) of the act, FDA has identified the above device as a device which requires tracking. You are required to adopt a method of tracking that follows the devices through the distribution chain and then identifies and follows the patients who receive them. The specific requirements of the regulation are found in 21 CFR 821 as described in the August 16, 1993, FEDERAL REGISTER beginning on page 43447.

If you have questions concerning this approvable letter please contact Doris Terry at (301) 594-2018 or Arnold Alpert, Ph.D., at (301) 594-2186.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Acting Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

MAR 17 1993

Ms. Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

RE: P920015
Transvene™ Lead System
Filed: April 1, 1992
Amended: September 21, 1992

Dear Ms. Marrone:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial scientific review of the above referenced premarket approval application (PMA). We regret to inform you that on the basis of this review, we have concluded that the PMA lacks information needed to complete the review and determine whether there is reasonable assurance that the device is safe and effective for its intended use.

We recognize the potential public health significance of this device and acknowledge the separate discussions underway to expedite the review. However, because of this lack of information, review of the PMA cannot continue and, accordingly, we have listed the following significant deficiencies which require the responses as indicated:

1. To clearly establish the purpose of the clinical data in the PMA application, please provide the following:

   a. the hypothesis and the objectives of your clinical study;

   b. a discussion of (i) how your clinical study addresses the use of a control, which is relevant to all clinical studies, (ii) the appropriateness of the AICD™ as a historical control, and (iii) your rationale for not using a concurrent control during an implantable cardioverter defibrillator (ICD) study;

   c. the endpoints of your study; and

   d. how the data provided in the PMA application support the specified endpoints.

2. Based on data provided in your PMA application, please prepare table(s) which include a side-by-side comparison of the PCD® Transvene™ and the PCD® Epicardial System and the PCD® Transvene™ and Ventak P AICD™ populations. The table must also include the inclusion and exclusion criteria which were used for each study. You must include a discussion of how these data may or may not represent a valid comparison, and other comments which justify and support the use of these groups as controls.

3. An update of the PMA clinical study population must be provided. The update must include the data as presented in the PMA application, and must include the clinical experience in the use of the new anchoring sleeves, which are aimed at decreasing the incidence of dislodgement, and a summary of the clinical experience (spontaneous treatment efficacy of ventricular tachycardia (VT) and ventricular fibrillation (VF), observations and complications, number of patient deaths and overall survival) of the patients followed for a year or more.

4. Please provide a clear description of how you identified the "patient who did not meet the implant criteria." Please discuss your implant criteria and how implant testing attempted to satisfy protocol requirements.

5. Of the 214 patients who did not meet the implant criteria and yet were implanted with the device, 170 patients had successful defibrillation with 24 Joules (J). Please provide an update of the clinical experience on these patients, as described in item 3 above. Also, please discuss how your proposed labeling will address this protocol deviation. Will implant criteria be changed?

6. There were 20 patients among the 214 who did not meet the implant criteria and were implanted without the 10 J safety margin. An update of the spontaneous episode experience in the treatment of VT and VF in these patients and the overall survival must be provided.

7. Table IK-4, page 151, compares the patients meeting the implant criteria to those who did not meet the criteria. However, many of the percentages were presented without numerical support. Please provide the appropriate numbers.

8. Please provide an update on the patients who are implanted with the Transvene™ System and were not counted in the PMA population. The update must include a summary of the clinical experience as referenced in item 3 above.

9. Based on your study protocol, please differentiate between defibrillation threshold (DFT) testing and lowest energy to defibrillate (LED) testing. Based on the individual patient report forms of the 757 patients, how many patients underwent what is described as DFT testing and how many had LED testing? Samples of the patient report forms showing the scheme of testing which was

categorized as DFT and LED testing must be provided. Please discuss how the DFT and LED data were reported and presented in the PMA application.

10. There is a statistically significant difference between the mean DFT obtained with the RV-CS-SQ lead configuration and the mean DFT obtained with the other lead configurations. How do you account for this difference? Was the DFT as reported and discussed for all lead configurations obtained using an identical or similar scheme? Please discuss. You must document that there were no significant differences between the scheme for performing DFT and LED testing between the Transvene™ and PCD® Epicardial patient populations, if that is the case.

11. Please elaborate on how the comparison of DFTs obtained from the PCD® Epicardial Lead study and the Transvene™ study can be considered as a valid comparison in that the majority of the patients (b)(4) (75.3 percent)) in the Transvene™ study were programmed with the sequential pathway an(b)(4) 23.4 percent) were programmed via the simultaneous pathway. The majority of the patients (b)(4) (65.2 percent)) in the PCD® Epicardial study were programmed with the single pathway. Based on your PCD® Epicardial study, please discuss the DFTs or energy requirements obtained with the use of the single defibrillation pathway versus the sequential and simultaneous pathways.

12. Please discuss the time between detection and delivery of therapy of the Transvene™ System versus the PCD® Epicardial System.

13. On page 125 of the application, please explain and/or discuss what is meant by "a 2:1 VF sensing margin", how it is determined, and if the patients met the criteria.

14. Of the 329 patients who were followed for 6 months, 130 patients had spontaneous episodes. What was the average number of VT and VF episodes per patient? Of the patients followed for a year, how many had spontaneous episodes of VT and VF and what was the mean number of episodes per patient in this group?

15. On page 130, Table IF-4, you report that there were 5362 episodes of VT successfully terminated. On page 131, paragraph 2, you state that (b)(4) (b)(4) (0.8 percent) episodes of sinus tachycardia or atrial fibrillation. Are these patients included in the success or failure category? Nine hundred and sixty-four episodes of VF were reported, however, 75 episodes were not actual VF. You must clarify how the successful and ineffective therapies and failures are discerned and categorized. Please prepare a table which includes a category of ineffective therapies with actual patient numbers and percentages. In addition, what assurance is there that an episode of supraventricular tachycardia or atrial fibrillation is not misinterpreted as VT or VF by the physician and considered a successful therapy?

16. Table IM-6, page 173 must be modified to include a column on inappropriate therapy or therapies delivered as the device was programmed so that the percentages add up to 100 percent.

17. On page 162, Table IL-2 lists a category "Fail to Cardiovert/Defibrillate" as 0.8 percent. Please clarify. If a patient survives an episode of an inappropriate therapy, is it categorized as a success? Please discuss. The tables must include percentages with the representative numerical support.

18. There were 38 inactive patients reported in Table IH-1, however, 34 patients were reported to be no longer active. Please clarify.

19. Please discuss how the 1 year sudden cardiac death survival, as reported in Table IF-2 page 128, was calculated. The numbers and an explanation of patient classification must be included. Was every patient included who had a prior cardiac arrest regardless of the arrhythmia?.

20. On page 177, the number of patients must be provided so that the percentages and calculated p-values can be confirmed.

21. Table IV-C, page 649 of the original submission shows a comparison of patient variables for the three lead systems and provides p-values for the variables tested, but the hypothesis was not clearly stated. Please state the hypothesis and discuss the p-values obtained when reporting by primary indication, and the chi-square test of the data set and how it was computed.

22. For purposes of justification of data pooling and data analysis of Table IV-C, please discuss why the multiple statistical significant difference was not adjusted at a 0.05 significance level using a more widely accepted procedure such as the Hochberg procedure (Dunnett and Tarnhoue: A Step-up Multiple Test Procedure, Journal of the American Statistical Association, March, 1992, Vol 87: pp.162-170).

23. You claim that confidence interval analysis was performed to compare the overall mortality of the PCD® and AICD™ populations. What was the confidence interval?

24. Please clarify and/or discuss the following regarding Table XB-1, page 378, Volume 2:

    a. the total number of patients in the Ventak P population (292) versus those reported by primary indication (291); and

    b. a chi-square test of primary indication, using the (b)(4) computer software, yields a p-value of nearly 0. This is statistically significant, indicating the PCD® and Ventak P populations are significantly different.

25. Please discuss the incidence of inappropriate therapies reported as observations in the Transvene™ study. It appears as if there has only been a slight improvement over the PCD® Epicardial study as it relates to programming and patient management (drug therapy). Please discuss the experience of both studies and how the labeling supports effective programming of the device parameters and the use of the Onset and Stability algorithms. How many patients in the Transvene™ study have the Onset and Stability algorithms programmed ON? At what interval during the study were the majority of patients programmed with the algorithms? Your experience in the treatment of induced and spontaneous episodes with use of the algorithms must be discussed.

26. Please discuss the "device related" complications reported for the Transvene™ and the PCD® Epicardial System.

27. Please describe in detail the complications reported in the patients followed for a year.

28. There was a substantial increase in the number of infections reported in the Transvene™ study. Even though you discussed why there was an increase, based on your experience, how will your labeling address the procedures for reduction in the number of infections? Please validate these procedures.

29. A discussion of your experience in the use of the different entry sites for the placement of the Transvene™ leads, and how your labeling assists in the selection of an entry site, must be provided.

30. Of the 22 deaths, 15 systems were explanted and returned for analysis. The results of the analyses (PCD® and Transvene™ leads) must be provided. What did device interrogation reveal? How many of the 41 Transvene™ lead systems which were explanted were returned and analyzed? How long were the leads implanted? A description of the protocol for analysis and the results of the analyses on all leads and devices must be provided. The PMA application must document how your study has addressed the need for the return and analysis of all Transvene™ leads and the PCD®.

31. Please discuss the circumstances surrounding the death of the patient who died 22.5 months post implant. What did interrogation of the device reveal?

32. Of the perioperative deaths, how many devices were programmed OFF? Please discuss the circumstances surrounding each death. The number of perioperative deaths must be reported in a table and be identified as sudden cardiac, non-sudden cardiac or non-cardiac. Were there other deaths when the device was programmed OFF?

33. You state that there have been no reported patient deaths in the group with a 1 year sudden cardiac death survival and overall

actuarial survival of 100 percent. Does this include the perioperative deaths and the patients who have been followed out for a year?

34. Please provide an engineering drawing of each Transvene™ lead model which identifies the segments of the lead and a description of the tests that each segment and the full lead body underwent.

35. Since flex testing exerts a considerable amount of stress on the lead, and is essential to life testing, why was it considered that (b)(4) cycles at a bend radius of (b)(4) inch per lead model over (b)(4) month period would be sufficient? Describe how the full lead and different segments were flexed. Did you do a finite element stress analysis to validate the flex testing stress?

36. In light of the failure of your platinum sputtered polyurethane bradycardia pacing leads, and since the Transvene™ lead Model 6966 is also a platinum sputtered polyurethane lead, please provide documentation regarding the failure mechanism of the pacing leads and all relevant information pertaining to these cases. How can we be assured that the failure may be restricted to the bradycardia pacing leads? Based on your testing to date regarding the pacing leads and the testing of the Model 6966 lead, discuss the potential and the probability of failure of the Model 6966 lead. A side by side comparison of the Model 6966 and the 4,000 series bradycardia pacing leads must be provided. The comparison must include material, design, dimensions, function, tests performed and a schematic drawing.

37. A copy of the Summary of Safety and Effectiveness which includes the updated data must be provided.

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period up to 180 days. As provided by 21 CFR 814.37(c), you may decline to submit a major amendment requested by FDA in which case the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

As provided under 21 CFR 814.44(g), FDA will consider this PMA to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA amendment. You may, however, amend the PMA within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA with in the 180-day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA and will be assigned a new number.

You may amend the PMA to provide the above requested information (12 copies), voluntarily withdraw the PMA (3 copies), direct CDRH to complete processing the PMA without the submission of additional information (3 copies) or request an extension. The required copies of the amended PMA should include the FDA reference number for this PMA and should be submitted to the following address:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

Upon receipt of an amendment adequately addressing the above requests or a written response declining to submit the requested amendment, CDRH may schedule an advisory panel meeting at which your PMA will be reviewed. You will be notified of the location and date of this meeting should one be necessary. In order to provide adequate time for CDRH and advisory panel review, information received by FDA less than 6 weeks in advance of any scheduled advisory committee meeting will not be considered or reviewed at the meeting and may delay consideration of your PMA until a subsequent advisory committee meeting.

If you have questions concerning this deficiency letter, please contact Doris Terry at (301) 427-1018 or Arnold Alpert, Ph.D., at (301) 427-1186.

Sincerely yours,

F. Alan Andersen

F. Alan Andersen, Ph.D.
Acting Director
Office of Device Evaluation
Center for Devices and
Radiological Health

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville MD 20850

Ms. Jennifer Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

AUG - 6 1992

Re: P920015
Transvene™ Lead System
Filed: April 1, 1992

Dear Ms. Marrone:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial scientific review of the above referenced premarket approval application (PMA). We regret to inform you that on the basis of this review, we have concluded that the PMA lacks information needed to complete the review and determine whether there is reasonable assurance that the device is safe and effective for its intended use.

Because of this lack of information, review of the PMA cannot continue and, accordingly, we have listed the following significant deficiencies which require the responses as indicated:

1. Discuss how the use of a (b)(4) prevents tissue in-growth in the Model 6963 lead. Where is the adhesive placed? From experience, discuss the use of polyurethane and silicone in leads to prevent tissue in-growth.

2. Please provide the results of mutagenicity testing for the (b)(4) and the (b)(4) (anchor sleeve). If the tests have not been done please provide a justification for not doing so.

3. Provide a description of the helix electrode fixation tool and of the tests to verify the torsional force for implanting the helix electrode.

4. Based on your experience, identify the minimum number of flex cycles that a lead should withstand. Also, give the stress level exerted on the Model 6907 lead (from which the median failure time of (b)(4) cycles was observed), and on the Transvene™ leads.

5. Since the electrode coil is flexed separately from the insulated conductor, discuss the reliability of the section where the electrode is coaxial to the conductor. Is there friction between the electrode and the conductor when the section is flexed?

6. The Model 6999's (b)(4) electrode coil fails at a much lower flex cycle than the (b)(4) electrode coil. Discuss the reliability of the (b)(4) electrode coil, and the effects of its failure on the performance of the lead.

7. Please discuss how patient treatment is affected if one or two of the electrode coils of the Model 6999 patch lead becomes damaged.

8. Please specify the section of each lead assembly that was flexed during life testing. Does this section include the electrode coil? The results of the tests should be included.

9. Provide an update of the (b)(4) month life test.

10. The data indicate that a new lead is used for each (temperature tolerance, crush load, or life) test. Correlate the results from those tests to the worst case condition where the same lead has to face temperature differences, crushing, and flexing. Why was sequential testing not performed?

11. Discuss the differences in battery life or energy requirements between the epi-lead system and the Transvene™ system.

12. An update of the chronic animal studies should be provided.

13. An update of the clinical experience of the Transvene™ Lead System should be provided. The update should include all additional patients and the clinical experience to date. The data should be presented as done in your original PMA application, and should include, e.g., implant and follow-up data, lead orientations including patch location, spontaneous episode experience, analyses by different groups, complications/observations, and survival analysis. All remaining deficiencies listed below which pertain to your patient population should be addressed using the updated patient group.

14. Please discuss your clinical data which support the claim which states that the Transvene™ Lead System improves both perioperative and long term patient morbidity.

15. Based on your experience and on the data as reported in the literature, what is the percentage of patients who have been found unable to withstand a thoracotomy?

16. Data such as treatment efficacy, complications and survival analysis on the patients followed for 6 months should be provided.

17. Please discuss your clinical experience (treatment efficacy, lead orientation, complications and survival rates) of the patients who have been followed for 1 year and more.

18. Provide a detailed discussion of the clinical experience (implant duration, lead orientations, spontaneous episodes, treatment efficacy, survival analysis, complications, etc.) of the patients who did not meet the implant criteria and were implanted with the Transvene™ System. Also discuss the experience of the patients who were implanted without the 10 Joule safety margin.

19. A breakdown of the different lead orientations within the patient population, and the treatment efficacy reported for each configuration should be included.

20. Based upon your clinical experience, the Physician's Manual should recommend the sequence of testing with the different lead orientations during implant.

21. Please provide the P-values as listed in Table IV B and IV C of the original PMA application for the new patient population.

22. Please discuss the reasons why some patients dropped out of the study, either withdrawn alive or lost to follow-up. There were 224 patients at 1 month and only 154 patients at 3 months. Please explain the difference of 70 patients during this 2 month period.

23. For the comparison of complications/observations rates for the PCD™ versus the AICD™, please provide the following:

    a. the number of complications and patients for the PCD™ and AICD™ populations;

    b. the clinical success/failure criteria used for "Failure to Cardiovert/Defibrillate and Inappropriate Problematic VT/VF Therapy Delivery"; and

    c. a discussion of the pocket infection rate of the PCD™ and the AICD™ and the lead related complications of the PCD™ Transvene™ System versus the PCD™ Epicardial System.

24. Some Transvene™ patients were also evaluated with the Model 10388 hollow can electrode. Please compare the infection rate of these patients to those who did not undergo the hollow can evaluation.

25. Please discuss and/or provide the following regarding the 1 year actuarial survival comparison of mortality between the PCD™ and the AICD™:

    a. the statistical test that was used to compare survival; and

    b. the two survival or life tables by year of follow-up.

26. Please discuss the statistical techniques used to derive the P-values in Table XI G-2, page 862, Vol. 5 and Table J-2, page 54, Vol. 1.

The following additional deficiencies were noted in this initial scientific review and the indicated responses should be provided:

1. Discuss the properties of polyurethane which make it the ideal insulation material for the 6966 lead. Why was silicone not chosen?

2. Discuss the biostability tests (stress cracking, metal induced oxidation, etc.) performed on the two types of polyurethane. Why was a different polyurethane chosen for the inner coil?

3. Based on the results of the life test, what is the life expectancy of the leads? Please include your assumptions.

4. Provide a side-by-side comparison between the Model 6999 and the epicardial patch lead.

5. Discuss the possible interactions between implanted pacemaker leads and the Transvene™ leads. Also, discuss the effects of the leads on the tricuspid valve and the host vein.

6. The Transvene™ leads seem to tolerate crush testing better than the pacing leads. Please discuss the properties of the Transvene™ leads which support this capability.

7. Are there patients currently implanted with the Model 6895 and 10317 patch leads? If so, please provide a breakdown of the clinical data, e.g., complications, survival, etc. for each lead.

8. Please list the reasons for not performing pre-hospital discharge testing.

9. The number of spontaneous episodes of the patients followed for 6 months and beyond should be provided.

10. A copy of the Summary of Safety and Effectiveness with the updated clinical data should be submitted.

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period up to 180 days. As provided by 21 CFR 814.37(c), you may decline to submit a major amendment requested by FDA in which case the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

As provided under 21 CFR 814.44(g), FDA will consider this PMA to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA amendment. You may, however, amend the PMA within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180-day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA and will be assigned a new number.

You may amend the PMA to provide the above requested information 12 copies, voluntarily withdraw the PMA (3 copies), direct CDRH to complete processing the PMA without the submission of additional information (3 copies) or request an extension. The required copies of the amended PMA should include the FDA reference number for this PMA and should be submitted to the following address:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

Upon receipt of an amendment adequately addressing the above requests or a written response declining to submit the requested amendment, CDRH may schedule an advisory panel meeting at which your PMA will be reviewed. You will be notified of the location and date of this meeting should one be necessary. In order to provide adequate time for CDRH and advisory panel review, information received by FDA less than 8 weeks in advance of any scheduled advisory committee meeting will not be considered or reviewed at the meeting and may delay consideration of your PMA until a subsequent advisory committee meeting.

If you have questions concerning this deficiency letter, please contact Doris Terry at (301) 427-1018 or Arnold Alpert, Ph.D., at (301) 427-1186.

Sincerely yours,

for F. Alan Andersen, Ph.D.
Acting Director
Office of Device Evaluation
Center for Devices and
Radiological Health

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

JUN 17 1992

Ms. Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

Re: P920015
Medtronic® Transvene Lead System
Filed: April 1, 1992

Dear Ms. Marrone:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial review of your premarket approval application (PMA). We are pleased to inform you that we have made a threshold determination that the PMA is sufficiently complete to permit a substantive review and is, therefore, suitable for filing. The filing date is April 1, 1992, which is the date of CDRH receipt of the PMA.

Following receipt of a filing letter, an applicant is required by 21 CFR 814.20(e) to update their pending PMA 3 months after the filing date with new safety and effectiveness information learned about the device from ongoing or completed studies when the information may reasonably affect an evaluation of the safety or effectiveness of the device or may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling.

This updated reporting is limited to studies sponsored by the applicant or to which the applicant has reasonable access. The update report should be consistent with the data reporting provisions of the protocol. Please submit update reports in three copies as an amendment to the PMA and include the above PMA reference number assigned to the PMA.

This letter reflects the current progress of our review of your application. Please be advised that continued review of your application or any response to this letter may result in additional deficiencies.

The PMA cannot be approved until FDA has determined that the manufacturing facilities, methods and controls comply with applicable device Good Manufacturing Practice regulations (21 CFR Part 820). If you have not already done so, please notify CDRH as soon as possible in the form of an amendment to the PMA if there will be a delay in setting up your manufacturing facility for production of the device and provide the expected date that the facility will be prepared for an FDA inspection.

A meeting of the Circulatory System Devices Panel will be held at which your PMA will be reviewed. You will be notified of the location and date of this meeting. Any additional information to be included in your PMA must be submitted in the form of a PMA supplement amendment and be received by FDA at least 6 weeks in advance of the scheduled advisory committee meeting in order for FDA and the panel members to have adequate time to review the new information. Information received by CDRH less than 6 weeks in advance of a scheduled advisory committee meeting will not be considered or reviewed at the meeting.

For your information, there is an industry representative on this FDA advisory committee whose name, address and telephone number you can obtain by contacting the Committee Management Staff at (301) 443-4016. CDRH believes that the industry representatives will be better prepared to participate in panel discussions if they have been provided with a copy of the Summary of Safety and Effectiveness for review prior to the panel meeting. In accordance with 21 CFR 14.86(b), all panel members are subject to all rules and regulations adopted by FDA and the committee; therefore, even though the industry representatives usually are not given access to trade secret and confidential, commercial information, they are bound to protect the confidentiality of documents that would be sent to them in preparation for panel review of a PMA. If you would like the industry representative to have access to any portion of your PMA, including the Summary of Safety and Effectiveness, please provide a copy for that purpose and notify the executive secretary of the panel at (301) 427-1205. However, review of your PMA will not be prejudiced if you elect not to provide a Summary for industry representative review.

All correspondence regarding this PMA should be submitted in 3 copies in the form of a PMA amendment. Please address all submissions to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

If you have questions, please contact Doris Terry at (301) 427-1018 or Arnold Alpert, Ph.D., at (301) 427-1186.

Sincerely yours,

Debra Y. Lewis
for Philip J. Phillips
Director
Program Operations Staff
Office of Device Evaluation
Center for Devices and
Radiological Health

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

MAY 14 1992

Ms. Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576

Re: P920015
PCD Transvene System

Dear Ms. Marrone:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) is continuing to process the above named premarket approval application (PMA). Simultaneously with a review by the Office of Device Evaluation (ODE), the Office of Compliance and Surveillance (OCS) must review the manufacturing information in your PMA to determine that it is sufficiently complete and appropriately organized to permit FDA to determine whether your firm (or your contract manufacturer) has the capability of manufacturing your PMA device in accordance with (1) the conditions specified in the PMA application and (2) the requirements of the medical device GMP regulation.

The Division of Compliance Programs (DCP) of OCS has reviewed the manufacturing section of your PMA and believes that it lacks the information necessary to effectively complete a review and determine whether to initiate a PMA inspection (see enclosed). While the deficiencies outlined in the enclosure do not preclude further review of your PMA, if left uncorrected they may delay or preclude evaluation of your manufacturing process and final approval of your PMA application. We request that you respond as indicated. Please be advised that continued review by ODE of your application (including the manufacturing section) may identify additional deficiencies. Also, the OCS review of your response to this letter may identify additional deficiencies.

For your information a Guidance for Preparation of PMA Manufacturing Information was published on March 22, 1991 (a notice of availability was published in the August 20, 1991 Federal Register). It is also available as part of the PMA Manual Supplement which may be obtained from the Division of Small Manufacturer's Assistance at 1-800-638-2041.

Information supplied in response to the enclosed request should be submitted in the form of an amendment AND BE CLEARLY IDENTIFIED AS A RESPONSE TO AN OCS REQUEST IN YOUR REFERENCE BLOCK. FDA will consider the PMA to have been withdrawn voluntarily if you fail to respond in writing to this request for an amendment within 180 days of the date of this letter as provided under 21 CFR 814.44(g). You may, however, amend the PMA within the 180 day period to request an extension of time to respond. Any such request is subject to FDA approval and must justify the need

for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180 day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180 day period will be considered a resubmission of the PMA and will be assigned a new number. A resubmission should be complete and self-contained without reference to earlier submissions because of potential difficulties in assembling files from storage.

All correspondence regarding this PMA should be submitted in three (3) copies in the form of a PMA amendment to the address below and reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)
ATTN: MQAB
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

This letter reflects the current progress of our review of your application. Please be advised, however, that continued review of your application or questions arising from any response to this letter, may result in additional deficiencies being identified.

If you have any questions concerning this deficiency letter, please contact Frank Twardochleb at (301) 427-1128.

Sincerely yours,

for Philip J. Phillips
Director, Program Operations Staff
Office of Device Evaluation
Center for Devices and
Radiological Health

Deficiency List

The Office of Compliance and Surveillance (OCS) in the Center for Devices and Radiological Health (CDRH) has completed an initial review of your premarket approval application (PMA), P920004, with regard to the Good Manufacturing Practice (GMP) regulations. Please address the following issues and provide the requested documentation:

1. The Design Assurance Plan, Project 6884/6996, dated 2/7/91 for the new helix electrode, part (b)(4) is not representative of the manufacturing operations. The qualification report dated 4/16/91 does not address the effects of the sterilization process on the integrity of the helical electrode. [vol.2, pp.153-156]

2. Provide the locations of the biological indicators used during the sterilization validation and routine production for the 6966 lead. [vol.2, p.207]

3. Provide the product density and configuration pattern for the 6966 sterilization cycle. [vol.2, p.207]

4. Provide the maximum parameter of the humidity specification for the sterilization cycle of the 6966 lead. [vol.2, p.211]

5. The finished device evaluation for the 6966 lead does not adress the effect of sterilization on device performance. [vol.2, p.174]

6. The validation plan for 6963 lead does not address the effects of the sterilization cycle on device performance. [vol.3, p.327]

7. The process qualification report, (b)(4) does not address the effects of the sterilization cycle on the performance of the 6999 lead. [vol.3, p.335]

8. Provide the product location of biological indicator and spore inoculation for the validation and production sterilization cycles of the 6963 and 6999 leads. [vol.3, p.372]

9. Provide the maximum parameter of the (b)(4) exposure for the 6999 lead. [vol.3, p.376]

10. Explain the difference in the sterilization (b)(4) exposure parameters of the 7217B PCD Control Device between the two manufacturing facilities. The (b)(4) exposure parameter at the Rice Creek facility is (b)(4) minutes; the (b)(4) exposure parameter at the Kerkrade facility is (b)(4) minutes minimum. The Kerkrade facility does not specify a maximum (b)(4) exposure. [vol.4, p.415 and p. 432]

11. Provide the manufacturing methods, controls, and evaluation procedures for the facility identified as Medtronic Milaca, 900 6th Ave. N.E. Milaca, MN 56353. [vol.4, p. 437]

FOOD AND DRUG ADMINISTRATION

CIRCULATORY SYSTEM DEVICES PANEL

August 2, 1993

Bethesda Ramada
8400 Wisconsin Avenue
Bethesda, Maryland

This transcript has not been edited and FDA makes no representation regarding its accuracy

Proceedings by:

CASET Associates, Ltd.
3927 Old Lee Highway
Fairfax, Virginia 22030
(703)352-0091

List of Participants:

Jeffrey A. Brinker, M.D., Chair

Debra S. Echt, M.D.

Ronald M. Weintraub, M.D.

Mark H. Wholey, M.D.

Wolf Sapirstein, M.D.

Michael J. Domanski, M.D.

Gabriel Gregoratos, M.D.

Bruce A. Perler, M.D.

J. Lawrence Stevens

Salim Aziz, M.D.

Gulshan K. Sethi, M.D.

Tony W. Simmons, M.D

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P R O C E E D I N G S

DR. BRINKER: It's now 8:30. I'd like to call this session of the Circulatory Systems Device Panel to order. My name is Jeff Brinker, and I am acting chairperson for this session. I'm from Johns Hopkins University, and I suppose that one of the reasons that we've waited until the last minute is that a number of our panelists haven't made it in. Presumably they are at the Hubert Humphrey Building, or some other area along the Beltway. But I think we can go ahead now.

To start, we'll just have the panel who is here introduce themselves, and then allow Wolf to read the opening sermon. Mike, do you want to start?

DR. DOMANSKI: I'm Mike Domanski, National Heart, Lung and Blood Institute. I'm a cardiologist.

DR. SAPIRSTEIN: Wolf Sapirstein. I'm the executive secretary of this panel, and the chief medical officer at the Office of Device Regulation, Division of Cardiovascular, Respiratory and Neurological Devices.

DR. ECHT: Debra Echt, a cardiologist from Vanderbilt University.

DR. GREGORATOS: Gabe Gregoratos, University of California at Davis.

DR. AZIZ: Salim Aziz from the University of Washington in Seattle, cardiac surgeon.

DR. SIMMONS: Tony Simmons, cardiologist, Wake Forest University.

DR. STEVENS: My name is Larry Stevens. I'm the industry representative on the panel.

DR. BRINKER: Fine. Now Wolf will read the conflict of interest statement.

DR. SAPIRSTEIN: The following announcement addresses conflict of interest issues associated with this meeting, and is made a part of the record to preclude even the appearance of a conflict.

To determine if any conflict existed, the agency reviewed the submitted agenda and all financial experiments reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests. However, the agency has determined that the participation of certain consultants with financial interests are not so substantial as to be deemed likely to affect the integrity of a service which a government might expect from such employees, and the need for certain members whose service outweighs the potential conflict of interest created by the financial interests involved is in the best interests of the government.

Therefore, waivers have been granted to the following employees. Dr. Debra Echt is an unpaid principal

investigator for a product that competes with an application that will be discussed today for an implantable cardio defibrillator. A waiver has been granted for her participation in this matter. She is also an unpaid clinical investigator for an application that will be discussed today for a non-thoracotomy defibrillation lead system. A limited waiver has been granted for her participation in the discussions, but she will not vote on this application.

Dr. Jeffrey Brinker is an unpaid investigator for an application that will be discussed today for a balloon catheter for percutaneous transveneous mitral commiseratomy. A limited waiver has been granted for his participation and discussions, and as chairman, but he will not vote on this application in the event there is a tie. He will however be permitted to vote on the other two applications if there is a tie.

Dr. Tony Simmons is an unpaid investigator for a closely related product to one of the applications to be discussed today. Since there is no funding to Dr. Simmons or his employer, a full waiver has been granted for him to participate in this matter.

A copy of these waiver statements may be obtained from the agency's Freedom of Information office. We would also like to note for the record that the agency took into

consideration other matters regarding Dr. Brinker, Dr. Simmons and Dr. Echt, and found that they have other involvements with companies that could potentially be affected by the committee's deliberations. However, since these matters are not directly related to the specific matters before the panel, the agency has determined that these employees may participate fully in the panel discussions, except for those limitations that have already been mentioned.

We also would like to disclose that Dr. Gulshan Sethi, Dr. Michael Domanski, Dr. Ronald Weintraub have involvements with firms that could be affected by the committee's deliberations. These matters are not directly related to the specific matters before the panel. Therefore, the agency has determine that they may participate fully in the panel discussions today.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations to disclose any current or previous

financial involvement with any firm with products they may wish to comment upon. We generally classify these financial interests as compensation for time and services of clinical investigators and their staff, a direct stake in a product under review, such as the patent holder or owner shares of stock, and thirdly as owner or part owner of a company.

At this time, for the benefit of the panel members, their vote on recommendations should be in the nature of an approval, an approval with conditions, or non-approval of the PMA application, and recommendations are to be based on submissions made available with this PMA, which should stand on its own data and not be related to any other similar device available. Reasons for non-approval may also be added by members so voting, and can be for lack of safety, lack of efficacy or false or misleading labelling.

With the summer doldrums, we are short of some members. Under the terms of the panel advisory committee, we have taken this opportunity of making Dr. Tony Simmons and Dr. Salim Aziz voting members for this panel's session, if they are agreeable.

Dr. Brinker, can I have a few moments for another housekeeping procedure? Dr. Gregoratos has served this panel since 1988 as a consultant, voting member and chairman. Prior to that, he had appeared in 1977 as a panel member for four years. During this time, we have used his

expertise and knowledge which he has provided unstintingly. He has been associated with efforts to change the way this panel has been run. He has been able to develop consensus of a body of physicians, which is extremely difficult to accomplish. In appreciation of all his work over these many years, and his agreement to stay on as a consultant, the Commissioner has presented Dr. Gregoratos with this certificate and this letter of approval. Thank you. Dr. Gregoratos.

The other situation, Dr. Chakir has resigned from the FDA and is now present on the other side of the table, and Dr. Tom Callahan is acting director, sitting over there.

DR. BRINKER: I'd like to offer my congratulations to you, Gabe, also for the job that he has done over the last year, and hope that the panel with his assistance will continue to do such an admirable job.

Is there any old business to be undertaken? Any new business prior to the open committee discussion? Then I think we should launch into the first application, which is premarket application P920015, a transvene lead system from Medtronic. I would like the people from Medtronic and their physician investigators to identify themselves, please, also, for the non-employees of the company to give their classification as to their involvement with the company and the device. Class one compensation for time and services,

class two, a direct stake in the product or stock in the company, and class three, owner or part owner of the company. I dont think any of those exist, but I would like the company representatives to identity he or she and start the presentations.

MS. MARRONE: I'm Jennifer Marrone, manager of regulatory affairs.

DR. SCHABER: I'm Dan Schaber, manager of clinical evaluation and product planning.

DR. NORENBERG: Sue Norenberg, senior clinical evaluation manager

DR. SAKUN: Valerie Sakun, senior clinical evaluation manager.

DR. ZIPES: Doug Zipes, cardiologist from Indiana University, consultant, class one.

DR. STEINHAUS: I'm David Steinhaus, cardiologist for the Heart Institute in Kansas City, class one consultant.

DR. BARDY: Gus Bardy, investigator, University of Washington, class two.

DR. BRINKER: Fine. Would you like to start?

DR. SCHABER: Good morning. My name is Dan Schaber. I'm the manager of clinical evaluation and product planning for the Medtronic tachyarrhythmia division. Medtronic has been involved in the research, design and

development of products to treat tachyarrhythmias for nearly two decades now. In the next few minutes, I will be describing the transvene lead system and providing an overview of the clinical results.

In February of 1992, the FDA's circulatory devices panel unanimously recommended for approval the PCD epicardial system. In February of '93, the system was market released. Extensive data that had been collected worldwide continues to demonstrate the safe and effective performance of the PCD epicardial system. During this presentation, I will give an overview of the transvene lead system, its components and how they operate together, and of the clinical results.

As you will see from the data, sudden cardiac death survival is not statistically different between the two groups. Ninety-nine point five percent were transvened versus 98.9 percent with the epicardial system. Overall survival is statistically better for transvene, 93.3 percent for transvene versus 88.6 for the epicardial system. Hopsital stays have been significantly reduced, seven days for transvene versus ten days for the epicardial system.

The transvene system includes the transvenous leads, models number 6963 superior vena cava coronary sinus lead, the 6966 right ventricular lead and the 6999 subcutaneous patch. The only difference between the

approved epicardial system and the transvene system is the inclusion of the transveneous leads which are here highlighted in yellow.

The transvene system offers the clinician another therapeutic option. His performance has been as good as or better than the PCD epicardial system. The lead on the far left is the right ventricular lead. In the center is the superior vena cava coronary sinus lead, and on the right is the subcutaneous patch.

As with our epicardial system, the transvene system employed bipolar sensing. Sensing occurs between the tip and the ring electrode in the standard bipolar configuration. Pacing occurs between the tip and the common defibrillation electrode. Except for patients with a prosthetic heart valve, any patient who is a candidate for the epicardial system is also a candidate for the PCD transvene system. There are people, however, who are candidates for the transvene system and not for the epicardial system. For example, people who have previous open chest surgery, where their risk for surgery is greater.

The PCD device was designed to treat both sudden cardiac death and sustained ventricular tachycardia. Specifically, the transvene indications are identical to those recently approved for the PCD epicardial system.

The system allows for greater versatility in lead

placement. It also can accommodate a wide variety of patients with differing anatomical and physiological conditions. A variety of lead configurations has been used successfully during an investigation of the transvene system. The three that are shown here were the predominant ones used in the study. With these three three-lead systems, energy can be delivered simultaneously or sequentially. In approximately 66 percent of the cases, this configuration, RV SVC sub-Q was used. In an additional 29 percent of the cases, RV CS sub-Q was used. These two configurations comprise 95 percent of the cases in the clinical data to be presented today. There were 95 percent of the cases that totally transvenous, RV CS SVC configuration was used.

Of the 897 patients who were screened for and ultimately implanted with a PCD system, 757 patients received a three lead transvene system, representing 84.4 percent of the population. After trial with the transvene system, it was determined that 97 patients, 10.8 percent of the population, should receive the epicardial system because of high defibrillation thresholds. Forty-three patients, or 4.8 percent of the population, received other transvene systems, including combinations of transvene and epicardial leads. The 757 patients who received the three-lead transvene system formed the basis of the data that I will b`

sharing with you today.

Now let me proceed to a brief overview of the clinical results. The PCD transvene trial began in October, 1989. The 757 implants occurred under a common worldwide protocol that was conducted to evaluate the safety and efficacy of the transvene lead system. The recently approved epicardial system was studied concurrently under an identical protocol at the same centers. The 742 patient data cohort followed for a mean of 16.3 months has been used as a comparison throughout this study.

The 757 transvene devices had a mean implant follow-up time of 11.7 months, and the longest follow-up time now exceeds three years. For this group, as you can see, the most frequent indication was sustained ventricular tachycardia. Sudden cardiac death was the indication in 37.1 percent of the patients, and the combination of sudden cardiac death and ventricular tachycardia was the indication in 13.1 percent of the patients. The distribution of indications between the transvene and epicardial systems is similar. Our analysis indicates that primary indication does not affect sudden cardiac death survival.

An evaluation of other patient care characteristics shows that except for gender, the PCD epicardial and transvene systems are not statistically different. There were more female patients who received the

transvene system. Our analysis indicates that this difference in gender does not affect the study outcomes. As you can see by the mean rejection fraction and New York Heart Association classifications, the majority of patients exhibited moderately depressed left ventricular function.

Now let's look at spontaneous episode efficacy. Episode efficacy is defined as the number of episodes that were converted divided by the total number of episodes treated. As you can see for the two populations, VT episode efficacy was identical, 98.4 percent. You can also see that 88.1 percent of the time, cardia pacing was successful in terminating the episodes of VT in the epicardial population and 91.4 percent of the time in the transvene population. The remaining episodes were treated by cardioversion.

For spontaneous VF efficacy, the two populations were not statistically different, 98.4 percent for transvene versus 98.7 percent for the epicardial system. In the transvene population, 89.1 percent of the VF facilities were treated with the first VF therapy.

For the purposes of the epicardial and transvene trials, a complication was defined as a medical event that had to had surgical intervention for resolution. Because of the differences between the two lead systems, the complications associated with each lead system are different. For example, dislodgement is a complication

inherent in the transvenous system, whereas it is not an issue with an epicardial lead system. For the purposes of the presentation, I will be comparing complications that may be affected by the lead system. Except for pace sense, there is no statistical difference in the incidence of complication rates between the transvene and epicardial groups. There were more pace sense complications -- 3.5 percent with epicardial versus 0.8 percent with the transvene system. Infection, 2.9 percent in the transvene group versus 2.3 in the epicardial group -- was not statistically different.

We were initially concerned with the incidence of lead dislodgment that we observed in the transvene trial. Because of this, we instituted a program of increased education of our clinical investigators and added a second anchoring sleeve to the leads. The incidence of lead dislodgement has steadily declined throughout the study. As you can see, the acute dislodgement rate was 5.3 percent, and now with the additional patients reported in the PMA, it is down to 1.6 percent. The chronic dislodgement rate was 6.1 percent, and it's now 0.7 percent.

As I said, all of the 757 patients in the populations had the single anchoring sleeve. We have an additional 439 patients reported in the PMA that had two anchoring sleeves. Our analysis shows that 80 percent of

the dislodgements occur within three months of implant. As you can see from this graph, the dislodgement free survival, the probability of having a dislodgement with two anchoring sleeves is 3.3 percent at three months, versus 9.2 percent with a single anchoring sleeve. We believe that our program of increased education and the addition of a second anchoring sleeve has significantly reduced our dislodgement rate.

Extensive survival analyses have been performed on the transvene and epicardial populations. Overall survival includes peri-operative mortality. Peri-operative mortality is defined as those deaths that occur within 30 days postoperatively. There have been 51 deaths in the 757 transvene patients, and 113 deaths in the 742 epicardial patients. Our survival analysis shows that sudden cardiac death survival probability at one year is not statistically different for the two groups, 99.5 percent for transvene versus 98.9 percent for the epicardial system. It also shows that the transvene system is statistically better in enhancing overall survival, 93.3 percent and 88.6 percent for the epicardial.

In summary then, the transvene system has been shown to be equal to the epicardial system in enhancing sudden cardiac death survival. It has been shown to be better than the epicardial system for overall survival, 93.3

percent with transvene versus 88.6 percent with the epicardial system.

Finally, the benefit of the transvene system is that it allows placement of an IUCD without opening the patient's chest, and therefore reduces hospital stay to seven days and ten days.

Medtronic has established a large and thorough training and comprehensive support capability for clinicians who treat tachyarrhythmias, including the use of our transvenous lead system. We will continue to provide this service for new users of the system. In the nearly four years of clinical trials with this system involving 69 investigators worldwide, we have conducted a thorough and extensive evaluation of the system. Our clinical investigators have reviewed this data and unanimously support our application to the FDA for PMA approval. It is with their support that we bring you the transvene lead system for review today.

DR. BRINKER: Thank you. Does that conclude your presentation?

DR. SCHABER: It does.

DR. BRINKER: We can have lights up, please, and have the FDA reviewer, Doris Terry, present her summary and concerns.

DR. TERRY: Good morning. The manufacturer,

Medtronic Incorporated, is seeking approval of the PCD transvene lead system. The primary objective of the study of the PCD transvene lead system include to evaluate and monitor the system in the detection and treatment of VT and VF, and to estimate the survival from sudden cardiac death and the overall survival. These data intend to lend support to the end points of the study, conversion, efficacy and survival from sudden cardiac death and total death. The PMA population consists of 757 patients implanted with the transvene non-thoracotomy leads in either of two PCD models, the 7217 B or the 7216 A. The performance of the PMA population was compared to the historical control, the ventach PICD population and a concurrent control, the PCD epicardial population.

As of February 1, 1993, the clinical experience includes data from 762 implants, 447 U.S. and 315 foreign, in 757 patients. Data from the PMA population stratified according to different sub-groups include the following: results of testing at implant, pre-discharge and the follow-up intervals, efficacy of the treatment of induced and spontaneous episodes of VT and VF, complications and observations, patient deaths and survival data. Three hundred patients had DFT testing at implant. The mean DFT was 14.8 jewels, 702 patients had lowest energy to defibrillate, or LED testing at implant. The mean LED was

16 jewels.

Regarding the spontaneous and induced treatment efficacy, 597, 79.9 percent of the patients, had a spontaneous VT or VF episode, or had VT or VF induced post implant. Four hundred and fifty-eight, 60.5 percent of the patients, had a spontaneous episode of either VT and/or VF. Ninety point seven percent of the VT episodes were successfully treated with VT therapy number one; 89.1 percent of the VF episodes were successfully treated with VF therapy number one. Sixty patients experienced 163 -- 1.6 percent -- spontaneous VT episodes when the PCD transvene system was ineffective in determining the arrhythmia. Sixteen patients experienced 31 -- 1.3 percent -- spontaneous VF episodes, when the PCD transvene system was ineffective in terminating the arrhythmia. Of the 657 patients followed for six months or more, 544 -- 82.8 percent of the patients, had an induced or spontaneous episode at pre-discharge or later. One hundred and 13 patients did not have a chronic episode, however, pace sense parameters were measured at the different follow-up intervals.

One hundred and 76 complications occurred in 147 patients. The complications included pocket infections, 24, lead fracture, nine, patch crinkling, seven, explants, four, and total lead dislodgement, 91. Two hundred and twelve

observations occurred in 178 patients. The observations included an appropriate VT therapy, 57, over sensing, 52, patch crinkling, five and total dislodgement, 12. Sixty-three PCD transvene systems were explanted, patient death, 22, infection, 22, heart transplant, nine, low battery voltage, one, PCD performance issues, four, integrated circuit problems, one, and lead problems, four.

The results of analyses on 42 PCDs returned indicated that the devices were performing within specification. Of the 42 PCD transvene systems returned, 23 lead systems or portions of lead systems were returned and analyzed. Of these, the helix of one model, 6966 lead, was damaged. The remaining leads were found to be within specification. The results of analysis of 19 lead systems are pending. It should be noted that one model, 6884, an earlier version of model 6966 lead implanted for 27 months, which was explanted due to heart transplant, exhibited metal ion oxidation upon analysis.

There have been 51 deaths, sudden cardiac, five, non-sudden cardiac, 31, non-cardiac, 15. Five peri-operative deaths, sudden cardiac, two, non-sudden, two and non-cardiac, one, are counted within the 51 deaths. The survival rates for the patients who were implanted with the transvene leads are as follows: sudden cardiac death, 99.5 percent, non-sudden cardia, 96.2 percent, all cardiac, 95.8

percent, non-cardiac, 98.1 percent, and overall survival, 93.3 percent. The peri-operative mortality rate is .7 percent.

The questions for the panel include the following. Number one, 113 patients did not have a spontaneous or induced episode of VT or VF after pre-discharge testing. Therefore, the performance of the system in the treatment of VT and VF was not assessed. However, the pace sense parameters of these patients were measured at the different follow-up intervals. Are these measurements sufficient in assessing the chronic performance and integrity of the lead system in these patients.

Number two. In light of the differences between the U.S. and foreign patients within the PMA population, are there any concerns about the poolability of the data.

Number three. A statistically significant decrease in the peri-operative mortality was demonstrated for the PCD transvene system versus the PCD epicardial system. However, there was a statistically insignificant decrease in the peri-operative mortality for the PCD transvene system when calculated from the intention to treat, as compared to the historical control. Are there specific concerns regarding the peri-operative mortality rates reported for the PCD transvene system versus the historical control.

Number four. Are there concerns regarding the potential risks for dislodgement of the lead and the reported incidence of infection. What are considered as acceptable rates of lead dislodgement and infection as they relate to complications and observations.

Number five. The results of analysis of an explant of a transvene lead model 6884, an earlier version of the model 6966, have raised questions about the lead's chronic structural integrity. Are there significant concerns which would question the reliability of the lead. Do the benefits of the transvene lead model 6966 outweigh the risk which might be associated with this potential for MIO.

In addition, the labelling modification as referenced in my review memo should be considered. The modifications include but are not limited to the following: diagrams which show proper insertion of the endocardial leads, and the various positions for placing the patch lead, efficacy data of the lead configurations via the different pathways, stronger language regarding the use of dual anchoring sleeves, information about how the incidence of infection might be reduced, and number five, recommendations regarding the use of the different lead configurations.

DR. BRINKER: Thank you. The panel discussion will be led by myself. I would like to start by saying that

I think the panel has some basic understanding of the potential benefits of a transvene lead system, since we did approve one in the not-too-distant past. Most of the questions will not be aimed at discussing whether a transvenous system is as good as an epicardial system or better, but rather, this particular transvenous system and its efficacy.

I would like to first start by asking for information on patients with concomitant dual chamber pacemakers. I think there is some reference in here that patients with pacemakers should have them removed or something toads that end, and I want to know, what is the experience with dual chamber pacemakers and the amount of hardware that is in the heart.

DR. BARDY: I don't have a whole lot of experience with dual chamber pacemakers and transvene lead systems combined, but of the two patients that I do have, I can comment on that. I have put in 140 transvene systems, so it's an infrequent event to have that need for having both.

Usually, if there is an episodic heart block, I will just rely on the device itself to pace the patient for VVI mode for backup needs. On occasion, we will use a single AAI or AAIR pacing mode for a pseudo dual chamber system, where we will use the PCD for backup, should the AV node fail, but the AAI unit primarily to maintain antigrade

conduction through the AV node and to supply chronotropic competence.

But in two patients, we have had experience with a dual chamber transvene system combined with a transvene PCD, and in both of those people, they came to me on referral after they had the transvene pacemaker inserted, and in both cases, the transvene ventricular lead was placed fortuitously about two or three centimeters away from the RV apex, which is where I place the endocardial defibrillation lead, higher up in the septum. In those cases, there is no problem with sensing. Because of the pacemaker spike, there was no under sensing of ventricular fibrillation.

I think that might be an issue had those leads been closer to the pace sense leads of the PCD. But if I were to have the need to insert both of those simultaneously, I think I would do the same thing, that is, place one, screw an electrode up into the septum, and another down by the apex, and that should be sufficiently far apart to avoid pacemaker spikes from the dual chamber unit from inhibiting of VF detection.

But I just haven't seen it in those two people. I specifically put a magnet over their pacemakers at the time of the epiduction. I think that has to do with the bipolar sensing of the PCD system, and it's pretty good with respect to that.

DR. ZIPES: We have two patients with the dual chambered devices, both of whom received the device because they needed atrial kick because of reduced cardiac function. Both are bipolar, and with care we were able to place the electrodes such that the size of the spike was sufficiently small in terms of what was sensed by the PCD, that it was not a problem, and that the spikes did not inhibit PCD function in the event of ventricular tachycardia fibrillation, which were induced in the patient during pacing to be certain that that didn't happen.

I think a unipolar pacing should be precluded, and is a potential danger in the concomitant hardware. It would be preferable not to have a second pacing system if one could avoid it, but the PCD at the stage that it's at now, without providing dual chamber pacing in some patients who need it, I think you are forced on occasion to have combined hardware in a patient.

DR. STEINHAUS: I was just going to add two other caveats that I have thought about in this regard. One is that you have to be careful you don't choose a pacemaker that is going to have a power on reset. There are some pacemakers out there which -- that's not different to the transvene system versus an epicardial system, but there are pacemakers which will power on reset after a shock, which you don't want that to do.

I think the other issue would be how many leads you have across the tricuspid valve. We have experience with multiple leads across the tricuspid value in our older pacemaker patients, and it does not seem to be a particular problem.

DR. BRINKER: Thank you. There is one patient who had considerable pain with cardioversion shocks, and actually asked for his device to be turned off, and let to a DNR state. The question I have is, do you have any sense of the amount of sensation a patient feels from a sub-Q patch placed over the muscle as opposed to a epicardial patch?

DR. ZIPES: The patient whose device was turned off and subsequently removed was my patient. There was a major problem with him, in that he has significantly reduced left ventricular function, would run a chronic sinus tachycardia and had a slow ventricular tachycardia, such that there was overlap between the two rhythms. The device would sometimes sense the sinus tachycardia as a ventricular tachycardia, pacing into the ventricular tachycardia in an attempt to terminate what it thought was a VT but was a sinus tachycardia, and then attempt to pace him out of that, and if that didn't work, end up giving him a shock. Despite manipulation of the device settings, drugs, et cetera, we could never adequately resolve this problem.

He eventually asked us to turn it off, and

subsequently surgically we removed the pulse generator. Presently he has long episodes, days on end of chronic ventricular tachycardia, sits in a chair at home, and when he gets sufficiently short of breath, he comes in and gets cardioverted and then goes home again.

It wasn't so much the pain per se, though the shock in the awake state was uncomfortable. But it was a chronic problem of the device putting him into the VT. It just got too much psychologically for him.

DR. BRINKER: But getting back to the point, is there a difference, do you feel, in your experience between the sensation from a sub-Q patch as compared to an epicardial patch?

DR. ZIPES: I don't think so. I think if we go back a number of years when we were first working with just a single lead cardioversion device to terminate ventricular tachycardia, our perception was, once one got above a half jewel or so, that you could then go from there to 20 jewels, and there wasn't a significant difference in pain perception. I think it represented a contraction of the intercostal muscles as a large contributor to that. My sense is that the patch really doesn't seem to change that perception very much from the single lead cardioversion alone.

DR. STEINHAUS: I think I can speak to that. I

actually test all of my patients afterwards, both the epicardial leads in patients and the transvene lead system patients. I test them awake, because I want them to feel what a shock is like. I've done this hundreds of times, and I would say there is absolutely no difference in the way they're felt. In fact, I had the experience of a patient who had a device taken out, an epicardial system, for the same reason that your patient did, multiple shocks and just couldn't stand the discomfort. I really, truly don't think there is any difference in the way they're felt.

DR. BRINKER: Thank you. There is a recommendation in here, establishing an effective defibrillatory lead system that perhaps a cutaneous patch can be used to examine whether a subcutaneous patch would be appropriate. Do you have the feeling that the cutaneous patch is a realistic mimic of the subcutaneous patch?

DR. STEINHAUS: I'd be happy to take a stab at that, too. That is the way I do my implants. I do them all with -- I use a paddle. I take the paddle off the old defibrillator and hook it up. The advantage of that is, it allows me to move it around the chest, so I can try to find the best position. In fact, it's truly amazing how well it does mimic. It mimics closely also the resistances, which is sort of surprising. I would think the resistance would change when you use the subcutaneous patch versus the trans-

thoracic paddle, and it's actually not all that much different. So we found it a very good correlation. What I typically do is, I test it with the trans-thoracic paddle first with most of my shocks, and then I'll go and confirm that using the patch, and they are very similar.

DR. BRINKER: If I remember the data correctly, there were only about five percent of the patients that had a totally transvene defibrillatory system. Is that a function of a decreased efficacy of that configuration, or is that a function of vascular access, or what, in your feeling? I just point it up, because it's quite different from the other transvene system that we had to evaluate.

DR. BARDY: I think a lot of that is historically based on what lead systems were initially used and what you see in the database reflects initial recommendations for this particular lead system. My experience is that the flexibility of the system allows you to choose whatever you want, totally transveneous or mixed with a patch or a two-lead system. I have patients in all categories.

More lately, my experience has been to use simply two leads, and break away from older habits that work fine and use three leads when it doesn't. So I think that three-lead configuration with a patch is in large measure what we started out with in the early investigations, and as we've gotten more experience, we use two leads as well as three,

sometimes three totally transveneous lead systems. It's a matter of patient preference.

DR. BRINKER: Clearly it would be nice to have some logic behind -- if you can get away with two, why would you put three leads, especially an intravascular lead that has a high incidence of dislodgement, albeit steps have been made to improve that. One easy answer to this is that each patient is individual, and you would like to have the benefit to pick and choose. But is there a difference in defibrillatory efficacy between the configurations as a whole?

DR. BARDY: Sure. I've done plenty of studies to demonstrate that. But I guess from a practical perspective of an everyday user, one can easily make a series of recommendations on how to proceed through the implant procedure in a logical way without a lot of variations starting with that, with a high SVC to RV lead system, two leads, very efficient in defibrillation, because the vector is an appropriate vector, and if that doesn't work, to add a high subcutaneous patch through that same incision. That would be my recommendation for the initial approach to implantation.

DR. BRINKER: That kind of thinking, I think, is not clear in the labelling. I think there needs to be some recommendations along those lines to physicians, albeit they

can have the option of doing what they think is best in the individual case. I think that it would be good to have some real instruction as to what a logical course to take is, based a little bit more than on whether you want to put in a CS lead or not.

DR. BARDY: I wasn't even talking about a CS lead, unless there was trouble in defibrillation.

DR. BRINKER: I understand.

DR. STEINHAUS: To answer that question a little bit differently, why weren't there more -- I think the system was built as a three-lead system. To me, and the reason why I implanted the protocol is, it was billed as a subcutaneous patch. I'm not perhaps as creative as Dr. Bardy in trying to figure out different ways -- and I mean it seriously -- of using the device. But the reason why I think most of the implants were done that way is because that's the way the protocol was written, to be using a subcutaneous patch the two other leads.

The system is a three-lead system. I don't think it's -- I think it can be modified to a two-lead system. I think whatever works, works. But I think basically what we were asked to utilize in the protocol is --

DR. ZIPES: That is true, but there is a practical issue. At our institution, the surgeon implants the device with one of the electrophysiology people in attendance.

This is done in the OR. The surgeon -- not to be disparaging -- has not got a lot of experience finding the coronary sinus with a catheter, certainly nowhere near as much as we electrophysiologists do. Also, we have portable fleura, which is not as good as the fleura in our lab. He would make a few passes, give up, and then we would end up with an SVC RV apex and patch lead in the vast majority of our patients. It was a sheer practical decision, based on how it was being pt in.

In our labelling there are recommendations, and the recommendation is to start with RV SVC sub-Q. That has to do with the practical issues that Dr. Zipes is talking about, and with the fact that the majority of the data in the application is with that lead configuration. That is why we recommend that as the starting point.

DR. BRINKER: I think that's important from another point of view. There is a suggestion that the more times you fibrillate a patient to determine the efficacy of a system, the worse the prognosis might be for that patient, especially if you turn out after multiple manipulations with the transvene system, that the patient has to go onto an epicardial system. While you carefully say that these things should be kept to a minimum before you decide to go an epicardial system, is there any guidance that you can give -- and I guess it's patient dependent, but how many

times do you think it's reasonable to fibrillate a patient using different variations of the schema?

DR. BARDY: This is an interesting topic, because I don't think it relates to the number of times as much as it relates to the pause between inductions. I routinely do a great number of VF inductions on my patients, and I have no operative deaths out of 140, and I have a 98 percent implant success rate. But I do routinely 14 VF inductions in the operating room.

The key here is to instruct pausing between inductions rather than limiting the number of inductions. Waiting five minutes between a VF induction I think is the crucial issue, and a prompt rescue. One can go logically through a sequence of recommendations, lead system A, lead system B, lead system C and D, and that is four inductions before you can go through four steps and know yes or no, whether you've had an adequate defibrillation. Pick a number, 24 jewels, 20 jewels, 18 jewels, test configuration A. Does it work or not. If it works, you're probably there. If it doesn't work, move on to the next logical step and do so in the labelling very easily. I don't see that as a problem.

DR. BRINKER: You don't have to convince me, but I think there should be this guidance. Maybe if it's a general consensus about the interval between

defibrillations, but I think it would be helpful for people to get some better insight. I think that these things are going to be used because they are easier than putting in epicardial systems. I think many more patients are going to get these kinds of devices than previously had them. In many cases, it's going to be -- unlike your situation, Dr. Zipes, I know many of our EP people are putting in skin to skin systems of this sort. So I think the check and balance of having somebody else put in the system if you say the patient needs it is going to be a single operator. I think these kinds of guidelines will be helpful.

The next question has to do with the right ventricular lead. I notice that the inner and middle installation is (b)(4) (b)(4) That polyurethane has a mixed history associated with it. Can you tell me why you chose to use this instead of either the (b)(4) or (b)(4) for this lead?

MS. MARRONE: The design of that RV lead was based on a very similar Brady lead, screw-in lead. We have extensive history on that Brady pacing lead. Due to the similarities in design and wanting a screw-in lead for our RV lead, it was the most timely design that we had, and we also felt we had adequate chronic performance on that type of design, our Brady history.

DR. SCHABER: In addition to that, it has to do

with the size of the lead. Silicon increases the size of the lead, and in order to keep the lead a more manageable size and to have good handling, that was the reason for the selection of the polyurethane.

DR. BARDY: That size issue is not a minor one. The choice of (b)(4) over (b)(4) interdigitates with two other issues, true bipolar sensing versus integrated bipolar sensing, and crush injury. I think trying to have true bipolar sensing and a bipolar lead, if you were into (b)(4) you would probably end up with many more crush injuries between the clavicle and the first rib, where most people are going to pt this in. I think that alone outweighs the use of (b)(4) Plus the need for bipolar sensing which I favor strongly over integrated sensing because I think it enhances post-shock detection of ventricular fibrillation. I think those are other issues that might outweigh any concerns about (b)(4)

DR. BRINKER: I'm not sure that there is a difference between (b)(4) and (b)(4) in terms of the thickness of the material that you would use, if size was the primary concern. I am concerned with the MIO that has b been noted already in these leads, and the difference between a cosmetic problem and a failure of the lead may be only microns.

If the middle installation fails, can you get

make-break signals that would interfere with the functioning of the device?

DR. SCHABER: You could get make-break functions which could lead to over sensing and false positive therapies. But we have not seen that.

DR. BRINKER: Okay. This is an area of concern, I think. Obviously, you follow these for the longest duration leads you have, or what?

DR. SCHABER: Over three years now.

DR. BRINKER: Right, but from our past experience with other leads like this, you really don't see a big dropoff for four or five years, do you?

DR. SCHABER: That is correct. As Jennifer was saying earlier, this is patterned after one of our Brady leads that has longer duration.

MS. MARRONE: And actuarial survival on that similar design is --

DR. SCHABER: It's 99.7 percent at three years.

DR. BRINKER: The subclavian crush business. You advise physicians to use a lateral insertion site, but any subclavian stick is going to result in a medial placement of the leads, no matter what you do. It's not very easy to put these leads, all of them, especially if you use a three-lead system, through a cephalic vein, unless you use an introducer technique. Do we have any idea -- I guess you

do, since I saw the numbers, but how many three-lead systems have been placed through a cephalic vein?

DR. SCHABER: In general, two-thirds of the patients we implanted have used subclavian versus a cephalic vein approach. In terms of the three-lead totally transveneous, I don't think we have it broken out that way.

MS. MARRONE: In the patients that received a totally transveneous system, a cephalic vein cutdown was used for RV placement, and then a subclavian stick was either used for the CS and the SEC position. They are not all through the subclavian. They're using two vein accesses.

DR. BRINKER: But if you use an introducer technique, you could probably put as many of these things -- because we all have to go through the same vein, after all. They all go through the subclavian, and the cephalic is usually sacrificed once you put in more than one lead through it, anyway. So basically, you just have a more lateral access to the cephalic system.

I noticed with some glee that you only had four episodes of subclavian axillary thrombosis, which is kind of unique with this, I would imagine, especially if you put in three leads. Nothing more along those lines has surfaced. You're not getting any more than you reported.

DR. SCHABER: No.

MS. MARRONE: In fact, none of the subclavian vein thrombosis was reported in the patients with totally transveneous systems. There has been none of that reported in the totally three-lead transvened patient group.

DR. BRINKER: The next question I have concerns lead dislodgement, which is all too common with this system. Perhaps it has been fixed by a double anchor, and if it has, I think that it should be formally suggested in the labelling that physicians should use a double anchor.

But my real question is, why is the dislodgement for an SVC lead, for instance, so common, since there is really nothing pushing against it. The only thing is the pull of the device, I would imagine. Is this a major factor in epicardial systems that use a SVC lead as part of their system?

DR. STEINHAUS: I think much has been made of that, and I think a lot of it is a learning curve and experience. I know the engineers think they fixed it by putting a second sleeve on there. I don't really believe that's what fixed it. I think what fixed it is two things. One is, the sleeve is better, it holds the lead a little bit better, and the second thing is, people now know how you have to do this.

Remember, a lot of the people who started putting these things in were EP docs, and they weren't used to doing

a lot of pacemakers. The pacemaker doctors had a lower rate of lead dislodgement, because thy were used to putting the hub of the sleeve that holds it right up next to the subclavian vein, and using multiple sutures to hold it in place.

I think if one does that, that really does solve the problem of lead dislodgement. We have had a very low rate of lead dislodgement, and I only use the one connector, and always have. I really don't think it's the second sleeve that does it; I think it's the fact that you've got to get that first sleeve right up next to the vein. You've got to be careful how you tie it down, and I think also the sleeve itself is slightly different, so it ties down a little bit better. I think those are the three issues. I think it's a learning curve issue more than it is an issue of dislodgement. My lead dislodgement rate is very low.

DR. BARDY: I'll echo that, especially the anchoring design. It was not very good initially. It was quite loose, and one had to apply a great deal of pressure to make it approximate the lead. Once that was redesigned and we learned that the tension on these leads from body torsion and flexion was high, once those two issues were brought in focus, I think dislodgements dropped dramatically across the board. I know they did in my experience, because I had quite a few early on which I attributed to a

combination of the sleeve and ignorance in anchoring.

DR. BRINKER: The subcutaneous patch, that cannot be used in the epicardium, is that correct?

DR. SCHABER: Our labelling indicates that it should only be used for subcutaneous.

DR. BRINKER: I think that in a description of the three nodes that are on the side of the patch and how to position the patch, it would be nice if there was a picture showing what the three nodes looked like and how the patch should be applied to the subcutaneous tissue, because I found it a little bit difficult to envision that as I was reading this.

You add to the indications for use patients undergoing replacement of a previously implanted cardioverted defibrillator system. I would assume that this should not be done if the leads through the previous system are efficacious. In other words, this should only be done if the lead system is no longer functioning.

DR. SCHABER: The indication is that I think PCD manual is for use both with our epicardial and transveneous systems. So that is to cover -- if an epicardial system is in place, the device reaches end of life and you need to replace it with another PCD, that is an appropriate use of the system. What it is not to do is to say, if you have a functioning epicardial system and replace it with a

transvene system, that is not the intent.

DR. BRINKER: Let's say that you have a pre-existing epicardial system, and nobody wants to take out the -- it doesn't function well for whatever reason -- nobody wants to take out the epicardial patch electrodes. Some decision is made to put in a transveneous electrode system. Assuming that the epicardial patches are capped, would there be interference with the way the energy is delivered between a sub-Q system and the pre-existing epicardial systems?

DR. BARDY: I can talk about that directly, because I have a pig model of a field distribution across the thorax. Although much has been made of the epicardial defibrillation patch interfering with tarns-thoracic rescues or in this case, transveneous defibrillation, the problem really is non-existent. When you measure the field across the myocardium, it's almost totally uniform. The real field dropoff is not because of insulation from a patch around the epicardium, but rather the electrode-tissue interface from the shocking electrode. So I think that's a theoretical issue, but not one that can be measured.

DR. SCHABER: If you were to replace the system, our labelling addresses the fact that you should go through the standard implant testing, to show that you can meet the implant criteria and have a safety margin.

DR. BRINKER: I think I have reached a point where

I can pass the questions on to some of the other panel members. I guess we'll start with my right, Dr. Sethi.

DR. SETHI: About your subcutaneous patch electrode, during testing, could you tell us more about it, how you use it? In the labelling, it's not very clear how you use your subcutaneous patch electrode.

DR. STEINHAUS: Sure. What I will do is, I'll put the two intercardiac leads inside. I'll put the RV lead in first, and then get measurements on that lead. I'll then put the lead in the coronary sinus. I do like the coronary sinus positioning. It gives me a chance, while people are checking the lead, to go ahead and put the coronary sinus lead in. Then what we'll do is, we'll take a standard defibrillation paddle from a standard defibrillation device, which is almost the same size as the patch, and that will plug in -- there's a cable where all those leads plug into to mimic the device. We'll plug that into the cable as well. I usually start right at the apex, is where I like to go, underneath the left breast. If that works the first time, then I'll do several more defibrillations there to prove it's going to work there. If that does not work, then I'll either change the configuration, or I'll move my paddle either more laterally or more interiorly, or more superiorly. I'll just try to move it in a lightly different position.

The beauty of that is, I can do all of my testing non-invasively. I've made one incision up here, but I haven't yet committed myself to where I'm going to make my incision for the cutaneous electrode placement. Once I have found a good position, then I know where I want my patch to be. Then I can make my incision where I want to make it, and make a pacemaker patch pocket and just lay it right in there.

It's worked very well for me conveniently. It's been nice to be able to move that kind of electrode around. It's surprising how well they match.

DR. SETHI: How about Dr. Bardy? Do you use the same thing?

DR. BARDY: No. I used to do it that way, but I prefer -- my bias is to use a single incision for the pacemaker patch up high. I will resort to other methods if that doesn't work. I'll simply put the sub-Q patch up through the same incision that I used to get the transvenous leads in, if I'm going to use a sub-Q patch. That vector tends to be reliable in over 80 percent of people for defibrillation. It's a rare time for me to move it down anymore. I'll tend to move the SPC lead instead into the coronary sinus rather than move the sub-Q patch. One can make a pocket easily up here that usually goes down to the aureolus and to the lateral margin of the pectoralis, and

I'll place the patch over top of the fascia. That's the way I do it. I don't use the paddle testing technique anymore, because it's a pretty rare event to have a failure.

DR. SETHI: How about you, Doctor?

DR. ZIPES: We use pretty much what Dr. Steinhaus has indicated.

DR. SETHI: Is there any data available regarding use of the patch in the pectoral region?

DR. BARDY: I've done no randomized comparisons to the two. My techniques evolved over the years. Obviously, down here, if one uses the coronary sinus as your common electrode and you're pulsing out from the coronary sinus, you have a much better vector across the myocardium. But my interests lately have been towards speed and efficiency of implantation, minimization of incisions, and trying to translate all those more complicated implant methods down to a method that a general electrophysiologist can use easily.

So much of my work has been trying to test simpler things, so that it can be translated out into the community with ease, rather than coronary sinus systems, which are very effective, especially in difficult to defibrillate patients. But it's more complicated and convoluted to people that may not have a lot of experience. So by a two incision system, one for the pulse generator, one for the patch, high patch position, high SVC position, that works

very easily 80 percent of the time. It doesn't take a lot of expertise to implant.

DR. SETHI: Thank you. You had quite a few patients who had good DFTs at the initial implantation. When they were tested before discharge, the DFTs weren't markedly increased. Some of course are because of the lead displacement. Do you have any idea why other patients had high DFTs?

DR. BARDY: Actually, I've done a study and I've excluded all the lead dislodgements and drug superimpositions on the patient, and all the other things that can affect the defibrillation threshold, and just looked at change of DFT over time, when no other changes were present in the patient. This phenomenon is an interesting one to me, where you do get a rise in the defibrillation threshold in the first week to six weeks, maybe as long as three months.

I'm learning as we progress, and I think I can speculate the cause. That is thrombosis around the coil, clot formation, will give a marked rise and a dropoff of the field in the first few millimeters, not the first few centimeters. That clot is enough to raise the impedance at the electrode-tissue interface many times. It's after the clot dissolves or turns into a fiber sheath that that field then approaches what it was at the time of implantation.

In fact, you can see that rise in defibrillation efficacy if it's a long case. If you're in there for a few hours, you'll see your defibrillation threshold rise by the end of the case. I think it's because of the clot. In the days when we were putting these transvene lead systems in and then pulling them out before they were approved for implantation, if the leads were in for a half an hour to an hour, you would see this platelet slime cover the coil. As that builds up, I think that's what causes your rise in defibrillation requirements, but as soon as it shrinks back down, it returns to normal, as I have seen in a year follow-up.

DR. SCHABER: One thing I might comment about in addition to that is that we have seen the same phenomenon with the epicardial system, that is, the thresholds tend to rise in the immediate post-operative period and go back down. But there is a very rare circumstances where the thresholds rise enough where they have to do something with the lead system. The reason for a ten jewel safety margin is that that will allow for rises in the threshold. Usually when the thresholds do rise, they rise by a few jewels, so you can maintain the same lead system. Then after three months or so, they go back down to what they were initially.

DR. ZIPES: I think the acute changes also may be modulated at least to some degree by the autonomic nervous

system. Catecholamines have been reported to reduce defibrillation thresholds, and they are going to be very high intra-operatively, and might indeed be significantly lower during a pre-discharge test. That may play some role.

DR. SETHI: One of the concerns which have been discussed is about thrombosis of the subclavian vein. It's a pretty bad complication when a patient has it. Any thought been given regarding anticoagulation or something like that by the company?

DR. BARDY: I've had four patients out of 140, three of which I picked up on routine visits, just slight swelling in the left hand, and one that was more symptomatic with more marked swelling. My concern by making a recommendation of anticoagulation would be pocket hematomas, which I think would be much more of a problem than a left clavian vein thrombosis. I think the incidence of a two or three percent left subclavian vein thrombosis is probably going to be unchanged by anything other than really aggressive anticoagulation, which will probably get you in more trouble.

DR. STEINHAUS: I think that's an issue. Probably subclavian vein thrombosis is under reported in all the literature. If you look at studies that have been done in the pacemaker literature, it happens more frequently than we ever know clinically. I suspect that's a function of time.

If it develops over a long period of time, collaterals can form and you never see it.

I have not seen it with this system in any patient. That's not to say it hasn't happened. I suspect it has happened. I just suspect it's slow enough that we get collaterals.

DR. ZIPES: If you were to do a venous angiogram or fibrinogen labelling, I think you would find a much higher incidence than is clinically apparent. Most of the patients do very well, even though it may be a thrombosis.

DR. SETHI: I agree with you. I think the complication of coagulation would be very high, and I wanted to see what you all thought about it. One question I've got. I'm not an EP cardiologist, I'm just a surgeon. I'm concerned about the VT and V-fib therapy in your report here. I think there are 77 or 80 patients. Is that expected or accepted? Is that too high or too low?

DR. ZIPES: No, I think that's the state of the art with the present systems. In looking at primary cycle length, the system can easily be deceived by atrial fibrillation or other SVTs. I think the advances will come with better tachyarrhythmia identification. Measuring cycle length is done easily and with exquisite accuracy, but ultimately, the devices will look for AV disassociation, will have a measure of the duration of the electrogram to

distinguish a normal QRS from a wide QRS. There are a number of refinements. But I think that's the state of the art at the present time.

DR. BARDY: I think it also represents a degree of trigger-happiness on the part of programmers. That is that they tend to want to treat every little VT that comes by, instead of ignoring them. I would think a lot of those inappropriate therapies would be resolved if one simply programmed the tachycardia detection interval so aggressively low. It's a rare event for me to program a TDI greater than 400 milliseconds. I think that is where you get into trouble with these inappropriate therapies, when you start getting TDIs of 500 milliseconds.

If I were recommending labelling, I would put flags up at 400 and above.

DR. SETHI: One final question. There were significant incidents of lead dislodgement. There is not a single death during that period. Is that a function of luck? Could you explain that to me, how that happens?

DR. SCHABER: I think much of the reason is that half of the dislodgements are caught before the patient even leaves the hospital. So they are under medical supervision for this entire time. The majority of the risk is while they are in the hospital and there is other protection available. But the other ones occur between implant in the

first month, and it's a matter of the incidence of arrhythmias. There aren't that many patients who have an arrhythmia in the first 30 days post-operatively, so there is a short exposure time if there is a dislodgement at that time.

DR. SETHI: How about the late dislodgements? Two or three percent of the patients had late dislodgement. How do you follow those patients?

DR. SCHABER: The way we follow the patients is standard follow-up things, doing pacing and sensing thresholds and evaluating an X-ray to evaluate the position of the leads. The most frequent cause for a late dislodgement is a traumatic event in the case where someone is tumbling down a hill and reaches to grab a tree, so that they don't fall down the hill, and the extensive stretching pulled the leads out. But the vast majority of the lead dislodgements are associated with some event like that.

DR. ZIPES: I think you are right, luck has to play a role. A patient who has a late lead dislodgement and develops ventricular fibrillation may well die at that point, and fortunately it's not happened. I don't disagree with any of the things that have been elaborated, but luck does play a role.

DR. SETHI: I think some of the sudden deaths which the investigators and your committee have said they

are not the causes of the device could be because of lead dislodgement.

MS. MARRONE: I think you raise an interesting point, but all those patients when they were seen at follow-up prior to the death, there was no indication that there was a problem with the position of the lead system. Again, in getting intensive information from these patients' death by the physician or the referring physician with documentation of X-rays showed no dislodgement of the lead system. As you noted, we had a clinical event review committee review all these deaths, and felt there was no relation back to a dislodgement of the lead system.

You raise a point, but there is no data that would indicate that was the case in these patients.

DR. SETHI: Thank you.

DR. DOMANSKI: I have just a couple of questions for you. There was no change in peri-operative mortality. Can you discuss that?

MS. MARRONE: I'd like to comment on that. There is a difference in intention to treat peri-operative mortality. If you take the patients who were screened for a transvene system and you look at their peri-operative mortality, the incidence is 1.6 percent. If you compare that to the patients who were screened for an epicardial system, and their peri-operative mortality is 4.5 percent.

Looking at the statistical analysis, there is a statistical difference in that peri-operative mortality.

DR. DOMANSKI: Do you think that accounts for the overall lower mortality of the transvene system then? If there was no difference, then it would be interesting to know why the overall mortality was lower. But it sounds like that explains it.

MS. MARRONE: Exactly. We looked at the epicardial patients, and that data is provided in the panel package. We looked at the overall patient survival for the transvene system. I think what the reviewer may have been indicating is when you take the patients that have received the transvene system, their peri-operative mortality was 0.7 percent. If you take the patients that were screened for a transvene system, it was 1.6 percent. There is no difference there. But when you compare it to the epicardial group, there is a difference.

DR. DOMANSKI: Does that answer your concern about it?

DR. TERRY: It was a concern about this comparison of 1.6 percent versus a 2.2 or so that you would get from the historical control. Our statistician somehow felt that that was --

MS. MARRONE: We're making our comparison to our own PCD epicardial system. Because we don't have all the

data available from any of the historical controls to be able to do it without comparison, we're looking at our two systems. There is a difference.

DR. DOMANSKI: That answers my concern. That's the only question I have now.

DR. ECHT: I'll also start with a concern that was mentioned by the FDA review. That is a pooling of data from U.S. and international populations, which showed that the U.S. population was older, had a lower ejection fraction, more incidence of coronary disease, more incidence of cardiomyopathy. You state that this is statistically different, but probably not clinically significantly different. So I just wondered if you could explain what you mean by that.

DR. SCHABER: I think what we've done is, we've gone back and looked at the data in terms of the patients that were enrolled concurrently. Because of the way the system operates, what happens is that we do the evaluation concurrently worldwide. Once Medtronic is satisfied that the system is suitable for market release, then we market release it in areas where there is not a regulatory issue with doing that. At that time, we don't enter any further patients in from outside the U.S.

So if you look at the patients who are enrolled outside the U.S. up to the point of market release and the

patients that were enrolled in the U.S. up to the point of market release, and compare those patient populations -- that is what we did in our September submission -- those indeed are the same. The only differences is a couple of years' difference in age, but all of those other factors are the same.

It's our belief that as the study progressed, the patients with which the physician would try to implant the system changed. Early on, it was thought that patients with a low ejection fraction wouldn't do as well, so the system because of the limited supply of them were put more in patients who had a higher ejection fraction. As the study has progressed, that has changed now, so that the opposite is happening. They believe that patients who are sicker should get the transvene first and not the epicardial system.

DR. SAKUN: One point before I let the physicians speak, those points that you raised, do they make an impact on outcome. Doing that analysis showed that it did not. So we felt that based on statistical comparison and the initial analysis that it was appropriate to pool those patients.

DR. STEINHAUS: I don't like commenting on a pool data because I'm not a great statistician. But I looked at all the U.S. data alone. For a study that we're doing, it's U.S. and one Canadian center, and it turns out to be exactly

the same numbers. It's surprisingly close. So to me, it doesn't make a whole lot of difference whether you pool or not pool. It looks very similar, both in terms of ejection fraction and in terms of mortality statistics. That same mortality difference holds up. It was .6 percent in our study for the non-thoracotomy system and 3.4 percent at a PO of one level.

DR. ZIPES: There probably is some difference. I think the selection of patients in Europe for a device, depending upon the country, may be different from ours. Where budget crunches affect England so dramatically, they would probably tend to go with younger patients with better EFs, and possibly stay away from cardiomyopathies. So there may be some differences, but I think you need to ask outside of a statistically significant difference, does this have any clinical relevance in terms of the device function. I think there, the answer is no. I think these patients have sudden death, and the device works in them as well as it works in the American population. I think from that standpoint, it's perfectly reasonable to pool the data.

DR. ECHT: The Europeans used the exact same protocol and the same exclusion and inclusion criteria we used, right?

DR. SAKUN: Yes, identical protocol, same follow-up.

DR. ECHT: I personally have no problem with it, either, but it was brought up and I thought it was worth discussing. But as long as the exclusion-inclusion criteria are used and the protocol is exactly the same, and the target patients for marketing are receiving the device, I think it's clinically relevant myself.

To comment in terms of efficacy, I think the VP-VF determination efficacy and survival is excellent with this device. There are some safety issues, though, that I would like to talk to, some of which were already alluded to or mentioned, but I really want to get into this dislodgement thing a little bit more in detail.

My understanding from data in Appendix I is that of the 11 or 12 percent dislodgement rate, 3.2 percent were RV lead, 8.4 percent were CS lead and 8.4 percent were SVC lead. I would like to go through lead by lead and talk about how they're dislodging and how the anchors are going to help. As regards the SVC lead, I was wondering, how many of these were leads that were retracting, how many were leads that were falling down in the IVC, to start?

DR. SAKUN: I think that's a good question. We went back and polled each of the physicians to give us that information. Almost 70 percent are being pulled back. The remaining 30 percent are falling forward.

DR. ECHT: We luckily haven't had that much

problem with this, but with the old spring patch epicardial systems, it seemed that adding more anchors and putting a loop in and all those sorts of things really didn't help this retraction problem so much as it helped the falling down problem. So I'm not sure how having two anchors or the stronger anchor is going to necessarily prevent it from pulling out.

DR. SCHABER: In order for the anchoring sleeve to be effective, you really have to anchor the sleeve to the lead itself, and then anchor that to the vein. Initially, our first anchoring sleeve didn't anchor as tightly to the lead, so the lead could move back and forth within the sleeve. The new anchoring sleeve has tabs on it. In terms of pull strength, it's significantly better. So that does make a difference, that it's harder to pull through. With the addition of the two, and our increased education, talking about adding a loop or some other sort of redundancy, I think that really has addressed the pull-back.

DR. ECHT: The CS lead I think has two problems. I don't think any of them actually drift down farther into the CS, but they could either just flop out of the CS or be pulled out of the CS. I wondered what proportion of each you had seen.

DR. SAKUN: Interestingly enough, a great number of the CS leads that dislodge actually dislodge to an SC

position. Then the physician elected to repeat defibrillation efficacy testing and found that the system worked. So I think in the range of 60 to 70 percent came in in the SPC position. The remaining were still anchored in the os, but the coil was now sitting in the right atrium. So it kind of flopped out.

DR. ECHT: What you mean by flopping out, it's not pulled back at all, it flips and now it's hanging in the RV? That doesn't happen?

DR. SAKUN: We had none.

DR. BARDY: I think flopping out is almost -- dependent on the diameter of the coronary sinus. I've had two flop out, both big vessels. That lead being a (b)(4) lead, it's less rigid than the (b)(4) lead and more likely to do that. But there are ways around it, and the ways around it are selection of electrode polarity to guard against that, should it happen, and another is where it's positioned in the coronary sinus. The way I put it in, it's up to the point where it's wedged into the coronary sinus. That typically holds it into place without any sequelae from closing off this CS.

DR. ECHT: So in terms of polarity, would you guard against that by making the RV and CS the same polarity, so that if it would flop out and touch each other -- okay, that's what I thought you meant. So if

retraction is the main problem with the CS lead, you think anchors should help that a lot? Okay.

Then the last lead is the RV lead, the incidence being 3.2 percent, which is a lot lower than the other two leads. But 3.2 percent still seems to be maybe double what I would like to see. It surprises me some, because it's an active fixation lead.

One of the questions I have that is not exactly clear to me is whether or not these RV leads are also retracting, in which case this anchor might work, or whether or not something about the stiffness down there -- because there is that RV thing with that contracting ventricle might just pop it, because it's screwed in. So I was wondering whether those dislodgements are retractions or whether they're just unscrewing and still have the same length.

DR. SAKUN: I'll let Dr. Bardy describe some of his patients in detail, but all of the RV leads that dislodged were still in the RV. So they had not gone back across the valve.

DR. ECHT: So this is a different problem, then. It's not a --

DR. BARDY: I think it is a pull-back problem, but it's --

DR. ECHT: But it's pulled back out.

DR. SCHABER: Enough to lose pacing. The

incidence was 3.2 percent with a single anchoring sleeve, and with dual it's less than one percent in 400 and some patients. So we think between the education and this anchoring, that that really has addressed that.

DR. BARDY: Yes, I think it is mostly pull-back. Certainly all the ones that I've had with RVs have pulled back and have straightened up in the right ventricle, more than come out. The screws probably help keep them in place.

The other reason I think this dislodgement rate may be higher than what we would have liked is that the size of the leads are small, and they're not gripped by the first rib clavicular space. In a way, it's a kind of a paradox. The bigger the lead, the less likely you are to get dislodgement, because the first rib clavicle grip adds some active fixation. The smaller size leads dont' have that kind of limitation there, and they are going to be subjected to that incredible torsion and flexion, because of their length.

DR. ECHT: To follow up on what you said, Dan, subsequent to the 757 patients, found two pieces of data, one on 439 additional patients and one on 573. Was the 439 a subset of the added 573?

DR. SAKUN: Some of the 439 patients are in that new subset.

DR. ECHT: I read 439 patients, most recent

patients, had a 2.3 percent dislodgement, and then for the 573 patients, the dislodgement was stated to be 4.5 percent.

DR. SCHABER: Some of the 500 have a single anchoring sleeve, and the 439 were the ones --

DR. ECHT: Those were purely -- they all have two, okay. So in this group of patients who all have two anchors with the 2.3 percent --

DR. SCHABER: And that includes all leads, RV, SVC, CS.

DR. ECHT: What is the follow-up time on those? What is the mean follow-up in that group of 439 patients?

DR. SCHABER: It's over three months, and 80 percent of our dislodgements --

DR. ECHT: Were in the first three months, yes. Half were in the first month, and then the other half --

DR. SCHABER: The other half occurred between the one month and the three month interval.

DR. ECHT: You said that of that group -- was that the group said only had a one percent RV dislodgement?

DR. SCHABER: Right, less than one percent.

DR. ECHT: I just have another Valerie question. On the infection rates, because there were a couple of numbers, in one part of the PMA Volume two clinical report, page 74, it said as Dan showed in his presentation, there

was a 2.9 percent infection rate, and a 5.3 quote observation of infection. On page 52, Volume one summary, they list pocket infection as 3.2 percent complication, 1.3 percent observation. So my questions are, those are slightly different. Maybe you can just break it down in terms of infection -- I don't know what an observation versus a complication is. Does that mean whether or not it was explanted? Which ones needed explant, which ones were treated with observation, and which ones were treated with antibiotics and no explant? Could you clarify that?

DR. SAKUN: The clinical study as was stated in the presentation. A complication is a medical event that requires intervention. So when you talk about infection, there are going to be some patients who are explanted, and we would also count patients who had a pocket debrided and the device placed back in the pocket. So there were 24 patients where surgical intervention was required, 22 of those, the devices was explanted. That is where you get the 2.9 percent. So when we did the comparison of epi versus transvene, we wanted to compare apples to apples, how many resulted in explant. When you look at the total number of infections that required invasive intervention, that's 24. So that's 3.2 percent. The patients that are in the observation column, those are all patients that were treated with antibiotic therapy and the infection resolved.

DR. ECHT: Those were limited to the pocket?

DR. SAKUN: Exactly, they were all pocket infections. They had not seeded to a sub-Q patch, so there was no evidence of infection other than in the pocket.

DR. ECHT: I have a question regarding peri-operative mortality, which was extremely good in the transvene population. But I seem to remember seeing some data on patients who underwent testing for transvene, the DFT was too high and they went ahead and had an epicardial system, and it seemed like their peri-operative mortality is much higher. So I was interested in what their peri-operative mortality is. How many VF inductions they had as compared to the other patients, and whether or not they had thoracotomies performed at the same setting versus on a later date, and all that.

DR. SAKUN: What I would like to do is give you those numbers and then I would like to have some physician input on how they may manage those patients. There were 97 patients who were initially screened for a transvene system and went on to an epi. In that group, there were nine peri-operative deaths, which gives us a peri-operative mortality of 9.3 percent in that patient group. They are included back in when we do the intention to treat.

DR. ECHT: Right, but they're not separated out.

DR. SAKUN: Right. Your next question was, were

their implant procedures any different than the patients who did get a transvene system. Interestingly enough, the number of configurations tested is different, the mean number of configurations, from those who got the transvene, but the number of inductions is not.

Looking at them, seven died on same-day procedures, two died doing the implants on separate days.

DR. BARDY: I think when we reviewed those deaths, it was clear that the patients were being put through too much, too soon. The recommendation was to delay the epicardial for at least two days before proceeding, because they had been through a lot with their failed transvenous.

The other thing that came out of looking at those deaths was that many of those people were allowed to fibrillate too long. I think their deaths are in large measure related to prolonged episodes of VF, more so than difficulty in getting a system to work. It was being unprepared to rescue the patient. That is what struck me about several of those deaths, was the lack of preparation in the operating room.

DR. ZIPES: I don't think it should be mandatory that it be a two-day procedure if the transvene system is found to fail. I think if one decides early on after just a few inductions that the transvene system is not going to work, and then immediately go to a thoracotomy or a sub-

costal or sub-xiphoid or whatever for the patch, I think i's very reasonable to do it at the same time. I think it ought to be a clinical judgment.

I agree with Gus that prolonged episodes of VF -- and I disagree with him a little bit that the numbers have got to play a role, maybe 14 with a five-minute rest period in between is okay, but 20 with little rest period -- VF is harmful to your heart. I think those prolonged episodes, unquestionably, you ought to stop at that point and come back several days later. But I don't think it should be an obligatory statement.

DR. ECHT: Do you think there should be a recommendation in the physician's manual --

DR. ZIPES: Yes, and interestingly, I think some of the poor practices in the OR stem from some of the early dog studies, where it was said that you get the same numbers with a preposterously short interval between VF inductions, that that was part of some of the animal protocols, 30 seconds or a minute, or something very short between two VF inductions. It's ridiculous.

DR. STEINHAUS: I feel the same way Doug does, but I disagree a little bit with what Gus had to say, not in huge proportion. But I think after you have had a patient who has had multiple inductions and multiple configurations, you are now getting into two hours or so of anesthesia time.

There are patients who have VFs of 20 percent, and the anesthesiologist is now putting dopamine on the patient to boost up their blood pressures. I think that is the time not to do a thoracotomy. It's time to stop and reassess and let them recover.

DR. ECHT: My opinion is that there is a huge difference between 0.7 percent and 9.3 percent, so maybe we ought to be a little bit stronger about informing that this really is associated with a high peri-operative mortality. Even though there may be individual patients in whom it's perfectly safe, I think people should be aware of this 9.3 number.

DR. SAKUN: That particular percentage is not put into the labelling, but there is a specific note that says patients who failed to meet implant criteria and went on to epicardial, that there is an increased risk for peri-operative --

DR. ECHT: Yes. This is like more than a ten times risk. This is not a small-time difference.

DR. SAKUN: Right. If the panel feels we should actually put the percentage on, I don't think we would have any issue with that.

DR. ECHT: Next on my list are devices and leads out of service. I comment just that out of service percentage was very low, excellent, but I don't know what

(b)(4) -- what is it?

DR. SCHABER: (b)(4) is the name of an integrated circuit. That was the same issue that was reported on the epi system, where there was early on an issue with integrated circuit.

DR. ECHT: Because it was an FDA concern, we need to talk about this one case of metal ion oxidation. It seems to me it's just a really oddball case, in that there was damage 20 centimeters from the tip, but 20 centimeters from the tip was inside the RV. This patient must have had a strangely huge right heart. I would personally not want to make any extrapolations, but maybe we should talk about it anyway, because it was something that came up. Do you want to talk about that case a little bit?

DR. SCHABER: That was a case with, as you said, an extremely large boot-shaped heart. The reason that the lead was explanted was because their heart function was so bad, they had to have a heart transplant.

DR. ECHT: It was a functional lead?

DR. SCHABER: It was a functional lead, correct.

DR. ECHT: Had that patient received therapies?

DR. SCHABER: Right, that patient had received successful therapies. There had been no issues up to the time of explant with pacing sensing or detection or defibrillation. So the lead was explanted and returned as

part of our -- we asked for all of the investigational leads back when we do a transplant, and it was only upon microscopic evaluation that we found a cosmetic MIO.

DR. ECHT: VF re-detection after shock was never seen, which is wonderful. But what do you attribute to the absence of any post-shock signal attenuation with this system?

DR. BARDY: The detection algorithm I think is great, and it's based upon bipolar sensing, and the years of work Walter Olssen put in making sure that it doesn't fail following shock when amplitudes may fluctuate more or be smaller, or the spacing on it avoids polarization effects. It's been stressed a lot and hasn't really failed in that regard. The way it's defined, the decay of the sensing amplifier, it's an issue as well. Also, the sensitivity -- the fact that VF detection is 75 percent rather than a hundred percent requirement for detection, that helps. I think those are the main issues.

DR. SAKUN: We spent a lot of time going through the strips to insure that there weren't any reports of under sensing, either in sinus or under sensing that then related to delayed detection. We've had delayed re-detection, but we've had no reports of anything, because of the reasons that Dr. Bardy has outlined.

DR. ECHT: I think it's still hocus-pocus. I'm

still looking for the answer.

DR. SCHABER: It works, though.

DR. ECHT: I just have a couple of clinical kind of questions. As regards following patients, since half of the lead dislodgements occur after the first month, so even though a lot of them occur acutely, still more than half of them occur after the patient goes home. How should we be working for these things? What would we be doing? Chest X-rays, pacing thresholds, how often? Any other thoughts?

DR. SAKUN: What I'll do is outline what is in the labelling and then have physicians offer any additional recommendations to that. The patients are seen every few months because of the need to reform the capacitors and do measurements. That will remain unchanged. Labelling for the transvene system will recommend that X-rays be obtained in those follow-up visits to evaluate for the possibility of dislodgement. You do do the same routine kinds of measurements which are the pace sense threshold evaluation to look at capture threshold and sensing threshold, as well as in looking at the device and in looking at if any of this has occurred, are they appropriately being treated, is there any indication that there may have been an improvement. Those are the kinds of things that we have in the current labelling.

DR. ECHT: At what time, though? What about two

weeks, two months? When should they be seen at discharge to try to catch those?

DR. SAKUN: X-rays are required at the pre-hospital discharge. Whether or not one is done at the one month, we've left that to the -- the strong recommendation is that it be done, and the long-term is that at every follow-up from there on in, each three-month follow-up, that X-rays be done at that point in time.

DR. STEINHAUS: We have all looked at the insert, and I think those are reasonable recommendations. You've got to walk between overdoing things and carrying a lot of expense versus what seems reasonable. I think those are reasonable assessments.

DR. ECHT: Just one more, and then I'll stop. That is where to put the sub-Q patch. It seems like there are still a number of schools. In the physician's manual, it suggests that to do the mid-axillary line, which is a little different from Gus' anterior and John's posterior. We personally have found that to be the best position as well, and I wondered, is this a consensus.

The other is, the field clinical engineer that comes to our institution made a point of saying that not only should it be mid-axillary, but it's best if it's perpendicular either this way or this way, not this way.

PARTICIPANT: That's hocus-pocus.

DR. ECHT: All right. But we have had good luck with that. So I agree with the idea in the recommendation of starting at axillary. But what if that doesn't work? There are two different schools about the front and the back. Unless you do a cutaneous patch like David does, and a lot of people don't because you have to do a lot more testing to do it that way, most of us go to the front or the back at that point, and that means making more incisions in the patient. Once you have made the one, you would like to not have to make too many more extended anterior. So what are you going to suggest if the mid-axillary doesn't work, the interior-posterior?

DR. SCHABER: I might go back to say that with our data with RV SVC sub-Q in a mid-axillary position, that approximately 60 to 70 percent of the patients meet the implant criteria with that first configuration.

DR. ECHT: But what would be if you were in the other third? What do you suggest next? How do you guide physicians in that?

DR. NORBERG: As opposed to telling them to move the patch, we would do some recommendations on moving the electrical first, and possibly change the RV common to the sub-Q common, and change vectors and see if that would increase your probability for effective --

DR. SAKUN: And the second thing you could do is

that we recommend you start off sequential. If you can't meet the implant criteria, to reprogram to simultaneous. So there are things you can do both by reconnection and reprogramming before, and then pick up a good percentage of those patients who haven't met implant criteria, before you'd have to move on to the point of another incision and reposition the sub-Q patch.

DR. SCHABER: The flow chart in the PCD tech manual indicates, start with RVS VC sub-Q, and either sequential or simultaneous, and then first try that. Then try changing the common. That would be our recommendation, rather than moving the patch around a lot first. That is a simpler change.

DR. ECHT: My personal feeling is the sequential simultaneous is a little bit hocus-pocus, too. I think sequential works a lot better, because we're told to try it first.

DR. SCHABER: We do have paired data in a number of patients. You can see that having options allows you to get patients you can't get with one or the other. There's a fair amount of overlap.

DR. ECHT: I know that data. They always try sequential first, too, so it wasn't randomized, so I don't think that data is really great. But anyway, you've done all those things, and you want to move the patch. You don't

have any advice as to which direction to go?

DR. BARDY: I wouldn't use the approaches that you're doing. My labelling would be a two incision rather than a three incision. I would label a very high SPC, not one that most people use. I would put a patch up very high. If that didn't work, I'd move into the coronary sinus. I wouldn't move the patch, because I would try to avoid a third incision. I think that's a big deal for my practice, and moving into the coronary sinus isn't.

DR. ZIPES: I think we're hearing reflected here not only your comments, but the comments from this side. It's that this is an evolving state of the art, and we don't know exactly what is the best approach. I think Gus has suggested one that seems to work, and the others have as well. So I think the labelling needs to reflect that, that there isn't necessarily a hard and fast way that it should be done, but offer these as possibilities in the patient with a high DFT. Labelling may change in a year or two when we have more knowledge about it.

DR. STEINHAUS: I agree with you. We have all had the experience where what should work doesn't seem to. Then you try something that doesn't seem like it ought to have good field lines or whatever, and then it does. I think there is still a lot we don't know about this, and I think you just have to try to do your best. I think the bottom

line is, if you get a 24-jewel DFT, no matter how you did it, you're going to be okay.

DR. ECHT: It's gratifying to know I'm not the only one who doesn't know everything. I think I'll stop here.

DR. GREGORATOS: Paraphrasing Dr. Sethi, I'm not an electrophysiolgist, I'm only a clinician, so I don't have many questions. It seems to me that there has been ample demonstration that the device is effective for what it is supposed to do. I think the results of therapy are very gratifying.

So my questions will be few and related mainly to safety issues. First of all, I was a bit disappointed to find out that the mean hospital stay was only three days less for the transvenous system than the thoracotomy system. I would have thought that avoiding thoracotomy might lower the hospital stay a little bit more. Would you care to comment on that?

DR. SCHABER: In brief, that calculation is based on the first 757 patients entered into the population. That is what we are looking at. That was when physicians were more conservative about the testing that they were going to perform and how long to keep a patient in the hospital. Then I would like the physicians to talk about what their practice is now, after they have been up that learning path.

DR. STEINHAUS: I agree with you entirely. One of the major benefits is the decreased discomfort it is to the patient not to have a thoracotomy. Thoracotomies are not entirely benign procedures as we've learned, not only in terms of mortality, but also in terms of morbidity to the patient. It's a rare patient who is up doing all the things he wants to do after a thoracotomy before six weeks, whereas with this device, people can be up doing what they want to do very quickly. In fact, I send patients home now routinely at two days, so I will put it in on a Monday, they will get tested on a Wednesday, and they will go home the day they are tested, and that's it.

So I think you can achieve a significant decrease in hospital stay, and I think for the purposes of the study we're being pretty conservative. I think we will see that.

DR. GREGORATOS: Is that everybody's experience?

DR. ZIPES: I think that's absolutely right. If you know that this is the device for that patient, you don't have to do a lot of fumbling up front in terms of EP testing and whatever. They're in and they're out very quickly.

DR. GREGORATOS: Thank you. If I read the material correctly, the only thrombotic complications that were seen were subclavian. There was no coronary sinus thrombosis reported with CS leads, is that correct?

DR. SCHABER: That's correct. We've done a study

on that, on the patients that have died or have been transplanted, and have looked at their coronary sinus. I think we have about seven or eight. Our pathologist that we have worked with is here, and you don't see it. You do see a thin fiber sheath adhering to the endothelium on the coronary sinus, but no evidence of thrombosis.

DR. GREGORATOS: For my own edification, how far out do you insert the lead, in the sinus or in the great cardiac vein like the diagram up there seems to imply?

DR. BARDY: In large measure, it depends on where you have your other electrodes. One tries to triangulate the left ventricle, but with the other electrodes. So choice of cathode or anode affects where you put it.

Lately in my practice, I tend to put it more proximal into the coronary sinus rather than the great vein, because I use -- the patch here is common, and the vector is better if it's more proximal. But if I use the right ventricular electrode, it's common, or cathode, then I'll put it out in the great cardiac vein and wedge it in the vein. It works fine there, and doesn't cause any mechanical problems.

DR. GREGORATOS: Thank you. What type of training is Medtronic planning to give, if and when the device is marketed?

DR. SCHABER: We have an extensive program of

training, where we would go through an overview of the clinical results and what has been successful and what has not been successful, and go through the implant procedure, et cetera, with the implanting staff, meaning the electrophysiologist, the surgeon who is going to be in attendance, if that is the case, and the nursing staff that would be involved. The amount of education is tailored to the experience of the implanting group.

DR. GREGORATOS: Or lack thereof.

DR. SCHABER: Or lack thereof, correct. So if they have had experience with an epicardial system and another manufacturer's transvenous system, they would need less education than if this was their first experience with a transvenous system.

DR. GREGORATOS: Going back to Dr. Brinker's early question about the interaction with the DDT type of pacemaker and the response that was given, is there anything in the labelling about maintaining distance between the standard patient lead and the transvene lead? Or if there isn't, do you think that will be something to introduce into the labelling?

DR. SAKUN: The recommendations that are currently included in the labelling talk about the issues that the physicians brought up, which is the unipolar pacemaker, that those should be explanted. Though there are not specific

distance recommendations that are in the labelling, that was something the advisory panel would like to see included. We do recommend that the leads be separated as far as possible while still maintaining appropriate function of the pacemaker as well as appropriate function of the PCD.

DR. GREGORATOS: It seems to me that would be a useful sentence to include in the labelling.

DR. BRINKER: Doesn't the PCD labelling have something about, if there's the presence of a pacemaker, you have to test sensing with the pacing on?

DR. SAKUN: Yes, the labelling states that you should have sensing of the PCD with the pacer program to its full output, and then during defibrillation testing with VF being induced to make sure that there is no inappropriate non-detection.

DR. BRINKER: So that would cover that issue.

DR. GREGORATOS: Looking at the inappropriate therapies, it seems to me that the major culprit obviously is rapid atrial fib. I counted ten or 14 appropriate VT were due to A fib and 29 of 57 VFs were due to A fib. Obviously, everybody knows that, or at least I would hope everybody knows it, and would try to prevent it happening as much as possible. Is there a caution in the labelling related to that?

DR. SAKUN: One of the features available in the

PCD device is that there is a detection algorithm which we have labelled stability. In the section that talks about programming recommendations, we give programming recommendations for how that algorithm should be enabled and when it should be used, specifically, if the patient does have a history of atrial fibrillation, the physician may wish to consider enabling the algorithm. If there is then an appropriate therapy due to what the physician believes is atrial fibrillation, to go ahead and enable that algorithm. So we do have those kinds of recommendations about how do you use the other detection parameters within the PCD device.

In our warnings and cautions section, there is a discussion that there is a possibility of inappropriate therapies due to A fib or sinus tachycardia.

DR. GREGORATOS: Was this algorithm enabled in the episodes of A fib that resulted in inappropriate therapy?

DR. SAKUN: All the patients who had the inappropriate therapy did not have the algorithm enabled. In a percentage of patients it was enabled and no further inappropriate therapies were delivered.

DR. BARDY: I use the stability algorithm a lot, and will program fairly tight intervals on it, sometimes 30 milliseconds. It's a rare patient that continues to fool the device if we use that.

DR. GREGORATOS: So if I understood you then, the majority of the patients where the device was fooled did not have the stability algorithm?

DR. BARDY: Right.

DR. GREGORATOS: Good. That's all I have.

DR. AZIZ: I have one comment, although I think the questions have been well addressed. At the time of explanation, patients who have this device are a pleasure to have compared to the AICD older systems, where we couldn't get the patches off, particularly attached to the pericardium, and parts of the heart were left behind. So I think this is an advancement in those sorts of patients.

The other thing, addressing the subclavian vein thrombosis issue, this subset of patients who do transplantation are on anticoagulants. I think we probably will be seeing an increasing number of these patients. From my recollection, I don't think that they have had any increased incidence of hematomas, and Gus may be able to address that.

DR. BARDY: We do see pocket hematomas on the ones that are anticoagulated, who have valves, for example. Those are the patients where we're struggling to balance surgical bleeding against valve clotting. We often end up with pocket hematomas on them because of our reluctance to stop their anticoagulants completely. So I think it is an

issue. That concerns me more because of dehiscence, clots that favor infection early on. We've seen a patient get a pocket hematoma and then an infection. So I would still argue against anticoagulation in those patients.

DR. STEINHAUS: But that's early on you're talking about, not later.

DR. BARDY: That's right.

DR. AZIZ: The second issue, of crinkling of the subcutaneous patch. Does that tend to occur early, or is it that once they get over the socking-in stage, it doesn't occur?

DR. BARDY: I think that's a late phenomenon, and related to activity levels and anchoring technique.

DR. SIMMONS: Quite frankly, most of the questions have been asked by now. But a couple of issues, just for interest's sake. A lot of patients now get referred in our lab for extraction of these lead systems from pacemakers. Have you extracted very many of these leads from the CS for infection, and how late are you willing to pull these leads out, and is that going to make a difference in the type of patients you might chose to put one of these lead systems in?

DR. BARDY: I've had to pull two out for infection, put them in on the left side and then subsequently put them in on the right side after their

infection cleared. In both of those people, the infections were sub-acute, and in the three to six month time period. At that time, there was no difficulty pulling them out at all. Whether they would be more difficult four, five, six years down the road, I don't know; I would imagine they would be. But the lack of tines and the durability of that right ventricular lead I think makes it easier to pull it out.

The SPC lead, because I put them up high, is very simple to get out. I can't comment about four or five years. I would assume it would be harder, but probably not as hard as a tined --

DR. SIMMONS: You have pulled them out of the coronary sinus as well? Okay. I've gotten a lot of questions about the kinds of ablations we're doing with regular frequency, and whether or not doing them inside the CS is really -- is it dangerous. Seven patients that you have looked at for damage to the coronary sinus or coronary artery, or damage inside the CS really enough to make any kind of comment?

DR. BARDY: I happen to have a lot of experience in catheter ablation of the coronary sinus. I'm probably one of the people who influenced going away from the coronary sinus in the days when you used to use DC ablation, and exposed a great number of problems with doing that. But

that is a totally different therapy and a different energy technique, and much more traumatic than what we're doing now.

We would distribute 2,000 or 3,000 volts across two millimeters of electrode in the ablation base, and now we're talking 700 volts across five centimeters of electrode, a much different result from that doesn't create the problems.

DR. SIMMONS: But dont' you think still, just in these five or six hearts that you've had the opportunity to examine, the story isn't in on what may happen after several discharges from this device in the CS?

DR. BARDY: Well, I don't think that's an issue. The reason is, when you damage the coronary sinus with an electrical pulse, you will know it immediately, because the effect is an effect of trauma and burning, not an effect of an electric field that is not burning the tissue. If it's burning the tissue, you will know immediately because you'll see your voltage wave form change. That change is apparent on the oscilloscope. If you are burning, you will get a big rise in resistance and you will see your voltage wave form change immediately. You don't see that with this like you do see it presently with radio frequency ablation techniques.

DR. ZIPES: Whether those seven patients are

representative or not, I think my feeling would be they probably are, because clinically it's not a problem. Indeed, when we were still operating on WPW patients, the surgeon got into a CS tear, for example, they would often ligate the coronary sinus with impunity, and the patients did perfectly fine. I realize that surgeons don't tear the coronary sinus too often. And clinically, coronary sinus obstruction is not a problem. So I would tend to believe the data.

DR. SIMMONS: Probably also from the early days of pacing, all the coronary sinus leads were placed in for atrial pacing. So there is some body of evidence that says we're probably going to be able to get away with this. But still, I'm not going to be surprised the first time something comes up like --

DR. STEINHAUS: I don't think anybody is. We're probably going to be able to get away with this, but still, I'm not going to be surprised the first time something comes up like --

DR. STEINHAUS: I don't think anybody is.

DR. BARDY: Two issues. Art Moss put the first coronary sinus pacing unit in 25 years ago. He still has some of those patients in his practice. He has done long-term coronary angiograms with coronary sinus phases, showing they're patent 20 years later. That makes me sanguine. To

build upon Doug's comment on the surgical approach, George Guiridone when he did his epicardial WPW dissections, used to intentionally ligate the coronary sinus. So I don't see that as an issue.

DR. SIMMONS: There wee a couple of instances which sparked something in me. I always get these devices that I send back to the company, and then always come back, in spec. But there were two instances of these power on resets, two patient who had problems with that. Both of those devices came back as in spec. Do you have any comment on that?

DR. SCHABER: Other than there weren't reports of it being used around electrocautery. But there could have been electrocautery at the time of explant that would have caused it to do that, or some other strong electric field.

DR. SIMMONS: I guess I don't have anything else to say, other than to reiterate what other people have said. I think the majority of the lead fractures look like they have been in subclavian veins. I think the labelling should be very strong to suggest that all the leads should be placed through a cephalic vein when at all possible. The labelling has to be very strong about the follow-up. I don't think it should be left out that these patients need X-rays. There are a lot of people looking over our shoulders right now about the cost of these devices, and

their efficacy in the five-year long follow-ups and things like that. If we're ending up with one percent fracture rates and even three percent dislodgements and we're not taking care of those, those patients are going to end up as deaths on our overall nationwide statistics.

So I think the labelling should be very strong that the robustness of this design is not as strong as some of the others, and it needs a little more tinkering and a little more care. I think the labelling should be very strong, in my opinion.

DR. SAPIRSTEIN: Just one informational question. Can you dispense with the subcutaneous patch?

DR. SCHABER: Yes, you can. In this population, the majority of the patients had a subcutaneous patch, but there are a number of patients who had RV SVC without a patch, or RV CS SVC without a patch.

DR. SAPIRSTEIN: But they all had patches in this group of patients?

DR. SCHABER: Ninety-five percent of the 757 had a patch; five percent did not.

DR. SAPIRSTEIN: And all the infections had to have the device removed, did they?

DR. SCHABER: There were 3.4 percent of the patients who had an infection where the pocket had to be entered, 2.9 percent of the patients had the device

explanted. But there were other infections that were treated with antibiotics.

DR. BRINKER: I think we can have an expedited second round here. I just have a couple of questions. One is that you carefully label the devices to be used only with Medtronic PCV. It's unfortunate, I think, that these leads haven't reached a state of evolution between and betwixt and manufacturers that the pacemaker leads have. Why not have unified lead adapters for these devices?

DR. SCHABER: We are moving towards that. There's a DF-1 standard defibrillation standard, so that the leads could be interchangeable. It's our position right now that before we can recommend that any lead be used with any one of our pulse generators, or any one of our leads be used with anyone else's pulse generators, that we need to have data showing that that indeed is safe and effective.

DR. BRINKER: Do you make adapters, or are you thinking of making adapters?

DR. SCHABER: We're in the process of making adapters and making all of our leads available with the DF-1 connector, so that once all the manufacturers adopt that standard, they will be able to be used interchangeably. But it is still our position that that shouldn't be done until clinical data shows that it's safe and effective.

DR. BRINKER: On the complication review, there

are a number of patients that had perforations, which is a little bit higher than you would expect. These were serious perforations, tamponade or LV/RV. Do you think that this is due to the intrinsic stiffness of the lead, or perhaps due to the fact that when you deliver therapy, as part of the therapy, the lead shoots axially against the apex or against where it's positioned?

DR. SCHABER: It's our belief that it's implant technique, and the stiffness of the lead that is doing it. If you look at the lead in a patient's heart during defibrillation, it doesn't move.

DR. BRINKER: Does the heart move? The lead stays where it is, and the heart --

DR. SCHABER: The lead stays where it is relative to the heart.

DR. BRINKER: Some of these were not acutely obvious, which is what you would normally see with a technique problem, especially those leading to tamponade.

DR. BARDY: I've had it happen to me once. It was acutely obvious. It was technique.

DR. ZIPES: We see it with ablations. It's not that rare, unfortunately. We have learned, for example, that the little old lady, their hearts are very thin walled and it's so easy to perforate that heart, even when you go in knowing that they are at risk for tamponade. So I think

it's technique.

DR. BRINKER: But it has to do with the device, too, because this incidence of perforation, be it as small as it is, isn't seen with endocardial sensing leads, for instance, with the old devices, to the best of my knowledge.

One final comment from me. I wouldn't be so cavalier as Debby was about MIO, especially since most of these leads are going to continue to be placed in the subclavian access. We know that MIO is facilitated by stress or strain, even though this particular case was unusual, to have it at a spot in the right ventricle. I think when you're up against the subclavian site, there are two recent publications suggesting that installation problems can occur in this area, and that MIO plays a part in that.

MS. MARRONE: I would just like to note that there have been in the last few years a number of process changes, a net effect clinically, that has demonstrated that the incidence of MIO in that area relative to that position up in the subclavian is significantly reduced, due to some of these process changes.

DR. BRINKER: But MIO is peculiar to (b)(4) installation. I think that's the gist of my comments. If there was other installation, MIO would not be a consideration. I think as part of the overall post-

marketing surveillance anyway, this thing ought to be kept in view, because this usually isn't obvious for five years.

DR. SETHI: Have you seen any cases of -- insufficiency? This lead is pretty stiff.

PARTICIPANT: (Remarks off mike.)

DR. SETHI: The last question is about endocarditis. When the system gets infected, have you seen any case of endocarditis?

DR. SCHABER: It's a concern. But we haven't had endocarditis reported to us. We've had systems where they explained the explanted the pulse generators and the lead themselves, but not yet a report of endocarditis, although that is a concern.

DR. SETHI: Suppose the lead is infected. Do you treat this patient as a potential endocarditis patient?

DR. ZIPES: We recommend antibiotic prophylaxis for dental work and so on. I don't know that that's the right way to do it, but that's what we recommend.

DR. ECHT: I just had a couple of labelling comments. I agree with virtually all the labelling suggestions by the FDA.

DR. BRINKER: Do you want to hold those until after the meeting?

DR. ECHT: Yes, that's all I need to talk about.

DR. BRINKER: I want to just ask Doris whether

most of her queries have been answered during this debate.

DR. TERRY: Yes.

DR. BRINKER: Okay, I'd like to entertain proposals to recommend approval or disapproval of this device.

DR. SAPIRSTEIN: Jeff, could I just clarify the voting status? Dr. Gregoratos, Dr. Domanski were made voting members, and that was done prior to this meeting. At this meeting, Dr. Simmons and Dr. Zipes were made voting members temporarily. Dr. Echt is not permitted to vote on this PMA.

DR. DOMANSKI: I move approval.

DR. SIMMONS: Second.

DR. BRINKER: Can we have some discussion on that before we vote? I assume we would want to make a vote for approval with recommendations for labelling changes. Debby, why don't you now put in your recommended labelling changes, and then we'll have a motion as to whether we should vote on that?

DR. ECHT: I recommend that there be more specific recommendation to use two anchoring sleeves for each of the three types of -- not each of the three, but the RV and the SVC CS leads. I suggest that there should be a caution added to the sub-Q lead that says not to use it on the pericardium or epicardium, because it's too stiff. I

think that as the FDA suggested, it might be helpful to -- although this is very much of an evolving process, it might be helpful to add some of the results of testing of the various electrode configurations to serve as some sort of guide to physicians, and put it right in the physician's manual.

I also agree with the FDA that it would really be helpful that pictures of the various electrode configurations, including shoeing various polarity combinations, to help guide them in selecting. I suggest there be a little bit stronger recommendation about considering not doing a thoracotomy if you have done extensive testing with a non-thoracotomy system, and find that the defibrillation efficacy is too low. Perhaps even adding the .7 versus the 9.3 percent peri-operative data, which I think would be helpful to physicians.

I also suggest that there be a little bit more explicit recommendation regarding as Tony suggested to follow-up recommendations for getting chest X-rays and doing pace sense threshold testing in terms of timing. It's just a recommendation, but I think it would be helpful.

Then the only other one, there are all these electrode configuration recommendations and guidelines that are all in the pulse generator physician manual, and they're not in the lead manuals. I wonder, since you don't actually

open up the box for the pulse generator until you've retested all the leads, it doesn't seem like it's as helpful as to have that same information in each of the lead packages.

DR. SCHABER: We can do that. The rationale for not putting it in there is that in the future when there's different sorts of pulse generators available, the experience may be different with the different pulse generators. For example, in biphasic, the recommendation will likely be RV SVC as the starting point. But that doesn't preclude us from putting it in.

MS. MARRONE: Other things might be referring to that, the PCV tech manual and providing that at the same time you're providing leads, even though they may be reconnecting to the same pulse generator, as opposed to reproducing it once more in the tech manuals.

DR. ECHT: I think that would be acceptable. It just seems that after you do all this stuff, you open it up and say, oh, look what I should have done.

MS. MARRONE: Right now, it does refer you to the ICD tech manual for specifics.

DR. ECHT: That was one thing I really didn't feel particularly strongly about, but thought I would bring up.

DR. BRINKER: Are there any other labelling changes being proposed?

DR. SIMMONS: Should we consider something about suggesting the pre-discharge EPT testing is not -- many institutions consider pre-discharge EPT testing of devices to be optional, and that probably shouldn't be optional. Maybe they should be encouraged to be brought back for late EPT testing.

MS. MARRONE: In the current PCD manual, pre-hospital discharge testing is a requirement.

DR. SIMMONS: Maybe an encouragement should be made to bring these patients back at a later point for a three to six month check for defibrillation.

MS. MARRONE: It is requested at the six-month follow-up.

DR. STEINHAUS: I don't think that's necessary. I think first of all, patients really don't like to be tested an awful lot, as you undoubtedly are aware. Second of all, the data suggest that once it's --

DR. SIMMONS: I do mine when they're asleep.

DR. STEINHAUS: But I think even asleep, they don't like it. I think the system has been shown to be effective in the long term, provided you get a good short-term result. I don't think there have been enough problems with the system to justify asking everybody to go through another defibrillation test at six months, in my mind. It seems like that's a little bit overkill, I think.

DR. GREGORATOS: I would like the panel to consider whether we should ask, this issue of distance between standard pacing lead in the RV lead be mentioned in the labelling.

DR. SAKUN: There are specific recommendations in the manual already, that talk about the requirement to test the device during sinus rhythm, to make sure of appropriate interaction, and then during VF. Then based on that testing, repositioning of the leads may be required.

DR. GREGORATOS: That's in the PCD?

DR. SAKUN: That's in the PCD.

DR. BRINKER: I think Gabe would be happy if -- and I think you allude to this in your current recommendations, but in the leads, it's mostly the RV lead, that there is just a reminder that the likelihood of interaction between pacemaking leads is greater if the leads are juxtaposed as opposed to separated. I don't think there is any minimal distance that gives you any feeling better than another.

DR. GREGORATOS: Right, it's just a generic statement that function might --

MS. MARRONE: We can introduce that into what is already in for the PCD and add that to the lead tech manuals as well.

DR. GREGORATOS: Fine.

DR. BRINKER: We did this a little bit out of the rules of order here. If Mike would agree to accept these labelling amendments as Wolf will read them, rather than to vote on his blanket approval, is that okay?

DR. DOMANSKI: Sure, I'll move that we amend them as they are about to be read.

DR. SAPIRSTEIN: The amendments to the labelling were that specific anchoring of individual electrodes be incorporated, that caution -- that the subcutaneous patch should not be used as an epicardial patch, a guide to configuration and polarity with illustrations be provided in the manual, stronger recommendations to delay any needed thoracotomy after a prolonged period of EP testing, specific recommendations for post-operative X-ray and follow-up to determine lead displacement, and informational literature available apart from the packaging, and that a separation of implanted pacer leads from the device electrode leads should be noted as a precaution.

DR. GREGORATOS: A comment. My understanding from the investigators' discussion was that the importance of the fixation of the lead above and beyond the sleeve is an issue. Maybe in the labelling that should be emphasized.

DR. BRINKER: You mean above and beyond the double anchor?

DR. GREGORATOS: The double anchor, yes, the

double sleeve, right.

DR. BARDY: (Remarks off mike.)

DR. GREGORATOS: No, you specifically said that you think the double sleeve was as important as fixating the lead up against the vein to minimize migration either forward or a retraction. I think that statement should be incorporated.

DR. SAPIRSTEIN: So specific anchoring of individual electrodes and fixation to the vein.

DR. BRINKER: Yes, we can work out the specific wording with the FDA.

DR. ECHT: A tiny thing. In addition to chest X-rays, to follow up with special testing. I think it's a good way to pick up RV lead dislodgement.

MS. MARRONE: I've got that here in the notes.

DR. BRINKER: Any other comments? The motion is for approval with these amendments as Wolf mentioned. Can we have a vote of those in favor of this? Those opposed? It's approved with those recommendations. Thank you.

What I would like to do is, since we're about an hour early, I wonder if we could start the next one at noon rather than at 1 o'clock.

DR. STEINHAUS: I would just make one plea from an investigator standpoint and a doctor standpoint, with patients. I consider this a major advance, major difference

in the way we do things. Hospitalization now is going to be two days. Patients don't have to have a thoracotomy. They have a much lower mortality rate. This is better than the epicardial systems that we're all used to using. Is there any way this can be done in some reasonably quick way once it's approved? Can that be done by the FDA people in a semi-expedited way? I feel so strongly that this is a major difference for my patients that I wish I could convey that so it could get done.

DR. BRINKER: The exact same plea was made when we approved the first transvenous set of electrodes. I think that the FDA understands that particular thing, and I'm sure they will do it as expeditiously as possible.

DR. GREGORATOS: I think there is a lot of emphasis on streamlining and moving faster than previously, so maybe we'll see how it works.

DR. BRINKER: So we're going to start with the CPI device at noon. Thank you.

(The meeting was adjourned for lunch at 11:11 a.m., to reconvene at 12:00 p.m.)

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date 4/3/92

From Chemist
Premarket Approval Staff, ODE, HFZ-402

Subject Request for PMA Filing Review

To DCRND

PMA Application No.: P920015

PMA Applicant: MEDTRONIC, INC

Device Trade Name: MEDTRONIC® TRANVENE LEAD SYSTEM

Date of Document: 3/31/92

Date Received by DMC: 4/1/92

Date Received by PMA Staff from DMC: 4/2/92

Date letter and checklist due from ODE Division to PMA Staff: 5/11/92

Date Letter Due out of CDRH: 5/16/92

Please review the above referenced PMA for a filing/nonfiling determination. A complete checklist and "filed" or "not filed" letter should be returned to the PMA Staff by the due date specified above.

If the PMA is to be filed, please specify in the checklist special considerations or important aspects of the manufacturing process that should be included in the EDRO inspection of the manufacturing facility. A preliminary determination of whether the device is a "critical device" for purposes of the device Good Manufacturing Practice Regulations should be included (see checklist).

The biostatistics staff (HFZ-116) is notified of every PMA received and will notify the ODE Division as to the identity of the statistical reviewer. The biostatistics staff will review appropriate segments of the PMA and forward a statistical review memo to the reviewing ODE Division before the due date specified above. Please let me know if you need any further assistance.

Arnold Alpert, Ph.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date 4/3/92

From Arnold Alpert, Ph.D., Premarket Approval Section, ODE (HFZ-402)

Subject Request for Inspection/Compliance Review

To Rosa K. Forehand, Program Development and Analysis Branch
Division of Compliance Programs (HFZ-331)

PMA Number: P920015

Device Trade Name: MEDTRONIC® TRANSVENE LEAD SYSTEM

PMA Applicant: MEDTRONIC, INC.
7000 CENTRAL AVE., N.E.
MINNEAPOLIS, MN 55432

Date ~~PMA~~ Filed: (~~Filing letter~~ date).

Date Due:

Critical Device: This device (is / is not) on the 3/17/88 FR list of critical devices. The PMA Section thinks it (should / should not) be on the list. See comments.

Site for which clearance is requested:

SEE ATTACHED LETTER (page 2)

Comments:

ATTACHMENTS
1. LETTER
2. P920015 CS V1
" CS V2
" CS V3
" CS V4
" CS V7

cc:
HFZ-402
AA

The Transvene/PCD System clinical study (IDE G870102) includes 319 Transvene lead implants with a mean implant duration of 4.5 months and a total of 1426 device months experience. There are 116 patients with lead system implant duration equal to or greater than six months. The data included in this submission is all data that was received by Medtronic and entered onto the clinical database as of November 27, 1991. The results from the clinical study are provided in Volume 5 of this application.

Market approval is not being sought for use of the Transvene/PCD System with other manufacturers' implantable-cardioverter-defibrillators, nor is it sought for use of the PCD device with other manufacturers' transvenous defibrillation lead systems.

Two manufacturing facilities are to be used in the assembly, sterilization and packaging of the Transvene leads. These are:

1. Medtronic, Inc.
   Rice Creek Facility
   7000 Central Avenue N.E.
   Minneapolis, MN 55432
   Tel: 612-574-4000
   Establishment Registration Number: 2182208
   Is presently prepared for inspection.
   Most recent FDA inspection: January 21-February 8, 1992.

2. Medtronic, B.V.
   Wenckebachstraat 10
   6466 NC Kerkrade West
   The Netherlands
   Tel: 31-45-43-85-85
   Is presently prepared for inspection.
   Most recent FDA inspection: January 6-9, 1992.

The existence of this PMA application and the data and other information it contains are confidential, and the protection afforded to such confidential information by 18 USC 1905 and other applicable laws is hereby claimed.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date April 23, 1992

From Mathematical Statistician (T.C. Lu) HFZ-162
Statistical Branch, Division of Biometric Sciences, OST

Subject Statistical Review of PMA P920015, Medtronic Multiprogrammable Tachyarrhythmia Control System with Non-thoracotomy Cardioversion and Defibrillation Electrodes, Medtronic, Inc.

To Doris Terry - HFZ-450
Division of Cardiovascular, Respiratory, and Neurological Devices
Through: Director, Division of Biometric Sciences, OST MKB for RFC
Through: Chief, Statistical Branch, DBS, OST TCL

1. Background

The Medtronic Pacer-Cardioverter-Defibrillator (PCD) is an implantable, multiprogrammable, automatic tachyarrhythmia control device. This device is used for treatment of patients at risk of sudden cardiac death due to ventricular tachycardia (VT) and/or ventricular fibrillation (VF).

2. Reviewer's Comments

2.1 Pooling

There are a total of 319 implants in 317 patients of the PCD device. A total of 52 investigative centers participated in the clinical trials with 20 centers in the U.S. and 32 in foreign countries. In Vol 5, p 646 - p 650, a section was devoted to the justification for data pooling. Sponsor performed a comparison of U.S. and foreign patients and summarized the variables tested in Table IVA. Sponsor first combined and then compared all the data in U.S. centers and in foreign centers. However, much information was lost in these gross combinations. The initial design with centers nested within countries was reduced to a two-way classification. This is not good statistical practice.

This reviewer recomputed all the p-values listed in Table IVB and IVC; they were all found to be correct, except for the following:

Table IVC

NYHA Classification	p-value (sponsor)	p-value (reviewer)
Congestive Heart Failure	(b)(4)	(b)(4)
Cardiomyopathy		

2.2 Patient follow-up

Table E-2, p. 34, vol. 1, shows the follow-up time by type of data form. This is not an adequate presentation of the follow-up data. Sponsor should refer to p. 93, Table 4.6. in "Statistical Methods for Survival Data Analysis" by Elisa Lee for a more proper life-table analysis. Sponsor should also discuss the reason why some patients dropped out of the follow-up study, either withdrawn alive or lost to follow-up. For example, there are 224 patients at 1 month and only 154 patients at 3 months. Please explain the difference of 70 patients during this 2-month period.

2.3 PCD transvene system compared to AICD Epicardial System clinical experience

For the comparison of complication/observation rates for PCD vs AICD, as reported in Table IL-1, p634, vol 5, I have the following comments:

2.3.1. Please provide the numbers of complications and patients for PCD and AICD.

2.3.2. Please provide the clinical success/failure criteria used for "Failure to Cardiovert/Defibrillate and Inappropriate/Problematic VT/VF Therapy Delivery."

2.3.3. I am concerned that pocket infection is 3.5% for PCD as compared to 2.2% of AICD, even though the sponsor argues that the PCD System implant procedure requires multiple lead configurations. There are other "lead related" complications as reported on Table X1 F1 and F2, P857, Vol. 5. PCD Transvene System has more "lead related" complications than PCD Epicardial System.

2.4. One-year actuarial survival comparison of mortality between the PCD and AICD systems was discussed on p. 842, Vol. 5. Sponsor stated "there was a statistical difference in the reported (AICD) perioperative mortality ($p = 0.017$) with the PCD Transvene System having a lower reported perioperative mortality." I have the following comments concerning this statement:

2.4.1. What statistical test was used to compare survival?

2.4.2. Please provide the two survival or life tables by year of follow-up, so that this reviewer can reproduce the statistical test and the derived p-value.

2.5. Comparison to PCD Epicardial System.

P-values for one-year survival comparison of PCD Transvene System vs. PCD Epicardial System for freedom from death by "sudden cardiac", "non-sudden cardiac", "all cardiac" and "noncardiac" causes are provided in Table X1 G-2, p. 862, Vol. 5, also Table J-2, p. 54, Vol. 1. The sponsor should discuss the statistical techniques used to derive the p-values.

2.6. PCD device longevity data.

Sponsor stated in Section M.1. p. 66, Vol. 1: "Thus, the PCD device longevity, which is monitored, utilizing battery voltage and change time obtained via telemetry, was analyzed. The PCD device longevity data collected is consistent with the longevity projection." This reviewer needs to see the data and statistical test used to support the above statement.

3. Reviewer's Conclusion

The sponsor needs to adequately address the issues raised in Section 2 above before the safety and effectiveness of the PCD Transvene System can be evaluated from a statistical perspective.

T C Lu

T.C. Lu

cc: Abhijit Acharya, Ph.D. - HFZ-450
Donald F. Dahms - HFZ-450
Lynne A. Reamer - HFZ-450
PMS Group - HFZ-402
DCC - HFZ-401
Medical Device File
Board File

DEPARTMENT OF HEALTH & HUMAN SERVICES

Section 301
3-11-81

Memorandum

Date .

From

Subject Filing Review of PMA # P920015

To Premarket Approval Coordinator
Through: (Division Director) _____

Applicant: Medtronic, Inc

Device Trade Name: Medtronic Transvenous Lead System

1. Organizational and Administrative Elements (I and II in the PMA Guideline):

a.	adequate number of copies (check with DCC)	Yes ___ No ___
b.	copy provided with all confidential information deleted	Yes ___ No ___
c.	pages properly numbered	Yes ✓ No ___
d.	table of contents included	Yes ✓ No ___
e.	PMA is signed by applicant or representative in this country	Yes ✓ No ___
f.	complete English translation of PMA	Yes ___ No ✓
g.	Is there currently a pending 510(k) or reclassification petition for this device?	Yes ___ No ✓
h.	Could this device be found substantially equivalent to a Class I or Class II device?	Yes ___ No ✓

2. Summary of Safety and Effectiveness Data (III in Guideline):

a.	description of disease(s) or condition(s) for which the device is used	Adequate ___ Inadequate ___
b.	description of the device	Adequate ___ Inadequate ___
c.	description of alternative practices for the indicated use of the device	Adequate ___ Inadequate ___
d.	potential adverse effects of the device	Adequate ___ Inadequate ___
e.	summary of all studies on the device	Adequate ___ Inadequate ___
f.	conclusions from studies	Adequate ___ Inadequate ___

3. Laboratory Data for Each Investigation (IV in Guideline):

a.	statement of compliance with GLPs	Adequate ✓ Inadequate ___ N/A ___
b.	protocol	Adequate ✓ Inadequate ___ N/A ___
c.	results	Adequate ✓ Inadequate ___ N/A ___
d.	analysis	Adequate ✓ Inadequate ___ N/A ___
e.	conclusions	Adequate ✓ Inadequate ___ N/A ___
f.	Does laboratory data appear to be inadequate, i.e., any obvious studies not conducted?	Yes ___ No ✓

If yes, briefly specify: _____

4. Animal data (V in Guideline):

a.	statement of compliance with GLPs	Adequate	✓	Inadequate	___	N/A	___
b.	protocol	Adequate	✓	Inadequate	___	N/A	___
c.	results	Adequate	✓	Inadequate	___	N/A	___
d.	analysis	Adequate	✓	Inadequate	___	N/A	___
e.	conclusions	Adequate	✓	Inadequate	___	N/A	___

f. Does animal data appear to be inadequate, i.e., were any obvious studies not conducted? Yes ___ No ___

If yes, briefly specify: _____

_____

5. Clinical Data (Item VI, A and B in Guideline):

a. statement of compliance with applicable IDE or other applicable requirements or explanation for non-compliance Yes ✓ No ___ N/A ___

b. If the clinical investigation is ongoing, does this continuing study appear to be in compliance with IDE requirements? Yes ✓ No ___ N/A ___

If no, briefly explain: _____

_____

c. State number of independent clinical investigations. App. 50
If only one clinical investigator has participated in the investigation, is there an adequate justification that this is adequate? Yes ✓ No ___

d. complete description of each clinical study as in VI(A) of Guideline Adequate ✓ Inadequate ___

If not, briefly describe information needed: _____

_____

e. overall results and conclusion as in VI(B) of Guideline Adequate ✓ Inadequate ___

If not, briefly describe information needed: _____

_____

6. Device Characteristics (VII in Guideline):

a.	detailed description of device function	Adequate	✓	Inadequate	___	N/A	___
b.	if applicable, reliability testing provided	Adequate	✓	Inadequate	___	N/A	___

7. Performance Standards (VIII in Guideline):

reference to performance standard or statement of justification for deviation from standard — Adequate ✓ Inadequate ___ N/A ___

8. Labeling (IX in Guideline):

a. labeling in proper format — Adequate ___ Inadequate ___
b. Should patient labeling be required? — Yes ___ No ___ Included in PMA ___
c. Should promotional material be requested? — Yes ___ No ___ Included in PMA ___

9. Bibliography (X in Guideline):

a. bibliography provided — Yes ___ No ___
b. significant articles included — Yes ___ No ___

10. Manufacturing Data (XI in Guideline):

a. copy of labeling and items A-J in a separate volume for EDRO — Yes ___ No ___
b. location of all manufacturing facilities included — Yes ___ No ___
c. organization of firm included — Yes ___ No ___
d. description of physical plant included — Yes ___ No ___
environmental assessment or impact statement included — Yes ___ No ___
e. description of manufacturing equipment — Adequate ___ Inadequate ___ N/A ___
f. description of control system for components — Adequate ___ Inadequate ___ N/A ___
g. description of manufacturing process and flow chart of process — N/A___ Adequate ___ Inadequate ___
h. description of packaging, sterilization and labeling controls — Adequate ___ Inadequate ___ N/A ___

If sterile device, does the PMA include description of method of sterilization, validation data, and pyrogenicity testing and results? — Adequate ___ Inadequate ___ N/A ___

i. description of holding, distribution and installation controls — Adequate ___ Inadequate ___ N/A ___
j. description of finished device inspection — Adequate ___ Inadequate ___ N/A ___
k. description and location of device records — Adequate ___ Inadequate ___

11. Patient Report Forms (XIII in Guideline):

a. patient report forms included — Yes ___ No ___
b. Will additional PRFs be required? — Yes ___ No ___

12. Samples (XIV in Guideline):

Should FDA request a sample of the device? — Yes ___ No ___

Recommendation: Filed _____ Not Filed _____

Comments: _____

_____

_____

If the PMA is to be filed, please specify special considerations or important aspects of the manufacturing process that should be included in the EDRO inspection of the manufacturing facility. _____

_____

_____

Does the device meet the definition of a critical device? _____ Yes _____ No

Note: "Critical device" means a device that is intended for surgical implant into the body or to support or sustain life and whose failure to perform when properly used in accordance with instructions for use provided in the labeling can be reasonably expected to result in a significant injury to the user.

Provide a brief rationale why this device meets the above definition for a "critical device": _____

_____

_____

Is a color additive under section 706 of the act included in this device?
_____ Yes _____ No

Will a statistical review of the PMA be required? _____ Yes _____ No

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date: April 7, 1992

From: Mathematical Statistician (G. Kamer) HFZ-162
Statistics Branch, Division of Biometric Sciences, OST

Subject: PMA Review Statistical Checklist Recommendations for PMA P920015, Medtronic Multiprogrammable Tachyarrhythmia Control System with Non-thoracotomy Cardioversion and Defibrillation Electrodes, Medtronic, Inc.

To: Donald F. Dahms - HFZ-450
Division of Cardiovascular, Respiratory, and Neurological Devices
Through: Director, Division of Biometric Sciences, OST
Through: Chief, Statistics Branch, DBS, OST

The Statistics Branch, DBS, OST has received the PMA referenced above and evaluated it against the attached PMA Review Statistical Checklist. The failures to provide justification for sample size or pooling of data over investigational sites were the only non-serious omissions of a statistical nature. Therefore, we recommend this PMA be filed. We will now begin an in-depth statistical review of this PMA. This review should be completed and our comments sent to you within 30 days. If you have any questions, please contact me at 227-8629 or the statistical reviewer, T. C. Lu, at 227-8627. The omissions found are from the Clinical Investigations Section of the checklist and are stated below for your information:

1. This submission does not include any acceptable justification of sample size. Please provide a complete description of your sample-size determination. This should include effect criteria, alpha and beta statistical error tolerances, anticipated variance of the response variables, and any assumptions or statistical formulae with references that are required for sample-size determination.

2. This submission does not include any justification for pooling (combining) the patient data over site. Please review and analyze your prognostic variables to provide a detailed justification why the data may or may not be pooled for evaluation. Note that an analysis by site is always necessary in any case.

Gary L. Kamer

cc: Abhijit Acharya, Ph.D. - HFZ-450
Lynne A. Reamer - HFZ-450
Doris J. Terry - HFZ-450
T. C. Lu - HFZ-162
Mel Seidman - HFZ-162
PMS Group - HFZ-402
DCC - HFZ-401
Medical Device File
Board File

PMA P920015, Medtronic Multiprog
Tachyarrhythmia Control System with Non-thoracotomy
Cardioversion + Defibrillation Electrodes, Medtronic, Inc

PMA REVIEW STATISTICAL CHECKLIST

	Yes	No	Comment
I. Organizational and Administrative Elements including Table of Contents with volume and page numbers	✓		
II. Summary of Safety and Effectiveness			
A. Indications for use	✓		
B. Claims for the device	✓		
C. Summary of studies	✓		
III. Clinical Investigations			
A. Protocol			
1. included	✓		Summary
2. adhered to	✓	●	
3. deviations described	✓	●	
B. Patient Accountability			
1. patient inclusion/ exclusion criteria	✓		
2. follow-up schedule	✓		
3. study period completed	● ?		
4. all patients accounted for	✓		
C. Description of Safety and Effectiveness Parameters			
1. safety			
2. effectiveness			
~~a. sensitivity~~			
~~b. specificity~~			
~~c. false positive~~			
~~d. false negative~~			
~~e. reproducibility~~			
~~f. repeatability~~			
~~g. stability~~			
D. Documentation of Statistical Analysis and Results			
1. control (comparison) group	✓	●	Historical - AICD + PCD Epi
2. sample size justified		✓	
3. hypothesis test stated	✓		

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time
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only
comple
2 yr f

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	Yes	No	Comment
4. potential of bias adequately evaluated			
a. randomization or blinding techniques	—	—	NA
b. descriptive and stratified analyses			
(1) patient demographics	✓	✓	
(2) investigator	—	✓	
(3) site	✓	—	US vs Foreign
(4) surgical technique	—	✓	NA
5. pooling of data justified	✓	✓	US vs Foreign
6. statistical test given	✓	—	Vague + Device
7. clear presentation of data	✓	—	
8. statistical results stated	✓	—	Not by site
9. statistical conclusions drawn from results	✓	—	

MEMORANDUM

From: Doris Terry (HFZ-450)
To: File # P920015
Subject: Medtronic Transvene System
Date: June 5, 1992
Office: DCRND/ODE

On the basis of a further review of the referenced file, the following concerns have been identified. These deficiencies should be included in a major amendment letter for the manufacturer's response.

Questions and Concerns

1. An update of the clinical experience of the Transvene Lead System should be provided. The update should include all additional patients and the clinical experience to date. The data should be presented as done in your original PMA application, and should include, e.g., implant and follow-up data, spontaneous episode experience, analyses by different groups, complications/observations, and survival analysis. All remaining deficiencies listed below which pertain to your patient population should be addressed using the updated patient group.

2. What is the mean time of device activation for the patient population?

3. Please discuss your clinical data which support the claim which states that the Transvene Lead System improves both perioperative and long term patient morbidity.

4. A discussion of the data or past performance of similar marketed leads which support the adequacy of (b)(4) flex cycles in support of lead performance should be provided.

5. Please discuss how patient treatment is affected if one or two of the electrode coils of the Model 6999 patch lead becomes damaged.

6. Please specify the section of each lead assembly that was flexed during life testing. the results of the tests should be included.

7. Please provide a detailed discussion of all cases of crinkling and curling of the patch leads and dislodgement of the coronary sinus lead.

8. An update of the chronic animal studies should be provided.

9. Are there patients currently implanted with the Model 6895

and 10317 patch leads? If so, please provide a breakdown of the clinical data, e.g., complications, survival, etc. for each lead.

10. A side-by-side comparison of the Model 6897 epicardial patch lead and the Model 6999 patch lead should be provided.

11. Please discuss the results of tests performed with the Transvene System and the Model 2394.

12. Data such as treatment efficacy, complications and survival analysis on the patients followed for 6 months should be provided.

13. Please list the reasons for not performing pre-hospital discharge testing.

14. The number of spontaneous episodes of the patients followed for six months and beyond should be provided.

15. Based on your experience and on the data as reported in the literature, what is the percentage of patients who have been found unable to withstand a thoracotomy?

16. Provide a detailed discussion of the clinical experience (implant duration, spontaneous episodes, treatment efficacy, survival analysis, complications, etc.) of the patients who did not meet the implant criteria and were implanted with the Transvene System. Also discuss the experience of the patients who were implanted without the 10 Joule safety margin.

17. Please discuss your clinical experience (treatment efficacy, complications and survival rates) of the patients who have been followed for one year and more.

18. Based upon your clinical experience, the Physician's Manual should recommend the sequence of testing with the different lead configurations during implant.

19. A breakdown of the different lead configurations within the patient population, and the treatment efficacy reported for each configuration should be included.

20. An update of the life tests on the leads should be provided.

21. A discussion of the energy requirements of the Transvene versus the epicardial lead system should be provided.

22. A copy of the Summary of Safety and Effectiveness with the updated clinical data should be submitted.

MEMO

TO: Doris Terry

FR: Quynh Hoang

RE: Questions concerning the benchtest/prior investigations performed on the Transvene leads from Medtronic - P920015

DA: 6/5/92

SUMMARY

Medtronic requests market approval for the Transvene lead system. The Transvene leads are used with the Model 7217B PCD for pacing, sensing, cardioversion, and defibrillation of the heart. They require non-thoracotomy means for implantation. For a detailed summary of the prior investigations, please refer to the 5/7/92 memo.

Based on my review and the comments given at the working group and filing meetings, the questions for Medtronic include:

1. Discuss the use of a (b)(4) adhesive to prevent tissue in-growth in the Model 6963 lead. Where is the adhesive placed? From experience, discuss the use of (b)(4) and (b)(4) in leads to prevent tissue in-growth.

2. Provide a description of the helix electrode fixation tool and of the tests to verify the torsional force for implanting the helix electrode.

3. From experience, identify the minimum number of flex cycles that a lead should withstand. Also, give the stress level exerted on the Model 6907 lead (from which the median failure time of (b)(4) cycles was observed).

4. Since the electrode coil is flexed separately from the insulated conductor, discuss the reliability of the section where the electrode is coaxial to the conductor. Is there friction between the electrode and the conductor, when the section is flexed?

5. Model 6999's (b)(4) electrode coil fails at a much lower flex cycle than the (b)(4) electrode coil. Discuss the reliability of the (b)(4) electrode coil, and the effects of its failure on the performance of the lead.

6. Discuss the properties of polyurethane which make it the ideal insulation material for the 6966 lead. Why was silicone not chosen?

7. Discuss the biostability tests (stress cracking, MIO, etc.) performed on the two types of polyurethane. Why chose a

different polyurethane for the inner coil?

8. Discuss why the (b)(4) (b)(4) and the (b)(4) (b)(4) (b)(4) (b)(4) (anchor sleeve) have not undergone the mutagenicity test.

9. Based on the results of the lifetest, what is the life expectancy of the leads. Please include your assumptions.

10. What section of each lead was flexed in the lifetest? Does this section include the electrode coil?

11. Provide an update of the (b)(4) month lifetest.

12. The Transvene leads seem to tolerate crush testing better than the pacing leads. Please discuss the properties of the Tranvene leads which take them better.

13. The provided data indicate that a new lead is used for each (temperature tolerance, crush load, or life) test, correlate the results from those tests to the worst case condition where the same lead has to face temperature differences, crushing, and flexing. Why was sequential testing not performed?

14. Compare the 6999 against the epicardial patch leads.

15. Discuss any differences in battery life, between the epi-lead

system and the Transvene system.

16. Some Transvene subjects were also evaluated with the Model 10388 hollow can electrode. Please compare the infection rate of these subjects to the ones who did not undergo the hollow can evaluation.

17. Discuss any possible interaction between the pacemaker leads and the Transvene leads. Also, discuss the effects of these leads on the tricuspic valve and the host vein.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

MAY 14 1992

Ms. Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576

Re: P920015
PCD Transvene System

Dear Ms. Marrone:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) is continuing to process the above named premarket approval application (PMA). Simultaneously with a review by the Office of Device Evaluation (ODE), the Office of Compliance and Surveillance (OCS) must review the manufacturing information in your PMA to determine that it is sufficiently complete and appropriately organized to permit FDA to determine whether your firm (or your contract manufacturer) has the capability of manufacturing your PMA device in accordance with (1) the conditions specified in the PMA application and (2) the requirements of the medical device GMP regulation.

The Division of Compliance Programs (DCP) of OCS has reviewed the manufacturing section of your PMA and believes that it lacks the information necessary to effectively complete a review and determine whether to initiate a PMA inspection (see enclosed). While the deficiencies outlined in the enclosure do not preclude further review of your PMA, if left uncorrected they may delay or preclude evaluation of your manufacturing process and final approval of your PMA application. We request that you respond as indicated. Please be advised that continued review by ODE of your application (including the manufacturing section) may identify additional deficiencies. Also, the OCS review of your response to this letter may identify additional deficiencies.

For your information a Guidance for Preparation of PMA Manufacturing Information was published on March 22, 1991 (a notice of availability was published in the August 20, 1991 Federal Register). It is also available as part of the PMA Manual Supplement which may be obtained from the Division of Small Manufacturer's Assistance at 1-800-638-2041.

Information supplied in response to the enclosed request should be submitted in the form of an amendment **AND BE CLEARLY IDENTIFIED AS A RESPONSE TO AN OCS REQUEST IN YOUR REFERENCE BLOCK.** FDA will consider the PMA to have been withdrawn voluntarily if you fail to respond in writing to this request for an amendment within 180 days of the date of this letter as provided under 21 CFR 814.44(g). You may, however, amend the PMA within the 180 day period to request an extension of time to respond. Any such request is subject to FDA approval and must justify the need

for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180 day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180 day period will be considered a resubmission of the PMA and will be assigned a new number. A resubmission should be complete and self-contained without reference to earlier submissions because of potential difficulties in assembling files from storage.

All correspondence regarding this PMA should be submitted in three (3) copies in the form of a PMA amendment to the address below and reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)
ATTN: MQAB
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

This letter reflects the current progress of our review of your application. Please be advised, however, that continued review of your application or questions arising from any response to this letter, may result in additional deficiencies being identified.

If you have any questions concerning this deficiency letter, please contact Frank Twardochleb at (301) 427-1128.

Sincerely yours,

for Deborah J. Lewis

Philip J. Phillips
Director, Program Operations Staff
Office of Device Evaluation
Center for Devices and
Radiological Health

Deficiency List

The Office of Compliance and Surveillance (OCS) in the Center for Devices and Radiological Health (CDRH) has completed an initial review of your premarket approval application (PMA), P920004, with regard to the Good Manufacturing Practice (GMP) regulations. Please address the following issues and provide the requested documentation:

1. The Design Assurance Plan, (b)(4) (b)(4) dated 2/7/91 for the new helix electrode, part 136250-001, is not representative of the manufacturing operations. The qualification report dated 4/16/91 does not address the effects of the sterilization process on the integrity of the helical electrode. [vol.2, pp.153-156]

2. Provide the locations of the biological indicators used during the sterilization validation and routine production for the 6966 lead. [vol.2, p.207]

3. Provide the product density and configuration pattern for the 6966 sterilization cycle. [vol.2, p.207]

4. Provide the maximum parameter of the humidity specification for the sterilization cycle of the 6966 lead. [vol.2, p.211]

5. The finished device evaluation for the 6966 lead does not adress the effect of sterilization on device performance. [vol.2, p.174]

6. The validation plan for 6963 lead does not address the effects of the sterilization cycle on device performance. [vol.3, p.327]

7. The process qualification report, (b)(4) (b)(4) does not address the effects of the sterilization cycle on the performance of the 6999 lead. [vol.3, p.335]

8. Provide the product location of biological indicator and spore inoculation for the validation and production sterilization cycles of the 6963 and 6999 leads. [vol.3, p.372]

9. Provide the maximum parameter of the (b)(4) (b)(4) exposure for the 6999 lead. [vol.3, p.376]

10. Explain the difference in the sterilization (b)(4) exposure parameters of the 7217B PCD Control Device between the two manufacturing facilities. The (b)(4) exposure parameter at the Rice Creek facility is (b)(4) minutes; the (b)(4) exposure parameter at the Kerkrade facility is (b)(4) minutes minimum. The Kerkrade facility does not specify a maximum (b)(4) exposure. [vol.4, p.415 and p. 432]

11. Provide the manufacturing methods, controls, and evaluation procedures for the facility identified as Medtronic Milaca, 900 6th Ave. N.E. Milaca, MN 56353. [vol.4, p. 437]

MEMO

TO: Doris Terry
FR: Quynh Hoang
RE: Review of the benchtest/prior investigations performed on the Transvene leads from Medtronic - P920015
DA: 5/7/92

SUMMARY

Medtronic requests market approval for the Transvene lead system. The Transvene leads are used with the Model 7217B PCD for pacing, sensing, cardioversion, and defibrillation of the heart. They require non-thoracotomy means for implantation.

Device Descriptions

The Transvene lead system consists of three leads, Models 6963, 6966, and 6999. The leads contain conductor coils made of a (b)(4) core and a (b)(4) shell. Their electrodes are made of a platinum/iridium alloy.

Model 6963 is a unipolar, transvenous, coronary sinus/superior vena cava (CS/SVC) lead. It serves as an anode for cardioversion and defibrillation. It consists of a (b)(4) connector (b)(4) connector pin and (b)(4) rubber sleeve); a conductor coil insulated by (b)(4) rubber; and, a coil electrode of (b)(4) inches in length (b)(4) To prevent tissue in-growth, a (b)(4) adhesive is used with the lead.

Model 6966 is a tripolar, transvenous, right ventricular (RV), screw-in lead. It serves as the pacing/sensing, as well as a cathode (common) for cardioversion and defibrillation. It consists of a bipolar (b)(4) connector (b)(4) connector ring and rotatable pin, and (b)(4) rubber sleeve) for the ring and helix electrodes: an unipolar (b)(4) connector (b)(4) connector pin and (b)(4) rubber sleeve) for the coil electrode: a tri-layer conductor coil coated with (b)(4) and insulated by (b)(4) rubber; a coil electrode of (b)(4) inches in length (b)(4) a ring electrode with (b)(4) surface area; and, a helix electrode of (b)(4) surface area. Correlating the functions of the lead and its three electrodes: pacing takes place between the coil and helix electrodes; sensing takes place between the ring and helix electrodes; and, cardioversion/defibrillation takes place between the coil electrode and the other leads. (b)(4) tubing prevents tissue in-growth in the lead.

Model 6999 is a unipolar, sub-cutaneous (SQ), patch lead. It serves as an anode for cardioversion and defibrillation. It consists of a (b)(4) connector (b)(4) pin and (b)(4) rubber sleeve); a conductor coil insulated by (b)(4) rubber; and a (b)(4) rubber patch embedded with a (b)(4) and (b)(4) electrode coils. The

inside of the electrode coils is filled with (b)(4) rubber to prevent tissue in-growth in the patch.

Components for use with the leads are: a (b)(4) anchoring sleeve for stationing the lead body at the insertion site; a (b)(4) for stiffening the lead during insertion; and, an active fixation tool for entrenching the helix. Descriptions of the fixation tool have not been provided.

Performance Data

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

RECOMMENDATION

Based on the above review of the Transvene lead system, filing is recommended. A major amendment, regarding the concerns raised here, is expected.

APR 17 1992

MEMORANDUM TO FILE FOR P920015

From: Associate Director
Pacing and Neurological Devices
DCRND

Through: Chief
Pacing and Electrophysiology Devices Branch
DCRND

Subject: Request for Expedited Review Status for Non-Thoracotomy Leads

On February 11, 1992, Medtronic submitted a letter (copy attached) requesting that FDA consider Expedited Review Status for their yet to be submitted PMA for an implantable non-thoracotomy lead to be used with their implantable pacer cardioverter defibrillator (PCD) device. At a meeting held with Medtronic on March 13, 1992, we discussed the advantages and disadvantages of tagging the PMA for expedited review. The comments expressed at this meeting were excerpted from a review memo dated March 5, 1992 (copy attached). After some discussion, Medtronic agreed not to pursue "expedited review".

A response to Medtronic's February 11,1992 letter will not be sent and the PMA will be reviewed in the normal fashion.

Lynne Reamer

Lynne Reamer

Medtronic

Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576
Telephone: (612) 574-4000
Cable: Medtronic Telex: 29-0598
Telecopy: (612) 574-4879

February 11, 1992

Abhijit Acharya, Ph.D.
Director, Division of Cardiovascular,
Respiratory and Neurological Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

Dear Doctor Acharya:

With this letter. I am requesting a meeting with you and members of your staff regarding the PMA for our Non-Thoracotomy Lead (NTL) System for use with our PCD™ device. I am aware of your recent meeting with Bill Hogan and your discussion regarding the potential for expedited review. Naturally, we are very interested and believe the NTL System is an appropriate candidate.

The purpose of the meeting would be to understand the process for expedited review and what we need to do to obtain expedited review for the NTL PMA. In addition, we would like FDA feedback on the structure and content of the PMA. A proposed agenda for the meeting is attached. Your participation in the meeting is critical based on your previous discussions on this subject.

I had hoped to discuss this subject with you last week. At your suggestion, I followed up with Lynne Reamer. She was receptive to a meeting. She also recommended that we put the basis for expedited review in writing which is attached.

We will follow up in a few days to schedule a meeting time. In the meantime, if you have any questions, please call me.

Sincerely,

MEDTRONIC, INC.

Charles H. Swanson, Ph.D.
Director, Regulatory Affairs
Cardiac Pacing Business
(612) 574-3409

c: Lynne Reamer
Don Dahms
Doris Terry

PROPOSED FDA/MEDTRONIC MEETING AGENDA FOR THE NON-THORACOTOMY LEAD PMA

Medtronic Attendees:

Kris Johnson, Vice President and General Manager
Charles Swanson, Director of Regulatory Affairs
Jennifer Marrone, Manager of Regulatory Affairs
Dan Schaber, Manager of Tachyarrhythmia Clinical Evaluation
Sue Norenberg, Clinical Evaluation Manager

INTRODUCTION AND OBJECTIVES

DISCUSSION ON EXPEDITED REVIEW PROCESSES

What Is the Process?

Application to NTL PMA (See Attachment)

FDA SUGGESTIONS ON PMA CONTENT AND FORMAT

PMA Versus PMA-Supplement

Presentation of Clinical Data

Inclusion of Bench, Animal, Clinical Data on PCD Device

Attachment

EXPEDITED REVIEW FOR THE USE OF NON-THORACOTOMY LEADS WITH PCD™

In recent discussions between Medtronic and FDA, the concept of "Expedited PMA Review" has been raised. We are requesting a meeting with FDA to discuss its applicability to the Non-Thoracotomy Lead (NTL) System for use with our Implantable Pacer Cardioverter Defibrillator (PCD). This system is currently under clinical evaluation and we expect to submit a PMA or PMA Supplement in the near future. This paper presents Medtronic's view on why expedited review is warranted as a basis for further discussion.

It is our understanding that devices should receive expedited review if they meet either of the following criteria:

- Applies to a life-threatening or severely debilitating illness.
- Makes therapy available to patients who could not otherwise receive adequate therapy.
- Represents a major advancement in therapy that provides significant patient and/or public health benefits.

We believe that the NTL System meets these criteria. The data cited below is based on our clinical experience with the NTL System. These data were the basis for approval by Medtronic's Executive Committee for market release of the NTL System outside the U.S. These data will of course be included in FDA submissions as well.

Life-Threatening Disease

The PCD is indicated for patients who have experienced an episode of sudden cardiac death or who have recurrent sustained ventricular tachycardia that cannot be controlled effectively with drugs. The prognosis for these VT and VF patients is very poor (34-73% survival at one year when treated with drugs alone).

Patients With No Alternative Therapy

There is a class of patients who cannot tolerate the thoracotomy required for utilization of the patch lead system and who are at high risk of sudden death. For these patients, the NTL System is the only therapy available.

Current implantable cardioversion/defibrillation therapies use epicardial patch systems which require major procedures such as a sternotomy to introduce the lead systems. Because of the surgical risks and postsurgical complications, this critical life-saving therapy is not available to certain patient categories. These include:

- Patients that pose high surgical risk because of their state of health
- Potential heart transplant candidates
- Patients who for varying reasons refuse to submit to the major surgical procedure required

The NTL System simplifies and greatly reduces the risk associated with lead introduction, making therapy available to these patient groups. Because there is not a need to open the chest of these patients, options for future therapy remain available; e.g., CABG is associated with a decreased morbidity and mortality if there has been no prior open chest surgery.

Significant Patient and Public Health Benefits

In simplifying surgical procedures and reducing their attendant risks, the NTL System provides significant benefits to patients both in terms of safety and quality of life.

The benefits are clear in reduced mortality and morbidity. As reported in our current PCD/Patch Lead PMA application (N=434), perioperative mortality is 5.5% and overall mortality is 14.4%. With the NTL System (N=319), perioperative mortality is 0.4% and overall mortality is 3.6%.

The NTL System is also associated with a reduction in postoperative complications, faster recovery and shorter hospitalization, which mean an improved patient quality of life. These clear benefits are obtained for all patients without any change in effectiveness of VT/VF therapies versus PCD/Patch Systems.

Finally, the NTL System also offers clear public health benefits in this era of concern about increasing health care costs. The ease of introduction of the NTL System reduces surgical costs and the reduction in surgical trauma decreases hospitalization time (average 8 days for patients with NTL Systems versus 12 days for patients with patch systems).

Time factor? MD comments?

We believe all these factors clearly establish the patient and public health benefits of the NTL System and justify expedited review and PMA approval by FDA.

MEMORANDUM

Date: March 5, 1992

To: Director, DCRND, ODE (HFZ-450)

From: ADPN, DCRND (HFZ-450)

Subject: Request for Expedited Review

Background

On February 11, 1992, Medtronic submitted a letter requesting that FDA consider expedited review status for an implantable (non-thoracotomy) lead to be used with their Pacer Cardioverter Defibrillator (PCD). The new lead would be in addition to the one (thoracotomy) presently being used with the PCD. The PCD and its attendant thoracotomy lead system was recently presented to the Circulatory System Devices Panel (February 3, 1992) and was recommended for approval. An approvable letter is currently being prepared for the PMA application.

The new implantable lead designed to be used with the PCD as an alternate lead system is a non-thoracotomy lead (NTL), i.e., the chest does not have to be opened to insert the lead. The NTL is being studied clinically under G870102. Currently, implantable defibrillators are used with leads that must be inserted by thoracotomy.

Medtronic's Position

Medtronic claims that there are significant patient and public health benefits using an NTL because the insertion procedure is simplified and shortened, the surgical risks are reduced, postoperative complications are reduced, hospitilization time is shortened, costs are reduced and mortality is reduced.

Medtronic also claims that use of the implantable defibrillator with its current thoracotomy lead system is not available to patients who fall into the following three categories: (1) patients who pose high surgical risk because of their state of health; (2) potential heart transplant candidates; and, (3) patients who for varying reasons refuse to submit to the major surgical procedure required.

FDA Concerns

The indications for use of a PCD are: (1) patients who have survived at least one episode of cardiac arrest due to ventricular arrhythmia not caused by an acute myocardial infarction; or (2) patients with recurrent sustained, ventricular tachycardia that remains inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most

efficacious antiarrhthymic drug therapy that can be tolerated by the patient chronically; and (3) patients who are undergoing a replacement of a previously implanted cardioverter defibrillator. Alternate therapies to treat ventricular tachyarrhythmias include antiarrhythmic drug therapy, ventricular tachycardia surgery, and transthoracic defibrillation.

According to General Program Memorandum #G89-2, expedited review is available for a new device use to treat "a life-threatening or severely debilitating illness for which there is no alternate diagnosis, therapy, or prevention modality." In the case of the PCD, patients are at risk of sudden cardiac death due to ventricular tachyarrhythmias. Estimates report that 450,000 people experience sudden cardiac death annually. Medtronic does not document how many patients cannot receive a PCD because thoracotomy leads are used. The second part of the definition of qualification for expedited review requires that there be no alternate diagnosis, therapy of treatment modality. There are in fact alternate treatment modalities as mentioned above.

However, at issue is not whether the PCD is of benefit or not, but whether the current lead system which must be inserted by thoracotomy poses more risk to the patient than the new NTL lead system. Medtronic did not mention expedited review when they originally proposed their clinical trial of the NTL. The IDE was approved on October 4, 1990, and was handled in a normal fashion with no emphasis on a feasibility study. To date, according to Medtronic, 319 patients have been implanted with the NTL. No special meetings have been requested by, or held with Medtronic to guide them in their clinical study. Because we have not closely worked with Medtronic during the clinical trial, we have no idea whether the clinical data support the premise that there is less morbidity and mortality with the NTL.

At issue is also the fact that we have under review an original PMA from a competitor for a non-thoracotomy lead system for their automatic implantable cardioverter defibrillator. When this PMA was submitted expedited review was not requested. Unlike the Medtronic PCD, which was just recommended for approval by the Circulatory System Devices panel, the competitor's defibrillator is on the market. If expedited review is to be granted for NTLs at all, it should be granted to the competitor's device first because their defibrillator is on the market and when their NTL is approved, their system will be the first available. Let's follow this scenario. The reviewer assigned to the competitor's NTL is the same reviewer who is working on the approval package for the Medtronic PCD. If expedited review status is granted for NTLs, the competitor's NTL moves to the top of the review pile and may delay the approval of the Medtronic PMA for their PCD. Since the Medtronic NTL can only be used with the Medtronic PCD, Medtronic has to have their PCD approved before the NTL can be used. If we follow this scenario, Medtronic's argument for expedited review falls apart, because there will be an alternate lead system available - the competitor's system, not Medtronic's.

FDA Position

There is an alternate implantable lead available to use with the Medtronic PCD. In addition, Medtronic did not approach us early on at the IDE stage regarding expedited review, we believe it is inappropriate to consider expedited review at the PMA stage. We did not work closely with them to design the clinical study and have not frequently monitored the data through progress reports. The IDE has been handled as a regular IDE and the number of patients entered in the study indicate that Medtronic was in no great hurry to get this over with. They had various opportunities to request expedited review when they submitted supplements to the IDE to request study expansion. But they did not. Only after the PMA for their PCD was recommended for approval did they approach us with the expedited review request.

(b)(4) did not request expedited review and were in a far better position to succeed if they had because they already have an approved automatic implantable cardioverter defibrillator on the market. If anyone should receive expedited review status, it should be (b)(4)

Based on the above, our recommendation is to deny Medtronic's request based on the fact that there is an alternate implantable lead available for use with Medtronic's PCD which is part of the recent PCD PMA, and on the language in Guidance Memorandum G 89-2, in that Medtronic did not fulfill the IDE requirements.

Action

Draft a letter to Medtronic explaining our position and denying their request.

Lynne Reamer

Lynne Reamer

MEMORANDUM

From: Doris Terry (HFZ-450)
To: File # P920015
Subject: Medtronic Transvene System
Date: April 13, 1992
Office: ODE/DCRND

The applicant seeks approval of its non-thoracotomy leads, the PCD Transvene System. The system is composed of the Model 6963 Unipolar Coronary Sinus or Superior Vena Cava lead for cardioversion and defibrillation; the Model 6966 Tripolar, Endocardial, Screw-In Lead for pacing, sensing and cardioversion and defibrillation and the Model 6999 unipolar, subcutaneous patch lead for cardioversion and defibrillation.

The indications for use of the Transvene System are similar to those of the Medtronic PCD models. The applicant contends that due to the less invasive nature of the non-thoracotomy leads, the system can be implanted in patients who may not be able to undergo a thoracotomy.

Description of the System

The Model 6963 is a (b)(4) unipolar, coronary sinus or superior vena cava lead with (b)(4) connector and (b)(4) electrode for delivery of cardioversion and defibrillation therapies.

The Model 6966 is a (b)(4) tripolar extendable/retractable, screw-in lead with a (b)(4) connector and (b)(4) electrode for cardioversion and defibrillation. The lead also has a (b)(4) connector for pacing and sensing.

The Model 6999 is a (b)(4) unipolar, oval subcutaneous patch with a (b)(4) connector and (b)(4) electrode coils embedded in the (b)(4) patch. The lead is intended for cardioversion and defibrillation.

Lead System Life Testing

(b)(4)

(b)(4)

(b)(4)

Clinical Studies

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Recommendation: There are no concerns regarding the data as submitted. Based on our review, to date. the determination has been made that the application is suitable for filing.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
1390 Piccard Drive
Rockville, Maryland 20850

April 3, 1992

JENNIFER M. MARRONE
MEDTRONIC INC.
7000 CENTRAL AVENUE, N.E.
MINNEAPOLIS, MN 554323576

PMA Number: P920015 SUP 000
Letter Dated: 03/31/92
Received: 04/01/92
Product: MEDTRONIC(R)
TRANSVENE LEAD
SYSTEM

Dear MS. MARRONE:

The Center for Devices and Radiological Health (CDRH) acknowledges its receipt of the premarket approval application (PMA) supplement submitted by you for the above referenced device. This PMA supplement has been assigned an unique document control number. Failure to reference this supplement number in further correspondence may result in processing delays. All further correspondence shall be referred to as amendments to the PMA supplement, and the required number of copies bearing the above PMA supplement number shall be submitted directly to:

Food and Drug Administration
Center for Devices and
Radiological Health
PMA Document Mail Center (HFZ-401)
1390 Piccard Drive
Rockville, Maryland 20850

You will be notified of any need for additional information and the CDRH filing decision. Questions concerning this submission may be directed to the PMA Staff at (301) 427-1186 or to the reviewing division within the CDRH Office of Device Evaluation.

Sincerely yours,

/S/

Charles H. Kyper
Director, Premarket Approval Staff
Office of Device Evaluation
Center for Devices and
Radiological Health

Medtronic

Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576
Telephone: (612) 574-4000
Cable: Medtronic Telex: 29-0598
Telecopy: (612) 574-4879

P920015/C2V1

March 31, 1992

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FDA/CORN/OBE/DMC

Office of Device Evaluation
PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

Re: Premarket Approval Application (PMA) for the Medtronic® Multiprogrammable Tachyarrhythmia Control System with Non-thoracotomy Cardioversion and Defibrillation Electrodes, i.e., the PCD™ Transvene System, Lead Models 6963, 6966 and 6999.

This submission is a PMA application for the Medtronic Transvene Lead System used in conjunction with the Model 7217B pacer-cardioverter-defibrillator (PCD), Model 5355 external tachyarrhythmia control device (ETCD) and Model 9788 MemoryMod Software Module.

The PCD and ETCD devices as used with an epicardial lead system were recommended for approval by the FDA Advisory Panel on February 3, 1992 (P900061). The purpose of this PMA application is to obtain approval for the use of the non-thoracotomy lead system for use with the Medtronic PCD and ETCD. The terms non-thoracotomy leads (NTL), transvenous leads and Transvene Lead System are synonymous and may be used interchangeably throughout this application.

The Transvene System, in conjunction with the PCD device, is intended to treat patients at risk of sudden cardiac death due to ventricular arrhythmias. Like the epicardial electrodes/PCD System, the primary benefits from the use of the Transvene/PCD System center on the detection and termination of these life-threatening ventricular arrhythmias. The incorporation of a non-thoracotomy lead system allows for a safer and effective implantation procedure, and improving both perioperative and long-term patient morbidity and mortality.

The Transvene/PCD System clinical study (IDE G870102) includes 319 Transvene lead implants with a mean implant duration of 4.5 months and a total of 1426 device months experience. There are 116 patients with lead system implant duration equal to or greater than six months. The data included in this submission is all data that was received by Medtronic and entered onto the clinical database as of November 27, 1991. The results from the clinical study are provided in Volume 5 of this application.

Market approval is not being sought for use of the Transvene/PCD System with other manufacturers' implantable-cardioverter-defibrillators, nor is it sought for use of the PCD device with other manufacturers' transvenous defibrillation lead systems.

Two manufacturing facilities are to be used in the assembly, sterilization and packaging of the Transvene leads. These are:

1. Medtronic, Inc.
   Rice Creek Facility
   7000 Central Avenue N.E.
   Minneapolis, MN 55432
   Tel: 612-574-4000
   Establishment Registration Number: 2182208
   Is presently prepared for inspection.
   Most recent FDA inspection: January 21-February 8, 1992.

2. Medtronic, B.V.
   Wenckebachstraat 10
   6466 NC Kerkrade West
   The Netherlands
   Tel: 31-45-43-85-85
   Is presently prepared for inspection.
   Most recent FDA inspection: January 6-9, 1992.

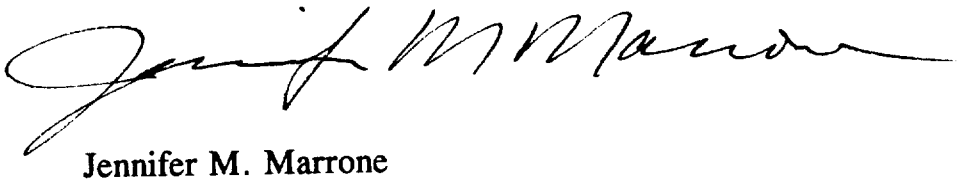
The existence of this PMA application and the data and other information it contains are confidential, and the protection afforded to such confidential information by 18 USC 1905 and other applicable laws is hereby claimed.

In accordance with 21 CFR 814.42(a), the FDA has 45 days from the date of receipt to notify Medtronic if this application is sufficiently complete for a substantive review and acceptable for filing.

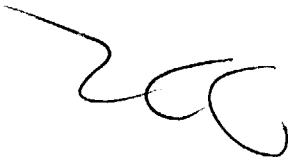
Six copies of this application are enclosed. Should additional information be required by the Agency, please contact the undersigned.

Sincerely,

MEDTRONIC, INC.

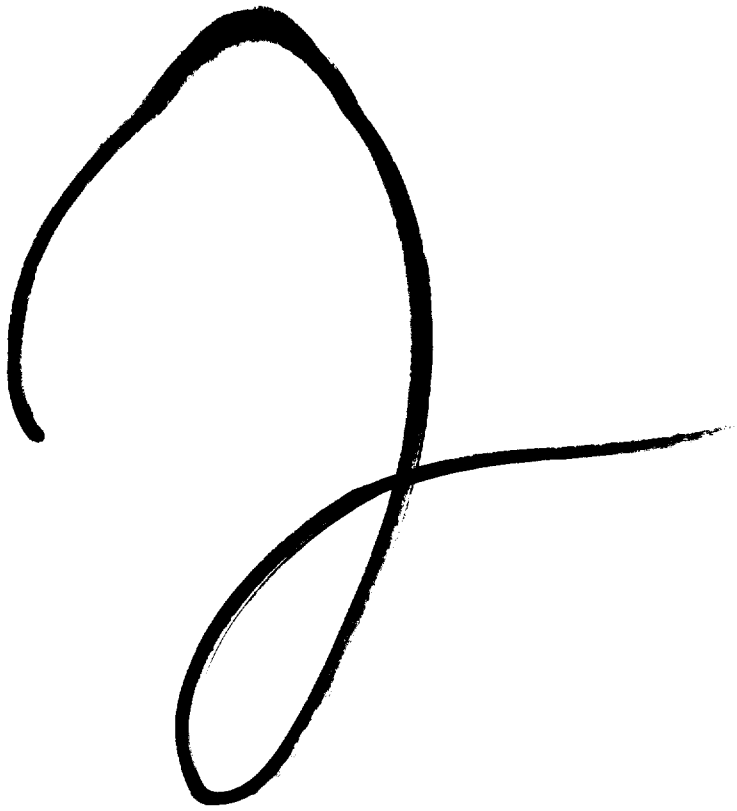


Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
(612) 574-4688
(612) 574-6424 FAX



I. Sponsor Name and Address

Medtronic, Inc.
7000 Central Avenue N.E.
Minneapolis, MN 55432



Medtronic® Transvene™ Non-thoracotomy Leads PMA

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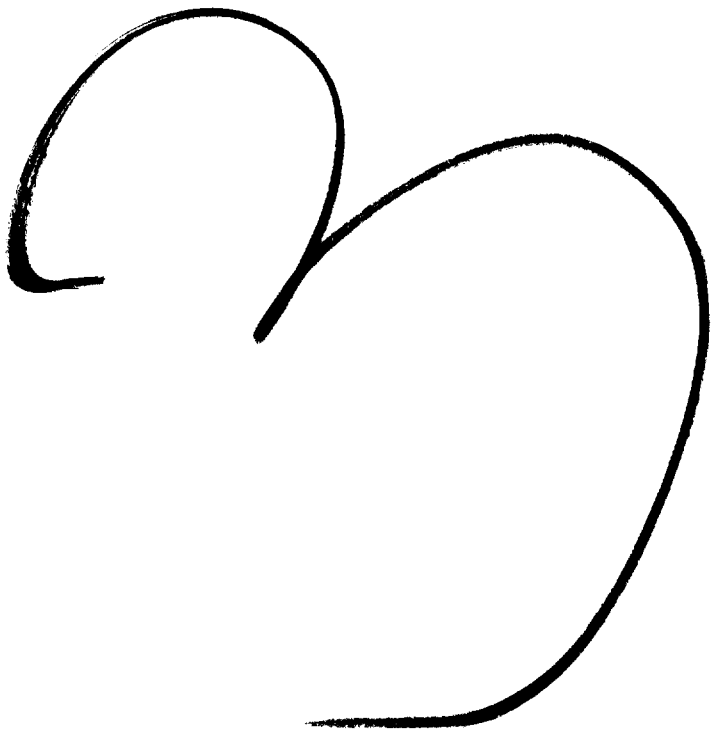

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III. Summary of Safety and Effectiveness

A. Indications For Use

The Medtronic PCD Model 7217B Multiprogrammable Tachyarrhythmia Control System with Nonthoracotomy Cardioversion and Defibrillation Electrodes (hereafter referred to as the PCD Transvene System) is intended to treat patients at risk of sudden cardiac death due to ventricular tachyarrhythmias. Indications for use include:

- Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or
- Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.
- Patients undergoing replacement of a previously implanted implantable cardioverter defibrillator.

The patients who meet the above patient selection criteria should have also undergone a complete cardiological evaluation that includes electrophysiological testing. Electrophysiologic evaluation and testing of the safety and efficacy of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the PCD Transvene System.

The PCD Transvene System components, except for the defibrillation lead system, are identical to the PCD Epicardial System which was unanimously recommended for approval by the FDA Advisory Panel on February 3, 1992.

Market approval **is not** being sought for use of the PCD Device with other manufacturers transvenous defibrillation lead systems. In addition, market approval **is not** being sought for the use of the PCD Transvene lead system with other manufacturers implantable cardioverter defibrillators.

B. Description of the Transvene Lead/PCD System

The Medtronic Tachyarrhythmia Control System consists of two fundamental configurations: (1) the implantable configuration and (2) the external configuration. Both configurations use the Transvene lead system. See Figure III B-1

The implantable configuration is composed of a Pacer-Cardioverter-Defibrillator (PCD) device, implantable leads, and a programmer. The PCD device is an implantable, multiprogrammable, automatic tachyarrhythmia control device.

The external configuration is composed of an External Tachyarrhythmia Control Device (ETCD), a patient cable, implantable leads, and a programmer. The ETCD is an externally-operated, multiprogrammable, tachyarrhythmia control device.

Intended Uses - Transvene Leads

Model 6963 Lead

The Medtronic Transvene Model 6963 Unipolar, Coronary Sinus or Superior Vena Cava, Transvenous Lead features an electrode for the delivery of cardioversion and defibrillation therapies. It is intended for long-term use in the coronary sinus or superior vena cava and is designed to be used with an implantable tachyarrhythmia control device along with at least one other lead, such as the Model 6966 Tripolar, Right Ventricular, Transvenous Lead.

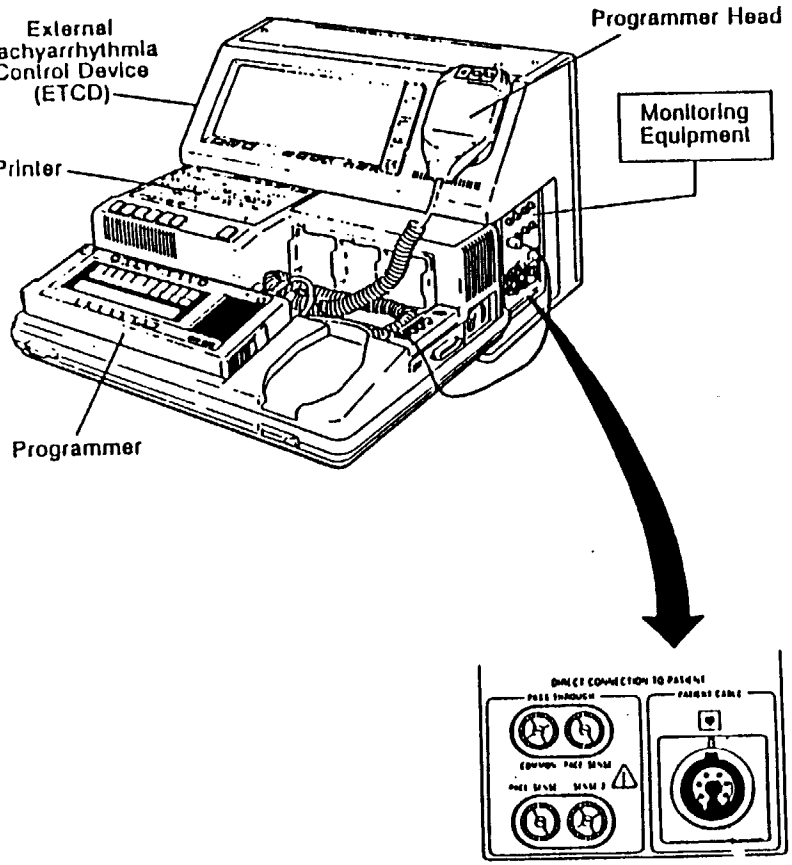
The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

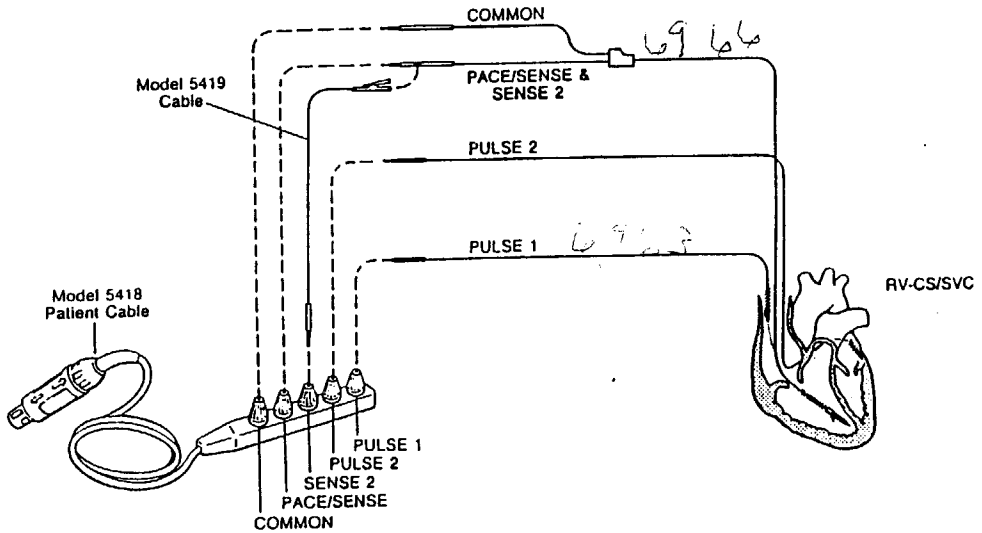
Model 6966 Lead

The Medtronic Transvene Model 6966 Tripolar, Endocardial, Screw-In Lead is designed for pacing, sensing, and delivering cardioversion and defibrillation pulses in the ventricle. The lead has application where implantable tachyarrhythmia control systems are indicated.

The Model 6966 lead has a helical electrode made of platinum alloy that can be actively fixed in the endocardium. The helix can be extended or retracted by rotating the lead connector pin with a special fixation tool.

FIGURE III B-1





Connections to Model 5418 Patient Cable for
Typical Simultaneous or Sequential Pathway (RV-CS/SVC).

Active fixation leads are particularly beneficial for patients who have smooth or hypertrophic hearts where lead dislodgement may be potential a problem.

The three electrodes of this lead are the coil, ring, and helix:

The defibrillating **coil electrode** is most proximal to the pulse generator and connects electrically to the connector pin of the unipolar leg of the bifurcation. This unipolar leg will not accept a stylet.

The **ring electrode** is proximal to the helix and connects electrically to the connector ring of the bipolar leg of the bifurcation.

The **helix tip electrode** is most distal to the pulse generator and provides active fixation in the endocardium. It can be extended or retracted by rotating the lead connector pin with a special fixation tool. The helix electrode connects electrically to the connector PIN of the bipolar leg of the bifurcation. This bipolar leg is the only one that will accept a stylet.

The helix tip electrode and the ring electrode may be used for bipolar pacing and sensing; the coil electrode is intended to be used for delivery of cardioversion and defibrillation pulses.

The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

Model 6999 Lead

The Medtronic Model 6999 Unipolar, Subcutaneous, Oval, Patch Lead features an electrode for the delivery of cardioversion and defibrillation therapies. It is intended for long-term use and is designed to be used with an implantable tachyarrhythmia control device along with at least one complementary defibrillating electrode and a pacing/sensing lead; a third defibrillating electrode may also be used.

The lead has application for patients in whom implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

Intended Uses - PCD Device

The Model 7217B PCD device is intended for use in patients who are at high risk of sudden death due to ventricular tachyarrhythmia.

Current medical research indicates that such patients should:

- have survived at least one episode of a cardiac arrest, presumably due to a ventricular tachyarrhythmia as evidenced by resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; or
- in the absence of a prior cardiac arrest, have recurrent, sustained ventricular tachycardia that occur spontaneously or can be induced, despite the most efficacious antiarrhythmic drug therapy that can be tolerated chronically.

Extensive electrophysiologic evaluation and testing of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the Model 7217B PCD device. Before permanently programming the PCD device to the automatic detection and delivery of the VT and/or VF therapies, the patient should have demonstrated a satisfactory response to the proposed therapy.

Intended Uses - ETCD

The Model 5355 External Tachyarrhythmia Control Device is intended for use in conjunction with an antitachycardia/defibrillation lead system during diagnostic studies for implanting the Model 7217B PCD device.

Indications for use of the ETCD include:

- Patients experiencing recurrent episodes of ventricular tachyarrhythmia,
- Patients who survived a cardiac arrest due to a ventricular tachyarrhythmia and are at risk for repeated episodes,
- Patients who are undergoing an assessment of the efficacy of antitachycardia pacing, cardioversion, or defibrillation therapies in anticipation of an implantable cardioverter-defibrillator.

Components of the System

A list of components used in the system is given below. It is separated into a listing of those components for which market approval is sought and those components that are now commercially available. Market approval is not being sought for use of the PCD Device with other manufacturers transvenous defibrillation lead systems or for the use of the PCD Transvene lead system with other manufacturers implantable cardioverter defibrillators.

Seeking Approval:

Transvene Leads
- Model 6963
- Model 6966
- Model 6999

Pacer-Cardioverter-Defibrillator (PCD) Device*
- Model 7217B

External Tachyarrhythmia Control Device (ETCD)*
- Model 5355 ETCD
- Model 5418 Patient Cable
- Model 5419 Patient Cable
- Model 5414 Test Load
- Model 5417 EGM Cable

Programmer Software Cartridge*
- Model 9788 - Memory Module for 7217B PCD Device and 5355 ETCD Devices

Lead Accessories*
- Model 6701 Lead End Cap

Commercially Available:

Programmers Model 9710 and accessories

Printers Model 9751/9712

* Indicates devices pending FDA approval, P900061

Components Used in the Implantable Configuration

The implantable configuration is composed of a PCD Device, lead system, and a 9710 Programmer with applicable software cartridge. The implantable device is a Model 7217B PCD Device. The PCD device requires an appropriate lead system consisting of up to three cardioversion/defibrillation electrodes. See Figure III B-2. The Transvene leads used with the Model 7217B PCD Device are the Models 6963, 6966, and 6999.

The Model 9710 Programmer is commercially available. Two printers are also commercially available. When higher printing speeds are desired, it is recommended that the programmer be used with the faster printer, the Model 9751. If slower printing speeds are acceptable, as may be the case in some follow-up situations, the Model 9710 Programmer can be used with the battery-powered Model 9712 Printer.

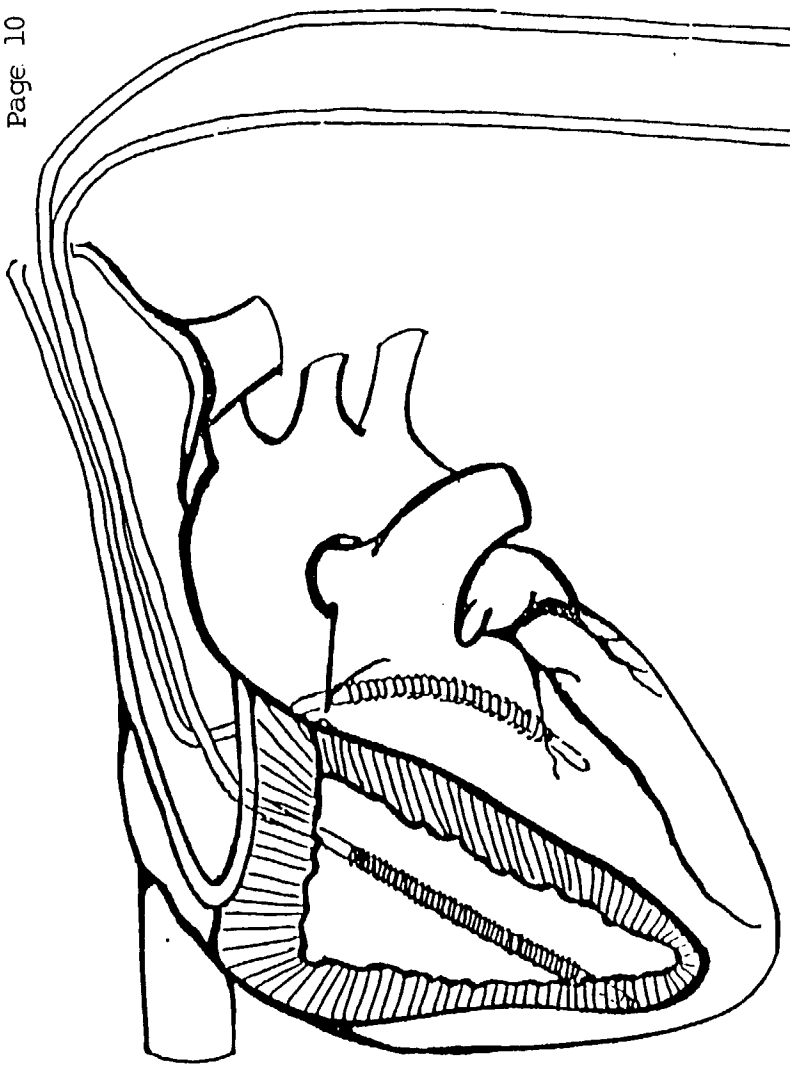
Components used in the External Configuration

The external tachyarrhythmia control system is composed of the Model 5355 ETCD, a Model 5418 Patient Cable, a Model 5419 cable, lead system, and a Model 9710 Programmer with applicable software cartridge, see Figures IV-A-3, 4. The ETCD uses replaceable batteries as its power source. The Model 5418 Patient Cable and Model 5419 Cable are designed to connect the Transvene leads to the ETCD. Like the implantable system, the ETCD uses the same Transvene leads (Models 6963, 6966, and 6999).

MEDTRONIC CONFIDENTIAL

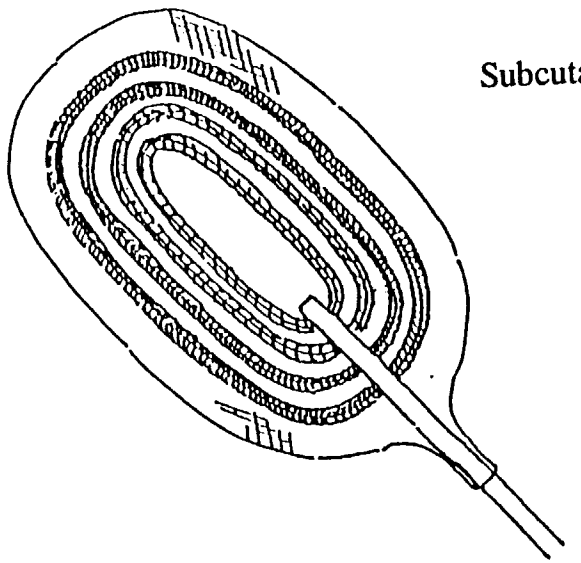
FIGURE III B--2
Page 10

Non-Thoracotomy Lead System for PCD



Model 6963 Coronary Sinus or Superior Vena Cava

Model 6966 Right Ventricle



Subcutaneous Patch

Model 6999

Purpose of the System

PCD System Configuration

The PCD Device is an implantable device designed to detect episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF), and upon detection, automatically deliver the appropriate therapy or a progression of therapies programmed by the physician for each patient. The available therapy types that can be programmed are overdrive pacing, cardioversion, and defibrillation. The PCD Device also has bradycardia pacing capability. The Transvene leads allow the PCD device to deliver these therapies to the heart.

ETCD System Configuration

The ETCD is an external tachyarrhythmia control device designed to deliver overdrive pacing, cardioversion, defibrillation, and bradycardia therapies in the same fashion as the PCD device. The ETCD can be programmed to automatically deliver overdrive pacing therapy upon detection of VT. When used as a component of a system that includes the appropriate Medtronic programmer and applicable software cartridge, the ETCD can deliver manually-initiated VT pacing, cardioversion, and defibrillation therapies. The ETCD allows the assessment of the Transvene lead system characteristics and aids in the assessment of lead system pacing and sensing characteristics.

Overview of System Features

General

The PCD device is designed to automatically detect episodes of VT or VF and, upon detection, deliver the appropriate programmed pacing, cardioversion, or defibrillation therapies. The device has two independently programmable detection and therapy procedures, one for VT and a second for VF.

When used as a component of a system that includes the appropriate Medtronic programmer and dedicated software, the ETCD is designed to deliver manually initiated cardioversion and defibrillation therapies. The ETCD is also designed to detect episodes of VT and VF. It can automatically deliver VT overdrive therapies (burst and ramp) upon detection of a VT.

VT Detection and Therapy

Both the PCD device and ETCD use a VT detection algorithm which can use up to three separately programmable criteria as it monitors the cardiac cycle length to identify the presence of a tachycardia. Upon detection, the devices deliver their first programmed VT therapy. If the VT episode persists and is again detected, up to three additional independently programmable VT therapies may be delivered to restore the patient's normal cardiac rhythm. This progression of four VT therapies can be tailored to each patient's need. For the PCD device the therapies may be selected from two methods of overdrive pacing (burst and ramp) and synchronized cardioversion.

For the ETCD the same overdrive pacing therapies can be automatically delivered, with cardioversion therapy being available as a manual therapy.

VF Detection and Therapy

The VF Detection algorithm monitors the cardiac cycle length to identify a VF episode. Upon detection, the PCD device provides a programmable high energy defibrillation pulse for VF therapy. Up to a maximum of four VF therapies may be delivered for ongoing detected VF episodes. Each defibrillation therapy consists of one (single pulse) or two (simultaneous or sequential) high voltage pulses designed to restore the normal cardiac rhythm.

For the ETCD, each cardioversion or defibrillation therapy, which must be initiated manually via the programmer, also consists of one high-voltage pulse or two (simultaneous or sequential) high-voltage pulses in the same fashion as the PCD devices.

Bradycardia Therapy

For both the ETCD and PCD devices, bradycardia pacing is delivered in the VVI mode. Asynchronous, (VOO), pacing is not available, and is avoided even with magnet application since this type of pacing has increased potential to initiate ventricular arrhythmias in patients receiving this system.

Lead Systems

The PCD Device and the ETCD perform pacing, sensing, cardioversion, and defibrillation through multiple electrodes in the lead system. Listed below are the electrodes and their function:

- The PACE/SENSE electrodes are incorporated in the right ventricular defibrillation lead. These electrodes function as the sensing circuit and deliver pacing pulses. The PACE/SENSE electrodes are used for sensing in conjunction with the SENSE2 electrode.
- The COMMON electrode is an electrode coil that serves as the cathode for cardioversion, defibrillation, and pacing.
- The PULSE2 electrode is an electrode coil that serves as the anode for cardioversion and defibrillation.
- The PULSE1 electrode is an optional electrode coil that serves as an additional anode for sequential and simultaneous cardioversion and defibrillation.

Cardioversion and defibrillation current pathways are between the PULSE2 and COMMON electrode coils and, if the additional lead is implanted, between the PULSE1 and COMMON electrode coils.

Other Capabilities

The physician may use the ETCD or the PCD devices to conduct noninvasive electrophysiologic studies (EPS) via the programmer with the appropriate software cartridge. The physician can also manually deliver various therapies via the programmer to manage an induced or spontaneous tachyarrhythmia.

The PCD device will provide the physician with information, via the Programmer, about its present programmed status and data on its operation accumulated between office visits. This information may be printed and retained in the patient's file.

The PCD Device and ETCD can also transmit an electrogram to the programmer. The electrogram is the electrical signal sensed on the leads.

A programmer-generated set of symbols, termed Marker Channel™, allows real-time visualization of sensing, pacing, detection, and therapy events occurring within the device.

In addition, the ETCD provides a display of measurements and other information related to delivered cardioversion and defibrillation pulses. With this information and other features, the ETCD can be used to assess the suitability of the lead system and its placement for individual patients.

PCD Battery Longevity Expectations

The longevity of the Model 7217B PCD Device depends upon several factors, including programmed bradycardia pacing parameters, the percentage of paced to sensed events, the pacing load, and on the frequency of high voltage capacitor charging. The longevity projections found in Table IV-A-1 apply under the following conditions:

- 65 ppm pacing rate,
- 5.4 V pacing pulse amplitude,
- 0.49 ms pacing pulse width, and
- 500 ohm pacing lead.

Projected Longevity[1]
Table IV-A-1

Pacing/Sensing	34 Joule Charging Frequency	Average Longevity Model 7217B
100% Sensing	Quarterly	5.0 years
15% Pacing	Monthly	4.2 years
100% Pacing	Monthly	3.4 years

The longevity of the device decreases with the following:

- An increase in pacing rate,
- An increase in pacing amplitude,
- A decrease in pacing impedance,
- An increase in pacing pulse width,
- An increase in the percentage of bradycardia paced to sensed events, or
- An increase in the charging frequency.

Each 34 Joule charging cycle will typically decrease the longevity of the device by approximately four to six days.

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1 These preliminary longevity projections are based upon accelerated battery data and device modeling. With the stated condition, 100% pacing and monthly 34 Joule charging cycles, the minimum longevity of the device will be 2.5 years (7217B). Average refers to the projected mean longevity of the modeled run of PCD devices at the stated conditions. Minimum longevity means that virtually all (i.e., 99.9%) of all modeled production run of PCD devices will attain the value given.

C. Alternative Practices and Procedures

The use of implantable defibrillators in patients with drug refractory ventricular tachycardia/ fibrillation (VT/VF) and in survivors of sudden cardiac death has reduced the arrhythmic mortality in these patients. Other treatments available to treat ventricular tachyarrhythmias include antiarrhythmic drug therapy, ventricular tachycardia surgery, transthoracic defibrillation and other market released implantable defibrillators with epicardial defibrillation lead systems.

D. Marketing History

All of the Medtronic Tachyarrhythmia Control System device components which have been implanted in the U.S. to date have been part of the IDE clinical study and have followed the FDA approved investigational protocol. In November 1991, the Medtronic PCD Transvene System, and respective components described in this submission, were market released in Europe. In March 1991, the Medtronic PCD Epicardial System, and respective components, were market released in Europe. And in February 1992, the FDA Advisory Panel recommended the approval of the Medtronic PCD Epicardial System.

E. Adverse Effects

Potential adverse effects which may be associated with the use of the PCD Device include but are not limited to: failure to detect ventricular tachycardia or ventricular fibrillation; failure to terminate ventricular tachycardia or ventricular fibrillation; delivery of pacing or shock therapy when no ventricular tachyarrhythmia is present, which would precipitate an episode of ventricular tachycardia or ventricular fibrillation; acceleration of a ventricular arrhythmia; failure to capture after a shock delivery; discomfort or pain during or following the delivery of electrical shock; or infection.

The following additional, potential adverse effects associated with all pacemaker systems include loss of normal pacemaker function due to battery failure or other component failure, inability to program a pacemaker pulse generator because of programmer failure, infection, erosion, undesired muscle or nerve stimulation, and inadequate sensing or pacing. Any demand pulse generator can be affected by magnetic, electrical and electromagnetic signals of sufficient strength or with characteristics which mimic cardiac function. Possible effects of electrical interference on pulse generator operation include reversion to asynchronous pacing, inhibition of output pulses and rapid synchronous pacing. Certain environmental sources can couple sufficient energy into a cardiac pacing system to damage the pulse generator or cardiac tissue adjacent to the electrodes.

Failure of the pulse generator system to function properly may result in the patient experiencing the symptoms for which the pulse generator was originally indicated.

The potential complications related to the use of the PCD Transvene Lead System include, but are not limited to, the following patient-related conditions: fibrillation, air embolism, cardiac perforation, heart wall rupture, cardiac tamponade, pericardial rub, infection, myocarditis, constrictive pericarditis, pneumothorax and hemothorax. Other potential complications related to the lead system include, but are not limited to, the following: lead dislodgement, lead conductor fracture, and insulation failure.

The above referenced information is provided in the labelling of the PCD Transvene System.

F. Summary of Studies

To validate the performance of the Medtronic Tachyarrhythmia Control System nonclinical laboratory (bench) testing, animal studies and human clinical trials were performed. All of the nonclinical bench and animal testing demonstrated that the devices are safe and performed according to design intent.

The nonclinical laboratory (bench) testing provides information relative to the Model 6966, Model 6963 and Model 6999 Transvene Leads, Model 7217B PCD, Model 5355 ETCD, and Model 9788 Memory Module.

The animal studies were performed to evaluate acute and chronic performance PCD Transvene System and to validate that the PCD and ETCD System are safe for human use.

Finally, human clinical trials were performed to evaluate the safety and effectiveness of the PCD Transvene System in treating patients with life-threatening ventricular arrhythmias.

All of the studies have demonstrated that the PCD Transvene System functions safely and is appropriate for human use.

The following summaries are provided in this section.

1. Model 6966, Model 6963 and Model 6999 Nonclinical Testing
2. Non-clinical Testing of the Related Components of the Transvene Lead system: Models 7217B PCD, Model 5355 ETCD and Model 9788 MemoryMod Model 7217B PCD Nonclinical Testing
3. Animal Testing
4. Clinical Study of the PCD Transvene System

1. Model 6966, Model 6963 and Model 6999 Defibrillation Leads: Summary of Nonclinical Testing

To validate the performance of the Medtronic Tachyarrhythmia Control System nonclinical laboratory (bench) testing, animal studies and human clinical trials were performed. All of the nonclinical bench and animal testing demonstrated that the devices are safe and performed according to design intent.

The nonclinical laboratory (bench) testing provides information relative to the Model 6963 CS/SVC lead, Model 6966 RV lead, Model 6999 SQ patch lead, and related system components.

a. Electrical Testing

Electrical D.C. resistance testing was performed to ensure proper functioning of the Model 6963, 6966 and 6999 leads.

Seventeen Model 6963, thirty-five Model 6966 and eighteen Model 6999 leads were submitted for testing. Electrical resistance was measured utilizing a milliammeter under ambient room conditions. All samples measured were within the individual design specifications.

b. Environmental Analysis Testing

The purpose of the testing was to subject the lead to temperature extremes to determine the lead's resistance to the thermal stresses when transported from extremes of climate.

Thermal Shock

Fifteen Model 6963 and thirty-five Model 6966 leads were subjected to five cycles from -45°C to 70°C with a soak time of thirty minutes at each temperature extreme with a transfer time of one minute. Thirty-five Model 6999 leads were subjected to five cycles from -40°C to 66°C with a soak time of thirty minutes at each temperature extreme with a transfer time of one minute.

After the thermal shock testing was completed visual inspection and electrical resistance measurements were performed. There were no visual defects and the electrical D.C. resistance of all the samples met the design specification.

c. Mechanical Testing

The purpose of the mechanical testing was to determine the mechanical integrity of the leads to ensure that the devices are safe, reliable, and suitable for their intended use and conform to design specifications. The leads and/or assemblies were subjected to the following:

- flex testing
- composite pull strength testing
- crimp/weld pull strength testing
- insertion/withdrawal force testing
- A.C. impedance/leakage testing

Flex Testing

The flex testing consisted of mounting the insulated conductor coils and uninsulated electrode coils of the Models 6963, 6966 and 6999 in a lead flex test fixture. The insulated conductor coils and uninsulated electrode coils were flexed under ambient room conditions at a specified radius. Eleven samples were used in each test. Samples exceeded specifications and therefore are considered to be satisfactory for their intended use.

Lead Joint Tensile Strengths

Pull testing of the various lead joints is conducted to ensure that the integrity of the joint meets the design specification and is, therefore, adequate for its intended application. The testing conducted consists of a composite pull test which evaluates the overall pull strength of the lead and crimp pull testing that evaluates the crimped connections of the leads to assure specification conformance.

Composite Pull Strength

Leads were boiled in Ringer's solution or soaked in normal saline and pull tested, while wet (the lead is usually cut in half to facilitate fixturing limitations) utilizing a tensile testing machine. The samples were pulled until failure at a rate of five inches per minute. The initial failures were then analyzed statistically for the confidence level in meeting the specification for the composite lead which is 1.0 lb. minimum.

Model 6963 data demonstrates that with a 95% confidence at least 97% (distal) and 99.9% (proximal) of the leads will meet or exceed the specification.

Model 6966 data demonstrate that with a 99% confidence at least 99.9% of the leads will meet or exceed the specification.

Model 6999 data demonstrate that with a 99% confidence at least 99.9% of the leads will meet or exceed the specification.

Therefore, Models 6963, 6966 and 6999 leads, with respect to composite pull strength, are adequate for their intended use.

Crimp/Weld Pull Strengths

Crimp and weld pull strength tests were conducted to evaluate the strength of the connections to ensure that they meet the design specification and are, therefore, adequate for their intended application. The connections tested are:

- Distal crimp sleeve to conductor coil crimp (6963)
- Double crimp core to conductor coil crimp (6963)
- Electrode coil to double crimp core weld (6963)
- Electrode coil to distal crimp sleeve weld (6963)
- Tip crimp sleeve to conductor coil crimp (6963)
- Connector pin to conductor coil crimp (6963 and 6999)
- Helix electrode to inner conductor coil crimp (6966)
- Electrode ring to middle conductor coil crimp (6966)
- Transition sleeve to electrode coil weld (6966)
- Transition sleeve to outer conductor coil crimp (6966)
- Fixed connector pin to outer conductor coil crimp (6966)
- Connector ring to middle conductor coil crimp (6966)
- Rotating connector pin to inner conductor coil crimp (6966)
- Manifold crimp sleeve to conductor coil crimp (6999)
- Manifold crimp sleeve to electrode coil (b)(4) (b)(4) crimp (6999)
- Manifold crimp sleeve to electrode coil (b)(4) (b)(4) crimp (6999)

Subassemblies were submitted for testing and pull tested by using a tensile testing machine. The samples were pulled until failure at a rate of four inches per minute.

Pull strength testing consisted of a minimum of 15 subassemblies of each crimp connection and a minimum of 7 subassemblies of each weld connection All samples tested exceeded the individual specification. The test results indicated that with a 95% confidence, at least 95% of the leads will have crimp and weld strengths that exceed the specification.

Therefore, the Model 6963, 6966 and 6999 leads, with respect to crimp and weld connection pull strengths, are adequate for their intended use.

Insertion/Withdrawal Forces

Insertion/withdrawal forces are measured to ensure compatibility with the implantable device without causing damage to the lead. Twenty five each of the lead Models 6963, 6966 and 6999 were tested with the Model 7217B PCD Device connector modules. There were no physical changes and all measurements met the design specification.

A.C Impedance/Leakage Testing

Fluid leakage tests are conducted on the lead assemblies/implantable device connector to determine leakage. Ten of each lead model Models 6963, 6966 and 6999 were tested with the Model 7217B connector modules. A.C. impedance was measured from the PCD device case to the lead connections while immersed in fluid. All samples met the design specification.

d. Biocompatibility Testing

The materials used in the Models 6963, 6966 and 6999 that are directly exposed to body tissue are:

- Polyurethane
- Silicone rubber (methylvinylpolysiloxane)
- Silicone rubber/titanium dioxide
- Platinum/Iridium

These materials have been shown to be biocompatible through many years of use in Medtronic permanent implantable endocardial/myocardial permanent pacing leads. In addition to extensive implant experience with these materials, standard biocompatibility tests have been performed to verify the biocompatibility of the above-listed materials. Testing has demonstrated that all materials are nonhemolytic, nonpyrogenic, nontoxic, nonmutagenic and biocompatible. Therefore, the materials passed the tests and are considered suitable for human implant. The materials used in the Models 6963, 6966 and 6999 are identical to those used in other commercially available Medtronic pacing leads.

e. Lead Life Testing

In-vitro bench testing is performed to determine the chronic performance (integrity) of the non-thoracotomy leads. The leads were subjected to accelerated life testing. Testing included subjecting the

leads to visual, mechanical, and electrical evaluations before and after soaking, flexing, and high voltage pulsing under simulated use conditions.

D.C. resistance values and intermittence data measured before and after being subjected to multiple flexing and high voltage pulsing demonstrated the non-thoracotomy leads satisfy requirements and are acceptable for their intended use.

2. Non-clinical Testing of the Related Components of the Transvene Lead system: Models 7217B PCD, Model 5355 ETCD and Model 9788 MemoryMod

Non-clinical testing of these components was provided Volume 4 of the original PMA application (P900061) dated September 27, 1990, Volume 3 of the amendment dated March 8, 1991, and Volume 2 of the amendment dated August 30, 1991. A summary of the test results for each of the components is provided.

Model 7217B PCD: Summary of Nonclinical Testing

Testing of the Model 7217B pulse generators and the peripheral devices that comprise the system, i.e., the Pacing System Analyzers, the Model 9710 Programmer utilizing the Model 9788 MemoryMod and the Model 9751 Printer have been tested and found to be acceptable. All aspects of system interaction and operation are in accordance with the Model 7217B PCD Device and Model 9788 technical manuals and system specifications. Therefore, the Medtronic Tachyarrhythmia Control System, in its entirety, is acceptable for its intended use.

Model 9788 Memory Module: Summary of Nonclinical Testing

The Medtronic Model 9788 MemoryMod Cartridge was designed for insertion into the commercially available Model 9710 Programmer. When inserted, it becomes an integral part of the non-invasive programming system for the implantable PCD devices to establish pacing, ventricular tachycardia (VT) detection and therapy, ventricular fibrillation (VF) detection and therapy, and electrophysiological study (EPS) capabilities of an implanted pacemaker/ cardioverter/defibrillator (PCD). Both the Model 7217B PCD device and the Model 5355 ETCD are programmed with the Model 9788 MemoryMod cartridge when used with the Model 9710 Programmer.

Testing of the Model 9788 MemoryMod cartridge has demonstrated conformance to specification requirements. Therefore, the Model 9788 MemoryMod is acceptable for its intended use with the Model 7217B PCD Devices and the Model 5355 ETCD Device.

Model 5355 ETCD: Summary of Nonclinical Testing

Testing of the Model 5355 ETCD and respective accessories has shown conformance to specification requirements. Therefore, the Model 5355 ETCD Device/accessories are acceptable for their intended use.

3. Animal Testing

The information presented in this section is an accumulation of several studies, some of which FDA has previously reviewed in IDE submissions (G870102). These studies demonstrate the safety of the Transvene lead Models 6963, 6966 and 6999.

A variety of non-thoracotomy leads were evaluated in a series of four canine studies. Descriptions of the leads, as well as the study number(s) (1, 2, 3 or 4) in which they were evaluated, are presented below.

Description: Non-thoracotomy Leads

CORONARY SINUS/SUPERIOR VENA CAVA LEADS

(b)(4)

Model 6963, evaluated in Study No. 4, is a silicone, unipolar, coronary sinus or superior vena cava lead with a 6.5 mm connector and platinum alloy electrode for delivery of cardioversion and defibrillation therapies.

Model 6881, evaluated in Study Nos. 2, 3 and 4 is functionally equivalent to the Model 6963 except the 6881 has a 3.2 mm connector.

(b)(4), (b)(5)

Model 10285, evaluated in Study No. 1, is the temporary version of the Model 6963/6881.

RIGHT VENTRICULAR LEADS

Model 6966, evaluated in Study No. 4, is a polyurethane, tripolar, extendable/retractable, screw-in lead with a 6.5 mm connector and platinum alloy electrode for delivery of cardioversion and defibrillation therapies. Additionally, the 6966 has a 3.2 mm connector for pacing and sensing.

Model 6884, evaluated in Study Nos. 2 and 3, is functionally equivalent to the Model 6966 except the 6884 has a 3.2 mm connector in place of the 6.5 mm connector for the cardioversion-defibrillation electrode.

Model 10284, evaluated in Study No. 1, is the temporary version of the Model 6966/6884.

SUBCUTANEOUS PATCH LEADS

Model 6999, evaluated in Study No. 4, is a silicone, unipolar, oval, subcutaneous patch with a 6.5 mm connector and platinum alloy electrode coils that are partially embedded in the silicone patch for delivery of cardioversion and defibrillation therapies. Additionally, the patch is embedded with [(b)(4) (b)(4)]

Model 6895, evaluated in Study Nos. 2 and 3, is functionally equivalent to the Model 6999 except the 6895 has a 3.2 mm connector and is covered with [(b)(4) (b)(4)]

Model 10317, evaluated in Study No. 3, is functionally equivalent to the 6895 except it is embedded on the outer edge with [(b)(4) (b)(4)]

Although model numbers differ, all leads in each of the three groups are functionally equivalent. The various model numbers reflect an evolution of temporary to transvenous lead development, as well as minor changes, such as the connector pin modification from 3.2 mm to 6.5 mm.

Additional devices were used to evaluate the non-thoracotomy lead studies in canines. These are described below.

External Devices for Implant Support

Model 5355 External Tachyarrhythmia Control Device (ETCD)

The Model 5355 ETCD provides the same detection capabilities as the implantable Model 7217B PCD Device. Therapies are identical except that the maximum output energy is 40 joules (J) and automatic defibrillation and cardioversion are not available in the Model 5355. The Model 5355 ETCD provides measurement and display of output waveform parameters and ETCD status, an isolated electrogram signal, and passthrough connections of pacing and sensing electrodes to external instrumentation.

Model 2394 External Cardioverter/Defibrillator (ECVD)

The Model 2394 ECVD instrument can deliver: (1) a single stimulation pulse on one output channel, or (2) a pair of pulses, delivered individually on the two different output channels. Monophasic and biphasic pulses are provided, output capacitance can be varied between 10 and 150 microFarads (mf) depending on which external capacitor modules are used, and pulse width can be specified as a fixed duration (0.1-19.9 ms) or "tilt" (10-90%). Pulse output voltages can range between 50 and 1090 volts and may be delivered asynchronously (upon manual command) or synchronized with an intrinsic sensed event.

Model 2376 External Cardioverter/Defibrillator (ECVD)

The output stimulation parameters of the Model 2376 are very similar to those of the Model 2394 except for the following modifications:

- All pulses are monophasic, truncated, exponential waveforms.
- Output capacitance is fixed at 50 microFarads and pulse width is determined by a fixed pulse duration only.
- Pulse output voltages can range between 50 and 1090 volts and may be delivered asynchronously (upon manual command) or synchronized with an intrinsic sensed event.

Study Methods

All canine studies were conducted according to the 1966 and 1970 Animal Welfare Acts, 1985 NIH Laboratory Animal Use and Care Guidelines and GLP regulations. Adult mongrel canines were used for all studies. The dogs weighed 20 kg or more.

Specific details of each study are presented in the following "Animal Studies/Results" section.

Each study is briefly described below. Both acute and chronic studies were performed to assess the toxicity of the non-thoracotomy lead system as well as its stability over time.

Study #1: Acute Toxicity Testing of Non-thoracotomy Leads

The objective of this study was to quantify the amount and nature of shock-induced damage to the myocardial tissue resulting from multiple, high energy defibrillation shocks delivered through transvenous defibrillation leads and a subcutaneous patch. This information has previously been submitted to the agency in the Non-Thoracotomy IDE, reference Document Control Number G870102/S23; FDA Approved October 4, 1990. Lead models evaluated in this study are functionally equivalent to the Models 6963, 6966 and 6999. Results of these studies revealed only minimal shock-induced necrosis (<0.1-0.5 percent by weight), which did not result in functional impairment of the cardiac tissue. Therefore, the use of the Model 6963, 6966 and 6999 leads did not result in significant myocardial damage in canines and could be safely implanted in humans.

Study #2: Model 6881, 6884 and 6895 Chronic Lead Evaluation

The objective of this study was to evaluate the suitability of the lead system for human clinical use. Lead models evaluated in this study are functionally equivalent to the Models 6963, 6966 and 6999. Study results demonstrate that the performance of the non-thoracotomy lead system when used with the PCD and ETCD devices is in conformance with system design and expected operation.

Study #3: Model 6881, 6884 and 6895 Chronic Lead Defibrillation Study

This study is an evaluation of the chronic stability of the non-thoracotomy lead system via the monitoring of defibrillation and pacing thresholds. In addition, histopathological examinations have been performed to assess the amount and nature of shock-induced damage to the myocardial tissue resulting from defibrillation shocks. Lead models evaluated in this study are functionally equivalent to the Models 6963, 6966 and 6999. Results demonstrate stable pacing, sensing and defibrillation thresholds over time. Additionally, histopathology analysis shows no cardiac tissue damage due to delivery of defibrillation shocks.

Study #4: Model 6963, 6966 and 6999 Chronic Lead Defibrillation Study

This study is an ongoing evaluation of the non-thoracotomy lead system to assess chronic defibrillation threshold stability, pacing thresholds, intracardiac sensing capabilities and tissue damage. Results indicate the lead system performs as intended; DFTs and pacing thresholds have remained stable throughout the study (40 weeks) and intracardiac sensing is appropriate. Additionally there is minimal localized trauma to the cardiac tissue (<0.05 percent by weight).

Conclusion

All of these canine studies have demonstrated that the non-thoracotomy lead system, which includes the Model 6963 CS/SVC lead, 6966 RV lead and 6999 SQ patch lead, functions safely and is therefore appropriate for human use.

4. Summary of Clinical Experience

A. Introduction

The efficacy and safety of implantable cardioverter defibrillator (ICD) therapy for recurrent ventricular tachycardia (VT) and ventricular fibrillation (VF) have been well established. The current market released device provides defibrillation therapy for VF or hemodynamically unstable VT. However, this type of therapy may not be optimal for patients with stable, well tolerated VT that is amenable to antitachycardia pacing. Additionally, it is necessary to perform a significantly more invasive procedure, a thoracotomy, in order to implant the epicardial leads. Thus, the need to incorporate programmability, multiple detection and therapeutic options, and a less invasive lead system has lead to the development of a tiered therapy device, the PCD™ Transvene™ System.

This report is on Medtronic's clinical experience with the Medtronic PCD™ Multiprogrammable Tachyarrhythmia Control System with Transvene™ Cardioversion and Defibrillation Electrodes (Reference IDE G870102). The data included in this analysis is all data that was received by Medtronic and entered onto the clinical database as of November 27, 1991. Analysis includes a total of 319 implants of the PCD™ System with a mean implant duration of 4.5 months. The data is a clinical experience update on 317 patients.

The PCD Transvene System components, except for the defibrillation lead systems, is identical to the PCD Epicardial System which received a recommendation for approval by the FDA Advisory panel on February 3, 1992. The objectives and the clinical protocol were identical for the two systems.

The data analysis is organized in functional rather than chronological categories in order to present a complete picture of each of the PCD™ Device's various functions. The sections included in this summary are:

- Indicated Patient Population/Therapeutic Options
- PCD Therapy Applications
- Study Objectives and Protocol Summary
- Overview of Clinical Experience
  - Implant Data
  - Spontaneous VT/VF Episode Experience
  - Overall Success Rate
- Complications and Observations
- Inactive Patients
- Patient Deaths
- Clinical Experience by Primary Indication
- Patients not Meeting Implant Criteria
- Comparison to AICD Clinical Experience
- Comparison to PCD™ Epicardial Clinical Experience
- PCD™ System Performance

This summary provides an overview of the clinical experience which verifies that the PCD™ System is safe and effective in the indicated patient population.

B. Indicated Patient Population and Therapeutic Options

B.1 Patient Population

The PCD™ Transvene™ System is intended to treat patients at risk of sudden cardiac death due to ventricular tachyarrhythmias which have been shown to be reliably terminated, and in the case of VF, terminated at an energy level below the maximum output of the PCD™ Device.

Results provided in this summary support Medtronic's request for Market Release of the PCD™ Transvene™ System for use in the following patient population:

Patients who have survived at least one episode of cardiac arrest, presumably due to a ventricular tachyarrhythmia, as evidenced by resuscitation using a transthoracic defibrillator. The ventricular arrhythmia should not be caused by an acute myocardial infarction; OR

In the absence of a prior cardiac arrest, patients with recurrent, sustained ventricular tachycardia that occur spontaneously or can be induced, despite the most efficacious antiarrhythmic drug therapy that can be tolerated chronically.

Malignant ventricular tachyarrhythmias remain a major unsolved problem in the management and prevention of coronary artery disease. It is estimated that 450,000 people experience sudden cardiac death annually, and 80%-90% of these events are caused by ventricular fibrillation. (Gillum RF. Sudden coronary death in the United States. Circulation 1989; 79:756-765.)

Survivors of out-of-hospital cardiac arrest not associated with acute myocardial infarction are at risk for recurrent cardiac arrest as reported by Wilber, et al.(Wilber, et al. Out-of-Hospital Cardiac Arrest - Use of Electrophysiologic Testing in the Prediction of Long-Term Outcome. NEJM 1988; Vol.318:19-24.). In this study group of 166 survivors of out-of-hospital cardiac arrest, ventricular arrhythmias were inducible in 131 patients (79%) and were suppressed by antiarrhythmic drug therapy or surgery (or both) in 91 patients (72%). During a median follow-up of 21 months, cardiac arrest recurred in 29 patients: 11 in whom inducible arrhythmias had been suppressed, 12 in whom inducible arrhythmias persisted and 6 in whom arrhythmias could not be induced at initial electrophysiologic study.

B.2 Therapeutic Options

Therapeutic options for these patients include antiarrhythmic drug therapy, catheter ablation, surgical ablation, and electrical device therapy. The therapy indicated for a particular patient will be dependent on the patient's clinical ventricular tachyarrhythmia, the results of electrophysiologic evaluation, and the presence and severity of underlying cardiovascular disease.

There are currently multiple antiarrhythmic drugs available for the treatment of recurrent ventricular tachyarrhythmias. The sudden cardiac death survival at one year for patients treated with drug therapy alone ranges from 34 to 73% (Graboys, et al. Long Term Survival of Patients with Malignant Ventricular Arrhythmias Treated with Antiarrhythmic Drugs. American Journal of Cardiology. 1982; Vol 50:437-443 and Swerdlow, et al. Determinants of Survival in Patients with Ventricular Tachyarrhythmias. NEJM. 1983; Vol.308:1436-1442).

The success rate of catheter ablation for recurrent ventricular tachyarrhythmias averages 25% with no further need for drug therapy and 25% for suppression with drugs where drugs were previously ineffective. (Zipes, et al. Nonpharmacologic Therapy: Can it Replace Antiarrhythmic Drug Therapy? Journal of Cardiovascular Electrophysiology. Vol.2, No.3:255-272.)

A 10 year analysis of data from a multi-center registry on patients who underwent surgical ablation for recurrent ventricular tachyarrhythmias reveals survival of 78% at one year and 60% at 5 years. (Zipes, et al).

The reported one year sudden cardiac death survival for patients receiving an ICD for treatment of recurrent ventricular tachyarrhythmias is 98.0%. (Thomas,et al. Implantable Defibrillation: Eight Years Clinical Experience. PACE. 1988; 11(II):2053-8).

C. PCD™ Transvene System Therapy Applications

The PCD™ System is intended to treat patients at risk of sudden cardiac death due to ventricular tachyarrhythmias and/or recurrent ventricular tachycardia.

For this patient population, the primary benefits from the use of the PCD™ System center on the detection and termination of life-threatening ventricular arrhythmias. The use of the PCD™ Transvene™ system allows for the application of identical therapies as an epicardial system without requiring an open chest procedure for implantation of the lead system. This less invasive surgical approach allows the system to be applied in patients who may not be able to undergo an open chest procedure. The use of pacing therapies for the treatment of ventricular tachycardia reduces patient trauma associated with higher energy cardioversion pulses and extends the longevity of the PCD™ pulse generator.

The PCD™ System allows the titration of therapies for patients with ventricular tachycardia while providing critical defibrillation backup. Multiple detection algorithms are designed to allow the device to distinguish ventricular tachycardia from sinus tachycardia and atrial fibrillation. In addition, independent detection algorithms for VT and VF allow the delivery of different types of therapy for each of these two arrhythmias. The incorporation of antitachycardia pacing algorithms allows the use of pacing for the termination of well tolerated ventricular tachycardia. These algorithms, which are rate adaptive, can adapt to changes in the ventricular tachycardia and successfully terminate the episode. Defibrillation therapy is important in the event that an episode of VT accelerates to VF whether spontaneously or as a result of a delivered therapy. The incorporation of multiple cardioversion and defibrillation pathways (SINGLE, SEQUENTIAL and SIMULTANEOUS) allows the physician to provide an adequate cardioversion/defibrillation efficacy safety margin for all patients. The capacity to provide programmable extrastimuli pacing allows noninvasive electrophysiologic studies to be performed. The potential benefits from permanent cardiac pacing provide support for chronic and transient episodes of bradycardia.

Finally, the benefits of programmability of tachyarrhythmia detection and therapy parameters, VVI parameters, and stored telemetry data on the delivery of therapy may avert the need for reoperation in the event of changing patient conditions or complications.

D. Study Objectives

The clinical study was designed to evaluate the operation, safety, and effectiveness of the PCD™ System in detecting and treating episodes of ventricular tachycardia and ventricular fibrillation.

The analysis focuses on data supporting the safety and effectiveness of the PCD™ system, including the implantable pulse generator and associated Transvene™ lead system (Models 6895/6999, 6884/6966/SP2100, 6881/6963 and its use in this patient population. The analysis includes the clinical experience with the PCD™ system, pace/sense, detection, and therapy functions in both the acute and chronic settings. Data is provided on the PCD™ System efficacy in terminating spontaneous VT/VF episodes, clinical observations, clinical complications, and deaths in this patient population.

This summary presents safety and efficacy evaluation performed on 317 patients, 116 of which have implant durations equal to or greater than six months.

All patients underwent extensive pre-implant testing which included electrophysiologic evaluation of the patient's clinical ventricular tachyarrhythmias. Operative testing was performed to verify that the final implanted lead configuration properly detected and treated episodes of ventricular fibrillation, and when appropriate, ventricular tachycardia.

All patients were evaluated prior to hospital discharge, one (1) month post implant, three months post-implant, and then at intervals of every three months. In some cases, additional testing was performed at physician discretion to evaluate spontaneous events and/or potential clinical complications.

Medtronic collected all clinical data on the PCD™ System and its components under the clinical protocol outlined in the Investigational Plan. A common protocol was used on all study patients on a worldwide basis.

International centers were subject to the appropriate requirements (e.g. the Declaration of Helsinki) in order that the data met the statutory requirements of the FDA. All clinical data, U.S. and International, obtained with the PCD™ System with Transvene™ Leads is included in this report.

E. Overview of Clinical Experience

This report covers a total of 319 implants in 317 patients of the PCD™ Device with the Transvene™ Defibrillation Lead System. A total of 52 investigative centers participated in the clinical trial with 20 centers in the U.S. and 32 Internationally. The first implant occurred internationally on October 20, 1989, and the first implant in the U.S. occurred on October 16, 1990. Table E-1 shows the distribution of Model 7216A and Model 7217B patients between U.S. and International investigators.

PCD™ Transvene™ System Implant Distribution			
	Total	**U.S.**	**Int'l**
7216A	18 (5.6%)	3 (2.2%)	15 (8.2%)
7217B	301 (94.4%)	134 (97.8%)	167 (91.8%)

Table E-1: PCD™ Transvene™ System - Implant Distributions - 11/27/91

The mean documented implant duration for this patient population is 4.5 months and ranged from implant to 22.0 months. The cumulative implant duration is 1426 months. There are 116 patients with implant durations equal to or greater than six months. Table E-2 shows the follow-up time by type of data form. The number presented for the PHD includes 12 patients that had 2 PHD visits. Thirty seven patients did not have a PHD.

PCD™ Transvene™ System Follow-Up Quantity by Data Form Type									
	PHD	**1 M**	**3 M**	**6 M**	**9 M**	**12 M**	**15 M**	**18 M**	**21 M**
All Models	294	224	154	116	78	34	15	10	4

Table E-2: PCD™ Transvene™ System - Follow-Up Quantity - 11/27/91

The patient population enrolled in the clinical trial was predominately male (82.0%) with a mean age of 58.5 years. In the majority of patients (45.7%), the primary indication for implant was recurrent, sustained ventricular tachycardia without an episode of sudden cardiac death. Coronary artery disease was the primary heart disease in 72.2% of the patient population with a mean reported ejection fraction of 36.7% Table E-3 provides a data summary on these patients. Also included is the data summary of the patients with 6 months of follow-up and the data summary from the PCD™ Epicardial experience that formed the basis for the PCD™ Epicardial PMA submission.

PCD™ Transvene™ System Data Summary			
	All Patients (3 Electrode Systems)	Patients with 6 months of Follow-up	Patients with PCD™ Epicardial System
Number of Patients	317	116	434
Device Months Follow-up	1426.5	1159.2	4778.0
Mean Follow-up Time	4.5 mo	10.0 mo	11.0 mo
Maximum Follow-up Time	22.0 mo	22.0 mo	27.8 mo
Number, % Male **Number, % Female**	260 82.0% 57 18.0%	94 81.0% 22 19.0%	374 86.2% 60 13.8%
Mean Age	58.5 yrs	57.1 yrs	58.3 yrs
Primary Indication: **SCD** **VT** **SCD/VT**	 120 37.9% 145 45.7% 52 16.4%	 41 35.3% 54 46.6% 21 18.1%	 118 27.2% 233 53.7% 83 19.1%
Coronary Artery Disease	229 72.2%	83 71.6%	325 74.7%
Mean Ejection Fraction	290 36.7%	105 40.0%	415 34.6%
Defibrillation Pathway: **Sequential** **Simultaneous** **Single**	 247 77.4% 67 21.0% 5 1.6%	 85 73.3% 28 24.1% 3 2.6%	 184 42.4% 7 1.6% 243 56.0%
Mean LED	15.1J (N=288)	15.7J (N=106)	10.6J (N=395)
Mean DFT	13.7J (N=147)	14.2J (N=60)	9.2 (N=264)
Spontaneous VT: **Number of Patients** **Number of Episodes** **% Success**	 79 1648 99.2%	 52 1099 99.1%	 277 8672 97.7%
Spontaneous VF: **Number of Patients** **Number of Episodes** **% Success**	 61 376 99.2%	 31 212 98.6%	 177 1034 98.1%
One Year SCD Survival	100.0%	100.0%	98.8%

Table E-3: PCD™ System Data Summary - All Transvene™ Patients vs Transvene™ Patients with 6 mo Follow-up vs Epicardial Patients - 11/27/91

E.1 Implant Data

Implants of the PCD™ Device may use two or three Transvene™ leads. The physician has the flexibility to use whichever lead system best meets the patient's needs.

Table E-4 illustrates the lowest mean energy of defibrillation (LED) and mean defibrillation threshold (DFT) for the implanted lead systems. The implant criteria for the PCD™ Device was 3 of 4 episodes of VF successfully terminated at 18 Joules or less with a given lead configuration. All patients may not have a LED at implant. The LED is only identified if the investigator reported the induced rhythm as VF. Conversion of VT or V Flutter to sinus rhythm was not included in the determination of the LED. In addition, it is not a protocol requirement to obtain a DFT at implant. However, recommendations have been provided to those institutions that prefer to obtain DFT's during the implant procedure.

PCD™ Transvene™ System LED and DFT Values				
Lead System	**Implant Frequency**	**LED**	**Implant Frequency**	**DFT**
All Systems	289	15.1J	147	13.7J
RV-SVC-SQ	186	15.9J	84	14.6J
RV-CS-SQ	77	13.6J	48	11.6J
RV-CS-SVC	26	14.4J	15	15.5J

Table E-4: PCD™ Transvene™ System - LED and DFT Values - 11/27/91

The mean implant Lowest Energy of Defibrillation (LED) for all lead systems was 15.1J and mean implant Defibrillation threshold (DFT) for all lead systems was 13.7J. As the mean DFT's and LED's indicate, VF was reliably terminated at an energy value below the maximum output (34 Joules) of the PCD™ Device.

E.2 Spontaneous VT and VF Episode Experience

A total of 103 patients (32.5%) have experienced a spontaneous ventricular tachyarrhythmia episode that has been detected and treated by the PCD™ Device. Forty two patients (13.2%) experienced VT only, 24 patients (7.6%) experienced VF only and 37 patients (11.7%) experienced an episode of both VT and VF.

There have been a total of 2024 episodes of spontaneous VT or VF as detected by the PCD™. The overall PCD™ Device success rate in terminating spontaneous VT/VF episodes is presented in Table E-5.

PCD™ Transvene™ System Success Rate in Terminating Spontaneous VT/VF Episodes			
	Number of Episodes Successful	Total Number of Episodes	Efficacy Rate
VT	1634	1648	99.2%
VF	373	376	99.2%
Total	2007	2024	99.2%

Table E-5: PCD™ Transvene™ System - Success Rate for Spontaneous VT/VF Episodes - 11/27/91

E.2.1 Spontaneous VT

For the purposes of this clinical trial, spontaneous VT was defined as those episodes that satisfied the programmed VT detection criteria. Specifically, all programmed VT detection must be fulfilled to be detected as a VT episode. Successful termination of the episode was defined as satisfying the VT detection of episode termination criteria.

To date, 1648 spontaneous episodes of VT have been detected by the PCD™ Device in 79 patients. The mean number of episodes per patient was 9 and ranged from 1 - 254 episodes.

The majority of spontaneous VT episodes (93.4%) were successfully treated with VT Therapy #1 and 99.2% were successfully treated with one of the four programmable VT therapies.

Of the 1634 successfully terminated spontaneous VT episodes, 94.6% were treated with one of the programmed antitachycardia pacing therapies incorporated in the PCD™ Transvene™ System. The clinical benefit of tiered therapy is the reduction of delivery of high energy shocks for the treatment of stable recurrent ventricular tachycardia. This greatly enhances the patient acceptance of ICD therapy since antitachycardia pacing is often not perceptible by the patient.

Nine patients experienced 14 episodes (14/1648 - 0.8%) in which the PCD™ Device was ineffective in terminating a spontaneous episode of VT despite delivery of all four programmed VT therapies. Thirteen episodes were due to sinus tachycardia or atrial fibrillation with a rapid ventricular response that had been detected as VT. A modification of programmed parameters or of antiarrhythmic drug therapy was completed to reduce the incidence of detecting sinus tachycardia or atrial fibrillation in these patients. It should be noted that the PCD™ Transvene™ System responded appropriately in all cases based on the programmed detection parameters.

The remaining episode was in one patient in which the programmed VT therapies were ineffective in terminating a spontaneous VT episode. This patient's antiarrhythmic drug regimen was modified to improve therapy efficacy. **No patient deaths occurred as a result of ineffective VT therapy.**

E.2.2 Spontaneous VT Episode Experience By Primary Indication

The primary indications for implant of the PCD Transvene System were sudden cardiac death (**SCD**), recurrent sustained ventricular tachycardia (**VT**) and sudden cardiac death associated with recurrent sustained ventricular tachycardia (**SCD/VT**). Spontaneous VT episode efficacy by primary indication is provided in Table E-6. The overall efficacy for spontaneous VT episodes is greater than 98% for each of the patient groups. There is no difference in therapy efficacy among the patient's indications. Table E-6 contains the spontaneous VT episode therapeutic efficacy.

PCD™ Transvene™ System Spontaneous VT Episode Therapeutic Efficacy By Primary Indication			
Indication	**# Episodes Successful**	**# Total Episodes**	**% Success**
SCD	379	380	99.7%
VT	826	835	98.9%
SCD/VT	429	433	99.1%
TOTAL	1634	1648	99.2%

Table E-6: PCD™ Transvene™ System - Spontaneous VT Episode Efficacy by Primary Indication - 11/27/91

E.2.3 Spontaneous VT Episode Experience By Therapy Type

The PCD™ Device incorporates three programmable VT therapy types, RAMP, BURST and CARDIOVERSION, for the treatment of recurrent ventricular tachycardia. Spontaneous VT episode efficacy by programmed therapy type is provided in Table E-7.

PCD™ Transvene™ System Spontaneous VT Episode Efficacy By Programmed Therapy Type			
VT Therapy Type	**# Success**	**# Attempts**	**% Efficacy**
Ramp	1158	1245	93.0%
Burst	388	426	90.9%
Cardioversion	88	102	86.3%

Table E-7: Spontaneous VT Episode Efficacy by Therapy Type - 11/27/91

E.2.4 Spontaneous VF

For purposes of this clinical trial, VF is defined as those episodes that satisfy the programmed VF detection criteria. Specifically, all programmed VT detection must be fulfilled to be detected as a VT episode. Successful termination of the episode is defined as satisfying the VF detection criterion for episode termination.

To date, 376 spontaneous episodes of VF have been detected by the PCD™ Device in 61 patients. The mean number of episodes per patient was 4 and ranged from 1 - 75 episodes. A review of the chart for this patient that experienced the 75 episodes of VF revealed that this was most likely due to atrial fibrillation.

The majority (81.1%) of spontaneous VF episodes were successfully treated with VF Therapy #1 and 99.2% were successfully treated with one of the four programmable VF therapies.

Two patients experienced 3 episodes of spontaneous VF (3/376 - 0.8%) in which the PCD™ Device was ineffective in terminating the episode despite delivery of all four programmed VF therapies. One patient (b)(6) had two reported ineffective VF spontaneous episodes that were due to atrial fibrillation with rapid ventricular response rather than VF. Reprogramming and pharmacologic intervention resolved the problem. The other patient (b)(6) required external defibrillation to convert the VF episode. This patient's antiarrhythmic drug regimen was modified to improve defibrillation efficacy. Both of these patients have subsequently done well with no more reported ineffective VF therapies.

E.2.5 Spontaneous VF Episode Experience By Primary Indication

The primary indications for implant of the PCD™ Transvene™ System were sudden cardiac death (**SCD**), recurrent sustained ventricular tachycardia (**VT**) and sudden cardiac death associated with recurrent sustained ventricular tachycardia (**SCD/VT**). Spontaneous VF episode efficacy by primary indication is provided in Table E-8. There is no difference in therapy efficacy among the patient's indications. The overall efficacy for spontaneous VF episodes is greater than 98% for each of the patient groups.

PCD™ Transvene™ System
Spontaneous VF Episode Therapeutic Efficacy
By Primary Indication

Indication	# Episodes Successful	# Total Episodes	% Success
SCD	122	124	98.4%
VT	120	120	100.0%
SCD/VT	131	132	99.2%
TOTAL	373	376	99.2%

Table E-8: PCD™ Transvene™ System - Spontaneous VF Episode Efficacy by Primary Indication - 11/27/91

E.2.6 Spontaneous VF Episode Experience By Therapy Type

The PCD™ Device incorporates three programmable defibrillation pathways, SEQUENTIAL, SINGLE and SIMULTANEOUS, for the treatment of ventricular fibrillation. Spontaneous VF episode efficacy by programmed defibrillation pathway is provided in Table E-9.

PCD™ Transvene™ System Spontaneous VF Episode Efficacy By Programmed Therapy Type			
VF Therapy Type	**# Success**	**# Attempts**	**% Efficacy**
Sequential	317	320	99.1%
Simultaneous	56	56	100.0%

Table E-9: PCD™ Transvene™ System - Spontaneous VF Episode Efficacy by Therapy Type - 11/27/91

E.3 Overall Success Rate

Of the 317 patients who received a PCD™ Transvene™ System, 267 patients (84.2% - 267/317) have either experienced a spontaneous VT/VF episode or had VT/VF induced during a post implant electrophysiology study. The performance of the PCD™ Transvene™ System therapies have been thoroughly evaluated and been shown to be effective in detecting and terminating episodes of ventricular tachyarrhythmia.

There have been no reports of a patient death due to the PCD™ Transvene™ System not detecting a spontaneous episode of VT or VF.

The overall success rate of the PCD™ Transvene™ System in terminating spontaneous episodes of either VT or VF is 99.2% with a VT success rate of 99.2% and VF success rate of 99.2%.

The incidence of unsuccessful termination of an apparent "true" episode of ventricular tachycardia despite delivery of all four therapies was 0.06% (1/1648). The incidence of unsuccessful termination of an apparent "true" episode of ventricular fibrillation despite delivery of all four therapies was 0.3% (1/376).

The evaluation of spontaneous episode experience indicates that the PCD™ Transvene™ System's VT and VF detection and therapy functions have performed safely and effectively in the indicated patient population.

F. Complications and Observations

The introduction of a multiprogrammable implantable cardioverter defibrillator (ICD) device allows the physician to resolve the majority of relevant medical events by noninvasively changing programmed parameters rather than requiring invasive procedures. However, there will continue to be certain relevant medical events which will require invasive procedures for resolution.

For purposes of this clinical study, reported relevant medical events were divided into complications and observations based on the following definitions:

COMPLICATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which can NOT be treated or resolved by reprogramming the device and REQUIRES invasive intervention.

OBSERVATION: A symptomatic or asymptomatic clinical event with potential adverse effects, which either does NOT require invasive intervention, or which CAN be corrected by reprogramming the device.

As of November 27, 1991, there have been a total of 48 complications identified in 45 patients and 57 observations identified in 56 patients in the PCD™ Transvene™ System patient population. Thus, 14.2% (45/317) of the patients have experienced a clinical event which was defined as a complication and 17.7% (56/317) of the patients have experienced a clinical event which was defined as an observation. Table F-1 summarizes how these events were reported with U.S versus International.

PCD™ Transvene™ System
Reported Complications/Observations
U.S versus International

	Complications		Observations	
	# of Patients	# of Events	# of Patients	# of Events
U.S.	18	20	10	10
International	27	28	46	47
Total	45	48	56	57

Table F-1: PCD™ Transvene™ System Complications/Observations U.S. versus International - 11/27/91

Table F-2 summarizes the reported PCD™ Transvene™ System complications and observations by category. The category "Ineffective Therapies" included patients in whom increased defibrillation requirements were documented; "Inappropriate Therapies" includes patients in whom VT/VF therapies were delivered for nonpathological rhythms; "Pacing or Pace/Sense Related"

includes patients in whom undersensing, oversensing or loss of capture was documented; "Infection Related" includes reports of pocket infection, seroma, and hematoma was documented; "Lead Related" includes lead dislodgement, lead fracture, subcutaneous patch crinkling, and perforation; and "Device Related" includes patients in whom the device was explanted for reasons other than patient death, infection, or transplant.

The reported complications and observations are recognized clinical events that may occur with **any** of the current ICD devices. These complications and observations are discussed in the PCD™ device and Transvene™ manual.

PCD™ Transvene™ System Reported Complications/Observations By Category		
Category	**Complications**	**Observations**
Ineffective Therapies	0.9%	0.9%
Inappropriate Therapies	-	8.2%
Pacing or Pace/Sense Related	0.3%	2.2%
Infection Related	3.2%	5.4%
Lead Related	9.7%	0.6%
Device Related	0.6%	-

Table F-2: PCD™ Transvene™System - Complications/Observations - 11/27/91

The "**Lead Related**" complications/observations include perforation, lead fracture, subcutaneous patch crinkling, and lead dislodgement. Table F-3 contains a summary of the reported "**Lead Related**" complications and observations.

PCD™ Transvene™ System Lead Related Complications/Observations		
Category	**Complication**	**Observation**
Right Ventricular Perforation	2 (0.6%)	-
Subclavian Vein Thrombosis	-	-
Lead Fracture	2 (0.6%)	-
Subcutaneous Patch Crinkling	2 (0.6%)	2 (0.6%)
Seroma at SQ Patch	-	5 (1.6%)
Lead Dislodgement	25 (7.8%)	-

Table F-3: PCD™ Transvene™ System Lead Related Complications/Observations - 11/27/91

There have been a total of twenty five lead dislodgements reported in twenty patients over a mean implant duration of 4.5 months. Thus, the incidence of lead dislodgements in this patient population is 7.8% (25 dislodgements/319 implants). The incidence of right ventricular lead dislodgement was 2.0% (6 dislodgements/304 implants), the incidence of coronary sinus lead dislodgement was 6.3% (7 dislodgements/112 implants) and the superior vena cava lead dislodgement was 4.7% (11 dislodgements/234 implants).

None of the lead dislodgements resulted in an ineffective therapy for a spontaneous VT of VF episode or patient death. Lead dislodgements were documented by fluoroscopic examination during electrophysiologic evaluation, chest x-ray obtained during routine follow-up, or during pacing/sensing threshold evaluation during routine follow-up. In all twenty five cases, reoperation was required to reposition the lead and reestablish an effective defibrillation lead system.

Lead dislodgements are not specific to the PCD™ Transvene™ System and have been reported with dual chamber pacemakers and the current market released implantable cardioverter defibrillator (ICD) system. The early history of dual chamber pacemakers witnessed a high lead dislodgement rate of at least 20% (Smyth, PND, et al. Permanent pervenous atrial sensing and pacing with a new J-shaped lead. J Thoracic Cardiovascular Surgery. 1976;72:565-570). Winkle, et al reported that the incidence of dislodgement of the superior vena cava spring leads with the current market release ICD system to be 6.3%. (Winkle, et al. Automatic Implantable Cardioverter-Defibrillator: Efficacy, Complications, and Survival in Patients with Malignant Ventricular Arrhythmias. JACC. June 1988; Vol.11, No.6:1278-86).

G. Inactive Patients

There are a total of 17 patients who had received a PCD™ System and are no longer active in the study as of 11/27/91. Table G-1 shows the distribution of inactive patients by reason for no longer being active in the PCD™ Transvene™ System clinical study.

PCD™ Transvene™ System Inactive Patients	
Inactive Patients	**All Patients**
Patient Deaths	5
Infection (Explant)	8
Heart Transplant	4
Total	17

Table G-1: Inactive Patients - 11/27/91

H. Patient Deaths

The positive impact of implantable cardioverter defibrillator (ICD) therapy on sudden cardiac death mortality has been well documented in the medical literature. The use of device therapy for the treatment of recurrent ventricular arrhythmias has become an accepted and important clinical tool. An analysis of the sudden cardiac death survival in the PCD™ System patient population was performed.

For purposes of the clinical study, each of the patient deaths was categorized using the following definitions:

Non-Cardiac:	Deaths that occurred where the primary cause of death was determined to be non cardiac in nature, e.g. stroke, cancer, etc.
Cardiac:	Deaths that occurred where the primary cause of death was determined to be cardiac in nature.
Non-Sudden:	Deaths that occur greater than one hour after the onset of symptoms.
Sudden:	Deaths that occur within one hour of the onset of symptoms or where the death is unwitnessed. Sudden cardiac deaths were also categorized as being **Witnessed** or **Unwitnessed.**
Perioperative:	Deaths that occur within thirty days of implant.
System Related:	A death which results from a malfunction (operation not according to design specification) of a PCD™ System component, or as a result of a device induced arrhythmia, or an interaction between a PCD™ System component and the patient.
Procedure Related:	A death which occurs as a result of a procedure required to implant, follow or test a PCD™ System.

All deaths and significant complications have been and will continue to be reviewed by a committee comprised of PCD™ Transvene™ System investigators and other physicians. Two committees (Clinical Event Review Committees) have been formed, one to review North American deaths and complications, and the other to review European clinical events. The primary purpose of these reviews was to determine whether the PCD™ System was related to the deaths or significant complications that have occurred and, if so, what changes may be required to prevent such events in the future.

There have been a total of 5 patient deaths reported in the PCD™ Transvene™ System patient population. Table H-1 summarizes how these patient deaths have been classified. There have been no sudden cardiac deaths in this patient population.

PCD™ Transvene™ System Summary of Death Classifications	
Classifications	**All Patients (N=317)**
Sudden Cardiac	-
Non-Sudden Cardiac	4
Noncardiac	1
TOTAL	5

Table H-1: PCD™ Transvene™ System - Summary of Death Classifications - 11/27/91

None of the patient deaths were attributed to a malfunction of the PCD™ Transvene™ System.

Actuarial survival analysis on the PCD™ Transvene™ System was done on all patients in whom the device was implanted. Thus, the analysis is done from the perspective of **intention to treat**. Those patients in whom the PCD™ Device was OFF at the time of death or in whom no device was implanted are included in the survival analysis. Those patients that were screened for a PCD™ Transvene™ System but failed to receive a Transvene™ system are not included in this analysis.

Projected one year survival calculations for the various death classifications are provided in Table H-2. **The actuarial projections include perioperative deaths only in the calculation of one year survival from death due to all causes (shown in the row labelled Overall).** The perioperative death rate defined as deaths which occurred within thirty days of implant was 0.3% (1/317).

PCD™ Transvene™ System One Year Actuarial Survival	
Sudden Cardiac Death	100.0%
Non-Sudden Cardiac	97.9%
All Cardiac	97.9%
Noncardiac	99.3%
Perioperative	0.3%
Overall	96.8%

Table H-2: PCD™ Transvene™ System - One Year Actuarial Survival - 11/27/91

Overall, the PCD™ Transvene™ Device has been safe and effective in reducing the sudden cardiac arrhythmic death rate in the indicated patient population. The incorporation of programmable VT/VF detection and therapies has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

I. Clinical Experience By Primary Indication

Medtronic is requesting approval for use of the PCD™ Transvene™ System in the following patient population:

* Patients who have survived at least one episode of cardiac arrest due to a ventricular arrhythmia not caused by an acute myocardial infarction; or

* Patients with recurrent, sustained ventricular tachycardia that remain inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most efficacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

Sudden cardiac death without recurrent VT (**SCD**) was the indication for implant in 37.9% of the patients, recurrent ventricular tachycardia without an episode of sudden cardiac death (**VT**) was the indication for implant in 45.7% of the patients, and sudden cardiac death and recurrent VT (**SCD/VT**) was the indication for implant in 16.4% of the patients.

The performance of the PCD™ Transvene™ System in these three groups are summarized in Table I.1.

In all three patient groups, coronary artery disease was the predominant heart disease and the patients exhibited moderate left ventricular dysfunction as demonstrated by mean ejection fractions of less than 40%. The mean LED at the time of implant was similar among the patient groups as was the mean DFT.

The overall efficacy in terminating spontaneous VT/VF episodes in the SCD patient group was 99.4%, in the VT patient group 99.1%, and in the SCD/VT group 99.1%. Thus, independent of the indication for implant, the PCD™ Transvene™ System was highly effective in terminating spontaneous episodes of VT/VF.

The one year sudden cardiac death survival rates for all groups was 100%.

This analysis indicates that the PCD™ Transvene™ System has performed safely and effectively in the indicated patient groups and should be approved for use in the indicated patient population.

PCD™ Transvene™ System Data Summary by Primary Indication				
	SCD	**VT**	**SCD/VT**	**All Patients**
# of Patients	120	145	52	317
Number, % Male **Number, % Female**	92 76.7% 28 23.3%	121 83.5% 24 16.5%	47 90.4% 5 9.6%	260 82.0% 57 18.0%
Mean Age	56.7 yrs	60.0 yrs	58.5 yrs	58.5 yrs
Coronary Artery Disease	81 67.5%	108 74.5%	40 76.9%	229 72.2%
Mean Ejection Fraction	40.2% (N=110)	35.2% (N=132)	33.0% (N=48)	36.7% (N=290)
Defibrillation Pathway: **Sequential** **Simultaneous** **Single**	 89 74.1% 26 21.7% 5 4.2%	 112 76.2% 35 23.8% 0 --	 45 86.6% 6 11.5% 1 1.9%	 247 77.4% 67 21.0% 5 1.6%
Mean LED	14.1J (N=109)	15.3J (N=135)	17.1J (N=45)	15.1J (N=288)
Mean DFT	12.5J (N=54)	14.1J (N=68)	15.0J (N=25)	13.7J (N=147)
Spontaneous VT: **# of Patients** **# of Episodes** **% Success**	 14 380 99.7%	 47 835 98.9%	 18 433 99.1%	 79 1648 99.2%
Spontaneous VF: **# of Patients** **# of Episodes** **% Success**	 16 124 98.4%	 32 120 100.0%	 13 132 99.2%	 61 376 99.2%
1 Year SCD Survival	100.0%	100.0%	100.0%	100.0%

Table I-1: PCD™ Transvene™ System Data Summary by Primary Indication - 11/27/92

J. Patients Not Meeting Implant Criteria

The PCD™ Transvene™ System offers a simpler and safer implantation technique for an implantable cardioverter defibrillator system. In addition, the PCD™ Transvene™ System decreases the potential perioperative mortality and long term morbidity and mortality associated with current epicardial system implantation approaches.

There is a class of patients who cannot tolerate the thoracotomy required for the utilization of the epicardial patch lead defibrillation lead system and who are at high risk of sudden cardiac death. For these patients, the PCD™ Transvene™ System is the only therapy available. Because of the surgical risks and postsurgical complications associated with epicardial lead system, implantation in the following patient groups may not be possible - patients that pose high surgical risk because of their state of health, patients who are potential heart transplant candidates and patients who may eventually require open heart surgery for treatment of their coronary artery disease. The PCD™ Transvene™ System simplifies and greatly reduces the risk associated with lead introduction, making therapy available to these patient groups. Because there is no need to open the chest of these patients, options for future therapy remain available; e.g. CABG is associated with decreased morbidity and mortality if there has been no prior open chest surgery.

However, it is expected that nonthoracotomy lead systems will have higher mean implant defibrillation thresholds as compared to traditional epicardial lead systems. In a epicardial lead system, greater electrode surface area would theoretically decrease defibrillation requirements.

The smaller electrode surface areas of the PCD™ Transvene™ System might reduce the proportion of patients in whom the implant criteria could be met. Not meeting the implant criteria may reduce the chronic effectiveness of the lead system. Recent studies indicated that 70% of patients tested may be candidates for a nonthoracotomy defibrillation lead system (Wilber, D, et al. Clinical Advances in Nonepicardial Implantable Defibrillator Lead Systems. The Journal of Invasive Cardiology. Vol.3, No.6,November/December 1991).

For purposes of the PCD™ Transvene™ System, the implant criteria was defined as successful VF termination at least 3 times in 4 attempts with the final lead configuration with an output energy of 18 Joules or less. The determination of a defibrillation threshold was not necessary.

A defibrillation threshold (**DFT**) was defined as the energy at the lowest successful defibrillation attempt, provided the patient had a failure below the lowest success or a success at $\leq$ 5J. The lowest energy of defibrillation (**LED**) was defined as the lowest programmed energy that successfully defibrillated the patient. In both cases, conversion of ventricular tachycardia or ventricular flutter to sinus rhythm was **not** included in the determination of the DFT or LED.

A total of 368 patients were evaluated for implantation of the PCD™ Transvene™ System. The PCD™ Transvene™ System was implanted in 86.1% (317/368) of the patients who were screened for the system. A total of 257 patients, or 70%, met the recommended defibrillation implant criteria which compares favorably with the predicted success rates published in the literature (Wilber et al).

However, 18.9% (60/317) of the patients did not meet the recommended PCD™ Transvene™ System defibrillation efficacy implant criteria and still received the PCD™ Transvene™ System. The major reasons for not meeting implant criteria included 3/4 successes at 24 Joules or less (35%), two successes at 18 Joules (31.7%), failure to induce at least three episodes of VF at implant (20%), and deteoriating patient condition (11.7%). However, in 80% of the patients (48/60), at least one episode of induced VF was successfully reverted with 24 Joules or less.

The investigators felt in every case that the testing performed at the time of implant, though it did not meet the recommended implant criteria, did demonstrate an adequate defibrillation safety margin when programming VF Therapy #1.

This is particularly true in those patients (N=40) in whom 3/4 successes at 24 Joules or two successes at 18 Joules was documented. In these patients, a safety margin of 10 Joules was provided between the successful defibrillation energy (24 J or less) and the maximum output of the PCD™ Device (34 J). The investigators utilized this 10 Joule safety margin as a benchmark based on the clinical experience discussed in the article, Troup P., et al. The Implanted Defibrillator: Relation of Defibrillating Lead Configuration and Clinical Variables to Defibrillation Threshold. Journal of American College of Cardiology 1985; 6:1315-1321. Finally and perhaps most importantly, the investigators also felt that these patients medical condition precluded a PCD™ Epicardial System implant with a thoracotomy approach and its associated morbidity and mortality.

In the patients screened for the PCD™ Epicardial System, 11.0% did not meet the recommended implant criteria but ultimately received the system. The spontaneous VT/VF episode efficacy, one year sudden cardiac death survival and overall one year survival rate is similar in the two patients populations.

Thus, the patients who received the PCD™ Transvene™ System despite not meeting the recommended implant criteria were not a higher risk for sudden cardiac death.

There were 51 patients (13.9%) in whom the PCD™ Transvene™ System implant criteria could not be met despite multiple inductions and the evaluation of multiple PCD™ Transvene™ System lead configurations. In these patients, there was not a 10J safety margin between the lowest energy that successfully defibrillate the patient and the maximum output of the PCD™ Device (34J). These patients all received PCD™ Epicardial System implants and in all cases met the required defibrillation implant criteria.

Patients Receiving PCD™ Transvene™ System & Did Not Meet Implant Criteria

In order to determine if the patient's not meeting implant criteria had a higher risk for morbidity and mortality, a comparison of their clinical outcome was made with those patients who did meet the implant criteria. This comparison is provided in Table J-1.

The two patient groups had similar efficacy in the treatment of spontaneous VT/VF episodes. Importantly, in the patient population that did not meet the implant criteria there were no patients who experienced episodes of VT/VF where all four programmed therapies failed to terminate a "true" episode. Those episodes which were not terminated were delivery of inappropriate therapy for atrial fibrillation with rapid ventricular response or sinus tachycardia.

There was no difference in the one year sudden cardiac survival of the overall survival in the two groups. This indicates, that despite not meeting the implant criteria, these patients were not at higher risk of sudden cardiac death.

PCD™ Transvene™ System Patients Meeting Implant Criteria versus Patients Not Meeting Implant Criteria		
Implant Data		
Data	**Meeting Criteria**	**Not Meeting Criteria**
Number of Patients	257	60
Spontaneous VT Episode Efficacy	99.2%	99.1%
Spontaneous VF Episode Efficacy	99.7%	97.4%
Number of Patient Deaths	4	1
Perioperative Mortality	0.4%	-
One Year Survival		
Sudden Cardiac	100%	100%
Non-Sudden Cardiac	98.1%	96.9%
All Cardiac	98.1%	96.9%
Noncardiac	99.1%	100%
Overall	96.8%	96.9%

Table J-1: PCD™ Transvene™ System: Patients Not Meeting Implant Criteria versus Patients Meeting Implant Criteria - Comparison of Clinical Outcome - 11/27/91

The survival of patients receiving a PCD™ Transvene™ System without meeting implant criteria (N=60) was compared to patients receiving a PCD™ Epicardial System without meeting implant criteria (N=44). This comparison is provided in Table J-2. Though the PCD™ Transvene™ System had a higher incidence of patients not meeting implant criteria but receiving the system (18.9%), the overall survival of these patients was statistically significantly better as compared to the PCD™ Epicardial System patients not meeting implant criteria.

determined this to be an appropriate demonstration of device effectiveness and that the PCD Transvene System could be implanted.

The clinical outcome in these patients was not adversely affected by not meeting implant criteria since their spontaneous VF episode efficacy was 100% and the overall one year actuarial survival was also 100%.

PCD™ Transvene™ System Patients Not Meeting Implant Criteria 3/4 Success at ≤ 24 Joules	
Number of Patients	21
Lowest Energy of Defibrillation **20 Joules** **22 Joules** **24 Joules**	 9 5 7
Number of Patients with 1 Success at 18J	15
Overall Spontaneous VF Episode Efficacy	100%
One Year Survival **Sudden Cardiac** **Overall**	 100% 100%

Table J-3: PCD™ Transvene™ System: Patients Not Meeting Implant Criteria with 3/4 Successes at ≤ 24 Joules Clinical Experience - 11/27/91

Two Successes at 18 Joules

There were 19 patients in whom the PCD™ Transvene™ System was implanted with 2 successes at 18 Joules. A third success at 18 Joules was not obtained either because VF could not be induced or the physician felt that adequate testing had been completed to evaluate the PCD™ Transvene™ System.

The clinical outcome in these patients was not adversely affected by not meeting implant criteria since their spontaneous VF episode efficacy was 100% and the overall one year actuarial survival was also 100%.

Based on this analysis, of the sixty patients who received the PCD™ Transvene™ System despite not meeting the recommended implanted criteria, 40 (66.7%) had successful termination of VF at 24 Joules or less. There were no patient deaths in this group and the overall spontaneous VF episode efficacy was 100%. **Thus, there were no patients in whom the PCD™ Transvene™ System was implanted**

without a safety margin of at least 10 Joules provided between the successful defibrillation energy (24 J or less) and the maximum output of the PCD Device (34 J).

Failure to Induce Three Episodes of VF

There were 12 patients who did not meet the recommended PCD™ Transvene™ System implant criteria because at least three episodes of VF were not induced at the time of implant. The indication for implant was sudden cardiac death (SCD) in four patients, recurrent ventricular tachycardia (VT) in four patients and sudden cardiac death associated with recurrent ventricular tachycardia (SCD/VT) in four patients.

There were four patients (33.3%) who had at least one episode of VF induced which was successfully reverted with 18 Joules. In the remaining eight patients, there were no episodes of VF induced. Five of these patients were on Amiodarone therapy which may have contributed to the inability to induce VF. In the eight patients in whom no VF was induced at implant, either VT, polymorphic VT or ventricular flutter was induced and successfully reverted with 18 Joules or less. Since the indication for implant in these eight patients was either VT or SCD/VT, the investigator felt the effective termination of VT was adequate to allow implantation of the PCD™ Transvene™ System.

Of the 12 patients who did not meet the recommended PCD™ Transvene™ System implant criteria because at least three episodes of VF were not induced at the time of implant, seven (58.3%) have either experienced a spontaneous VF episode or have had VF induced during a electrophysiology study. In all cases, VF was successfully reverted by VF Therapy #1 (34J).

There has been one reported patient death, (Patient ID (b)(6), which was classified as non-sudden cardiac secondary to end stage heart failure. Thus the one year sudden cardiac death survival in this patient population is 100% while the one year overall survival is 88.9%.

Patient Condition

In seven patients the PCD™ Transvene™ System implant procedure was terminated prior to meeting the recommended implant criteria due to the patient's deteriorating condition. The mean ejection fraction of this group was 24.5% which may have placed the patients at increased risk for perioperative mortality and morbidity. This group had a mean of nine VF inductions and 2.5 lead configurations evaluated in an attempt to meet the recommended implant criteria.

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Patient Condition

In seven patients the PCD™ Transvene™ System implant procedure was terminated prior to meeting the recommended implant criteria due to the patient's deteriorating condition. The mean ejection fraction of this group was 24.5% which may have placed the patients at increased risk for perioperative mortality and morbidity. This group had a mean of nine VF inductions and 2.5 lead configurations evaluated in an attempt to meet the recommended implant criteria.

Four of the patients (57.1%), had at least one successful termination of VF at 18 Joules prior to the termination of the implant procedure. The lowest energy of defibrillation in this group ranged from 18-22 Joules. Thus at least a 10 Joule defibrillation margin was provided between the successful defibrillation energy and the maximum output (34J) of the PCD™ Device.

In two patients, VT, polymorphic VT or ventricular flutter was repeatedly induced and terminated however VF could not be induced. The physicians elected to terminate the procedure due to the patients poor hemodynamic status rather than attempt further inductions to obtain ventricular fibrillation.

One final patient (Patient ID (b)(6) VF could only be successfully terminated by 34 Joules despite evaluation of multiple configurations. The physician elected to implant the system and reevaluate the PCD™ Transvene™ System at the prior to hospital discharge electrophysiology study. At this evaluation, VF was still only successfully reverted by 34 Joules. The PCD™ Transvene™ System was explanted and the patient received a PCD™ Epicardial System with the lowest energy of defibrillation being 24 Joules.

The clinical outcome in these patients was not adversely affected by not meeting implant criteria since their spontaneous VF episode efficacy was 100% and the overall one year actuarial survival was also 100%.

Equipment

Finally, in one patient (Patient ID (b)(6) the implant procedure was terminated prior to meeting implant criteria due to inappropriate lead system impedance values measured on the Model 5335 ETCD. The patient has had induced episodes of ventricular fibrillation successfully reverted by VF Therapy #1 (34J). Analysis of the Model 5355 ETCD indicated appropriate performance of the device.

In conclusion, 60 patients received the PCD™ Transvene™ System despite not meeting the recommended implant criteria. The major reasons for not meeting implant criteria included 3/4 successes at 24 Joules or less (35%), two successes at 18 Joules (31.7%), failure to induce at least three episodes of VF at implant (20%), and deteoriating patient condition (11.7%). However, 80% of the patients (48/60) had at least one successful reversion of an induced episode of VF with 24 Joules or less.

The investigators felt in every case that the testing performed at the time of implant, though it did not meet the recommended implant criteria, did provide an adequate defibrillation safety margin when programming VF Therapy #1.

No patient received the PCD™ Transvene™ System without a safety margin of at least 10 Joules provided between the successful defibrillation energy (24 J or less) and the maximum output of the PCD Device (34 J).

The clinical outcome of the patients was not adversely affected by not meeting the recommended implant criteria as is seen by an overall spontaneous VF episode efficacy of 97.4%, one year sudden cardiac death survival rate of 100% and a one year overall survival rate of 96.9%. Thus, despite not meeting the recommended implant criteria, the PCD™ Transvene™ System performed safely and effectively in this patient population.

Patients Not Meeting Implant Criteria - Conclusion

The PCD™ Transvene™ System offers a simpler and safer implantation technique for implantable cardioverter defibrillator systems. However, it is expected that nonthoracotomy lead systems will have higher mean implant defibrillation thresholds than those obtained with traditional epicardial lead systems. Despite this, physicians elected to utilize the PCD™ Transvene™ System in patients who did not meet the recommended implant defibrillation criteria because of their cardiovascular condition and increased risk for morbidity and mortality associated with a thoracotomy. **It should be noted that the PCD™ Transvene™ System was not implanted in any patient without at least a 10 Joule defibrillation safety margin between the successful energy and the maximum output of the PCD Device (34J).**

A total of 368 patients were evaluated for the implantation of the PCD™ Transvene™ System. Of these, 86% (317/368) ultimately received the PCD™ Transvene™ System. A total of 257 patients, or 70%, met the recommended defibrillation criteria which compares favorably with the predicted success rates published in the literature (Wilber, et al).

There were 60 patients (18.9%) who received the PCD™ Transvene™ System and did not meet the recommended implant criteria. The reasons for not meeting implant criteria were 3/4 successes at 24 Joules or less (35%), 2 successes at 18 Joules (31.7%), failure to induce at least 3 episodes of VF at implant (20%), and deteoriating patient condition (11.7%). However, 80% of the patients (48/60) had at least one episode of VF successfully reverted with 24 Joules.

The investigators felt in every case that the testing performed at the time of implant, though it did not meet the recommended implant criteria, did provide an adequate defibrillation safety margin when programming VF Therapy #1.

The incidence of not meeting implant criteria in the PCD™ Transvene™ System (18.9%) is similar to that reported with the PCD™ Epicardial System (11.0%). More importantly, there is no difference in spontaneous VT/VF episode efficacy, one sudden cardiac death survival and overall one year survival in the two groups. Thus, despite not meeting the PCD™ Transvene™ System implant criteria, these patients were not a increased for sudden cardiac death. Though these results are important, Medtronic is **not recommending** a modification of the PCD™ Transvene™ System implant criteria.

There were 51 patients (13.9%) who did not meet the recommended implant criteria and received a PCD™ Epicardial System. Analysis indicated a increased perioperative mortality in patients undergoing both a PCD™ Transvene™ and Epicardial System evaluation. This was related to both a depressed left ventricular function and increased VF inductions and VF duration experienced during the implant procedure. Based on this clinical experience, Medtronic is modifying the labeling to 1) recommend that the physician limit the number of inductions and duration of VF during PCD™ Transvene™ System implants and 2) recommend that the physician consider the number of VF inductions performed and duration of VF episodes prior to preceding to an PCD Epicardial System implant.

The current recommended implant defibrillation criteria for the PCD™ Transvene™ System is 3/4 successes at 18 Joules or less. The clinical experience presented both in this section and the entire reports indicates that this criteria is safe and effective in predicting effective termination of a spontaneous VF episode. Medtronic does not intend to modify the implant criteria at this time.

There are patients, due to their underlying cardiovascular condition, who are not candidates for an epicardial system and who may not meet the recommended PCD™ Transvene™ System implant criteria. Clinical experience indicates that if a safety margin of 10 Joules is provided between the successful defibrillation energy and the maximum output of the PCD™ Device (34J) these patients are not at increased risk for sudden cardiac death.

K. Comparison to AICD Epicardial System Clinical Experience

The Automatic Implantable Cardioverter/Defibrillator produced by Cardiac Pacemakers, Inc. is the only device to have obtained approval from the U.S. FDA for Market release. This system represents the only market released device available to compare with the PCD™ Transvene™ System. There are important differences in the capabilities and operation of these two systems, particularly in the area of antibradycardia and anticardia pacing. In addition, the current market-approved AICD System is implanted only with defibrillation lead systems requiring a thoracotomy. Nevertheless, a comparison of those aspects that are similar is provided in Table K-1. Note that the percentage reported for the PCD™ Transvene™ System includes both complications and observations.

PCD™ Transvene™ System Comparison of Reported Complications/Observations PCD™ versus AICD		
Category	**PCD™%**	**AICD%**
Fail to Cardiovert/Defibrillate	1.9%	4.1%
Inappropriate/Problematic VT/VF Therapy Delivery	8.2%	20%
Pocket Infection	3.5%	2.2%
Erosion	0.3%	0.7%

Table K-1: PCD™ Transvene™ System versus AICD System: Comparison of Complication/Observation Rates - 11/27/91

The AICD complications are based on a recent published article (Winkle, et al. Long-Term Outcome With the Automatic Implantable Cardioverter-Defibrillator; JACC. May, 1989; 13(6); 135-161).

The incidence of failure to cardiovert and/or defibrillate was lower in the PCD™ Transvene™ System patient population. The instances of failure to cardiovert and/or defibrillate in the PCD™ Transvene™ System patient population were associated with increased defibrillation requirements, none of which resulted on patient death and all of which occurred during electrophysiologic testing. In three cases, the implanted lead system was modified to provide adequate defibrillation efficacy, in two cases, the patient's drug therapy was modified and, in the final case, reprogramming provided for defibrillation efficacy.

The instances of failure to cardiovert of defibrillate in the Winkle, et al article were associated with patch dislodgement, patch crinkling, lead conductor fracture, and elevated defibrillation thresholds.

The incidence of inappropriate/problematic VT/VF therapy delivery was lower in the PCD™ Transvene™ System patient population. This is to be anticipated since this device incorporates independently programmable detection algorithms for VT and VF. The reasons for inappropriate therapy included sinus tachycardia being detected as VT/VF and atrial fibrillation with rapid ventricular response being detected as VT/VF.

The circumstances reported in the Winkle, et al article were non-sustained VT, recurrent stable VT, sinus tachycardia, atrial fibrillation with rapid ventricular response and pacemaker interaction. The patients with VT complained of receiving multiple shocks with limited or no symptoms. The incorporation of antitachycardia pacing decreases the need for delivery of cardioversion shocks for the termination of stable VT and increases patient acceptance of ICD therapy.

The incidence of pocket infection is higher in the PCD™ Transvene™ System patient population. This is not unexpected since the PCD™ Transvene™ System implant procedure may require the evaluation of multiple lead orientations to obtain adequate defibrillation efficacy and may result i an increased procedure time. In the Winkle, et al experience all patients with pocket infection had the devices explanted. In the PCD™ Transvene™ System experience, the incidence of device explant secondary to pocket infection was 2.5%, which would then make the incidence of pocket infection comparable in the two patient groups.

Thus, the incidence of complications and observations was similar to that of the AICD in the categories of ineffective VT/VF therapy, infection, and erosion. Clinically significant, however, is that the incidence of inappropriate therapy delivery in the PCD™ Transvene™ System is lower than that of the AICD System.

This analysis indicates that the PCD™ Transvene™ System offers potential clinical advantages since the need for a thoracotomy is eliminated. The associated mortality and morbidity is reduced.

Table K-2 contains a comparison of the actuarial survival rate of the PCD™ Transvene™ System versus Ventak-P Epicardial System [The patient population used for comparison is the one described in the Summary of Safety and Effectiveness Data, PMA P890061, dated May 2, 1991 available through the Freedom of Information Act]. For purposes of this comparison, only the **overall** actuarial survival rate includes perioperative deaths. All other calculations in both the PCD™ Transvene™ and Ventak-P group exclude perioperative patient deaths.

For the Ventak-P Epicardial System, patient deaths were **censored** if the Ventak-P System had been either electively deactivated for various reasons prior to the patient's death, thus preventing the device from attempting to convert the arrhythmia or if the pulse generators were known to be nonfunctional and awaiting replacement. For purposes of this comparison, one patient death was **censored** in the PCD™ Transvene™ System patient population because the device was deactivated at the time of the patients death.

PCD™ Transvene™ System Comparison of Actuarial Survival Rate PCD™ versus Ventak-P		
One Year Survival	**PCD™**	**Ventak-P**
Number of Patients	317	292
Sudden Death	100%	98.6%
Overall	97.3%	90.8%

Table K-2: Comparison of the Actuarial Survival PCD™ Transvene™ System versus Ventak-P Epicardial System - 11/27/91

This comparison indicates that the projected survival from sudden cardiac death of patients receiving a PCD™ Transvene™ System is improved to that reported for the Ventak-P Epicardial System. Thus, the incorporation of programmable VT/VF detection and therapy algorithms has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

In addition, this comparison indicates that the projected survival from all causes of death (**Overall**) in patients receiving a PCD™ Transvene™ System is markedly improved as compared to the Overall one year survival reported for the Ventak-P Epicardial System. This improvement is directly related to the decrease in the perioperative mortality in patients receiving a PCD™ Transvene™ System due to the elimination of the requirement for a thoracotomy.

L. Comparison to PCD™ Epicardial System Clinical Experience

The PCD™ Epicardial System, which is a tiered therapy device, combines features of bradycardia support pacing, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. This system has incorporated programmability and multiple detection and therapeutic options that allows the titration of device therapy to a patient's specific clinical arrhythmia history.

However, the PCD™ Epicardial System requires a thoracotomy for implantation because of the need to insert epicardial patch leads. This exposes the patient to increased surgical risk an potentially limits the type of patient who may be considered for implant of the system. The need for a simpler and safer implantation technique is widely recognized. The incorporation of a nonthoracotomy lead system, such as the PCD™ Transvene™ System, would decrease the potential perioperative and long term mortality and morbidity associated with current epicardial system implantation approaches.

The PCD™ Epicardial System and PCD™ Transvene™ System are identical except for the implanted defibrillation lead system. Thus the performance of the PCD™ device is similar in the two systems and therefore a comparison of clinical experience should focus on those areas where the lead system implanted may impact clinical outcome.

This analysis will show that the incorporation of a nonthoracotomy defibrillation lead system has improved the type of therapy available for the treatment of recurrent VT/VF and decreased the potential mortality and morbidity associated with epicardial implant approaches while maintaining the positive impact of ICD therapy on VT/VF episode efficacy and patient survival.

In comparing the clinical experience with the PCD™ Transvene™ System to the PCD™ Epicardial System clinical experience, it is important to determine that the patients who received the device are comparable.

The patient characteristics of the patients receiving the PCD™ Transvene™ System were compared to the patients discussed in the PCD™ Epicardial System PreMarket Approval Application (P900061) dated December 16, 1991.

PCD™ Transvene™ System Comparison of Patient Characteristics		
	PCD™ Transvene™ System	**PCD™ Epicardial System**
Number of Patients	317	434
Mean Follow-Up Time	4.5 months	11.0 months
% Males **% Females**	260 82.0% 57 18.0%	374 86.2% 60 13.8%
Mean Age	58.5 years	58.3 years
Primary Indication*: **SCD** **VT** **SCD/VT**	 120 37.9% 145 45.7% 52 16.4%	 118 27.2% 233 53.7% 83 19.1%
Cardiovascular History **Coronary Artery Disease** **Cardiomyopathy**	 229 72.2% 45 14.2%	 325 74.7% 66 15.2%
Mean Ejection Fraction	36.7%	34.6%
Number of Drugs Failed	2.9	3.2
Spontaneous VT Efficacy	99.2%	97.7%
Spontaneous VF Efficacy	99.2%	98.1%
Incidence of Complications	14.2%	13.6%
Incidence of Observations*	17.7%	26.3%
Number of Deaths	5	64
Perioperative Mortality*	0.3%	5.5%
One Year Survival **Sudden Cardiac** **Overall***	 100% 96.8%	 98.8% 85.6%

* **Statistically Significant**

Table L-1: Comparison of Patient Characteristics, PCD™ Transvene System versus PCD Epicardial System - 11/27/91

The two patient groups are comparable in mean age and mean ejection fraction. Both groups had moderately depressed left ventricular function demonstrated by the mean ejection of 36.7% for the PCD™ Transvene™ System patient group and 34.6% for the PCD™ Epicardial patient group.

Analysis indicated that the PCD™ Transvene™ System patient population had a statistically significant higher percentage of patients whose indication for implant was sudden cardiac death ($p=0.008$). It

is not expected that this difference will result in a different clinical outcome in the PCD™ Transvene™ System patient population as compared to the PCD™ Epicardial System. This difference in patient indication is a reflection of the physicians use of the PCD™ Transvene™ System.

Despite their excellent clinical performance, epicardial defibrillation lead system have important limitations. The requirement for direct thoracic access contributes significantly to perioperative complications, patient discomfort and prolonged hospitalization. The availability of reliable nonthoracotomy lead systems should provide positive clinical impact on these issues while not negatively impacting patient survival.

There was a significant increase in overall survival in the patients receiving a PCD™ Transvene™ System. As previously noted, the Overall one year actuarial survival includes death from all causes. The overall one year survival for patients receiving the PCD™ Transvene™ System was 96.4%. This is significantly improved as compared to the overall one year actuarial survival for the PCD™ Epicardial System (85.6%) [p=0.001]. This improvement in overall survival is primarily due to the marked improvement in perioperative mortality, the PCD™ Transvene™ System having a 0.3% perioperative mortality versus the a perioperative mortality of 5.5% in the PCD™ Epicardial System. This improvement in perioperative mortality is primarily due to the elimination of the need for surgical thoracotomy and its associated morbidity and mortality.

A comparison of PCD™ Transvene™ System clinical experience and PCD™ Epicardial System clinical experience indicates that the devices are being used in patients with similar cardiovascular disease history.

The reported incidence of complications is comparable between the two systems. The reported incidence of observations was statistically lower in the PCD™ Transvene™ System.

Finally, the reported Sudden Cardiac Death survival rates in the two patient groups is very similar (PCD™ Transvene™ = 100%; PCD™ Epicardial = 98.8%). However, there is statistical improvement in the overall survival in the PCD™ Transvene™ System patient population. This is directly related to the decreased perioperative morbidity and mortality associated with the PCD™ Transvene™ System.

The PCD™ Transvene™ System eliminates the need for a thoracotomy for the implantation of defibrillation lead systems. This directly impacts the overall patient survival by decreasing the perioperative patient morbidity and mortality when compared to the PCD™ Epicardial System. This is added benefit however is not gained at the expense the PCD™ Transvene™ System efficacy in treating spontaneous VT/VF episodes when compared to the PCD™ Epicardial System.

M. PCD™ System Performance

M.1 PCD™ Device

Devices implanted for the treatment of recurrent ventricular tachyarrhythmias should perform safely and reliably in the indicated patient population. Device longevity, ventricular tachyarrhythmia detection and therapy performance and analysis of explanted devices were evaluated to assess the performance of the PCD™ Device.

Extended longevity of implantable cardioverter defibrillators should decrease the number of device replacements a given patient would experience over their lifetime and decrease unnecessary patient morbidity. Thus, the PCD™ Device longevity, which is monitored utilizing battery voltage and charge time obtained via telemetry, was analyzed. The PCD™ Device longevity data collected is consistent with the longevity projections.

The combined experience of induced and spontaneous VT/VF episode experience has shown that the PCD™ Device VT/VF detection and therapies have performed safely and according to design specifications when required to treat induced and spontaneous VT/VF episodes.

There have been a total of 19 devices explanted. Reasons for explant were patient death (5), infection (8), cardiac transplant (4), low battery voltage (1) and high voltage arcing (1). The analysis of the device that was explanted due to lower than expected battery voltage indicated that the decreased battery voltage measurement was due to hermetic leakage at the input to one of the integrated circuits. This leads to a voltage drop across a resistor where the voltage measurement is taken. Analysis indicated that the battery was performing to specifications and the hermetic leakage was a random event. Analysis of the other device indicated that arcing occurred between the conductors inside the hermetically enclosed brazed ring of the high power hybrid. As a result, high voltage was momentarily applied to the low power circuitry, including the

low power hybrid. This low power hybrid lost function including the capability to pace and transmit telemetry due to excessive voltage applied. Since this is the only device that exhibited this type of failure in the field and the hybrid manufacturing process has demonstrated that it will screen out infant mortality, this failure was assumed to be a random component failure.

This clinical data indicates the PCD™ Device has performed safely and reliably in the indicated patient population.

M.2 Transvene™ Lead Performance

The Transvene™ Lead System consists of a Right Ventricular Lead, a Coronary Sinus/Superior Vena Cava lead, and a Subcutaneous Patch lead. There have been a total of 319 Right Ventricular leads (15 with the SP2100 and 304 with the Model 6884/6966), 336 Coronary Sinus/Superior Vena Cava leads (Model 6881/6963), and 292 Subcutaneous Patch leads (Models 6895/10317/6999) implanted with a cumulative implant duration of 1426.5 months. The reported incidence of right ventricular conductor coil fracture is 0.6% (2/319).

Based on the clinical data collected, the Transvene™ leads have performed safely and reliably.

N. Summary

The overall clinical experience with the PCD™ Transvene™ System indicates that the system performed according to design and specification. The reported clinical complications and patient deaths are appropriately addressed in the required labelling for the system and the patient selection criteria for implant of the device is appropriate.

The following conclusions can be drawn from this analysis of the data collected in this clinical study:

Patient Deaths

- The projected one year survival probabilities for Sudden Cardiac Death, Non-Sudden Cardiac Death, all Cardiac Deaths and Noncardiac Death were found to be 100.0%, 97.9%, 97.9%, and 99.3%, respectively.

  The incorporation of programmable VT/VF detection and therapies has improved the type of therapy available for the treatment of recurrent VT/VF while maintaining the positive impact of ICD therapy on survival from sudden cardiac death.

- The sudden cardiac death survival of 100.0% at one year is comparable to that of the AICD patient population 98.0%.

- There have been no deaths due to a PCD™ Device malfunction.

Complications/Observations

- Complications were reported in 14.2% of the patient population and observations were reported in 17.7% of the patient population.

- The incidence of complications was comparable to that of the market released AICD system in the categories of ineffective VT/VF therapy, pocket infection, and pocket erosion and was lower than the AICD in the category of inappropriate delivery of VT/VF therapy.

Patient Indications

- All of the patients entered into this clinical evaluation met at least one of the primary indications. Sudden cardiac death (SCD) was the primary indication in 37.9% of the patients, recurrent ventricular tachycardia (VT) was the primary indication in 45.7 % of the patients and SCD/VT was the primary indication in 16.4% of the patients.

- The number of patients (32.5%) receiving VT/VF therapy for spontaneous episodes of ventricular arrhythmias supports the conclusion that the patient selection criteria are appropriate and that the PCD™ Transvene™ System was implanted in patients who benefit from this therapy.

- The one year sudden cardiac death survival rates for the SCD patient group was 100.0%, for the VT patient group 100.% and the SCD/VT patient group 100.0%.

VT/VF Detection and Therapy Performance

- The PCD™ Transvene™ System properly detects and treats VT as is demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VT was 99.2%.

- The PCD™ Transvene™ System properly detects and treats VF as is demonstrated by the spontaneous episode data. The overall success rate for detection and treatment of spontaneous VF was 99.2%.

- There were no reported patient deaths due to the nondetection of a spontaneous VT or VF episode by the PCD™ Transvene™ System.

PCD™ Transvene™ System Performance

- The PCD™ Transvene™ System components (Model 7216A/7217B and Model 6884/6966, 6881/6963, 6895/6999 Transvene™ leads) have performed according to design and specification and are, therefore, considered safe and effective in the indicated patient population.

O. Clinical Experience Summary Conclusions

The PCD™ Transvene™ System is a tiered therapy device which combines features of bradycardia pacing support, antitachycardia pacing, low energy cardioversion as well as defibrillation therapy. The incorporation of these features has allowed the physician to titrate the ICD therapy to meet specific patient clinical needs, allowed fewer shocks to be delivered for recurrent ventricular tachycardia because of antitachycardia pacing features, allowed fewer cases of inappropriate therapy delivery due to programmable detection and allowed a sudden cardiac death survival rate identical to the Ventak-P Epicardial System.

The incorporation of a nonthoracotomy lead system has allowed for a safer and as effective implantation procedure. The elimination of the need for a thoracotomy has improved both perioperative and long term patient morbidity and mortality.

Medtronic asserts and the PCD™ Transvene™ investigators unanimously agree that the findings of the clinical study support the conclusion that the Medtronic Tachyarrhythmia Control System and the Transvene™ Cardioversion and Defibrillation Electrodes are safe and effective in the indicated patient population. In addition, the continued excellent performance of the PCD Transvene System warrants the expansion of the clinical study to additional investigative centers as well as the submission of this PreMarket Approval Application.

G. Summary of Safety and Effectiveness Conclusion

The efficacy and safety of implantable cardioverter defibrillator (ICD) therapy for recurrent ventricular tachycardia (VT) and ventricular fibrillation (VF) has been well established. The current market released device provides defibrillation therapy for VF or hemodynamically unstable VT, however this type of therapy may not be optimal for patients with stable, well tolerated VT that is amenable to antitachycardia pacing. The need to incorporate programmability and multiple detection and therapeutic options has lead to the development of a tiered therapy device, the Medtronic PCD System.

However, the current market released system requires a thoracotomy for implantation because of the need to insert epicardial patch leads. This exposes the patient to increased surgical risk an potentially limits the type of patient who may be considered for implant of the system. The need for a simpler and safer implantation technique is widely recognized. The incorporation of a nonthoracotomy lead system, such as the PCD™ Transvene™ System, would decrease the potential perioperative and long term mortality and morbidity associated with current epicardial system implantation approaches.

For the indicated patient population, the primary benefits from the PCD Transvene System center on the detection and termination of life threatening ventricular arrhythmias. The use of pacing therapies for the treatment of ventricular tachycardia reduces patient trauma associated with higher energy cardioversion pulses and extends the longevity of the PCD Device pulse generator. In addition, the PCD Transvene System offers the potential for decreased patient morbidity and mortality due to the elimination of the need for a thoracotomy.

Extensive laboratory and animal testing and human clinical trials of the PCD System were performed to demonstrate the safety and efficacy of the PCD Transvene System and its components in the indicated patient population.

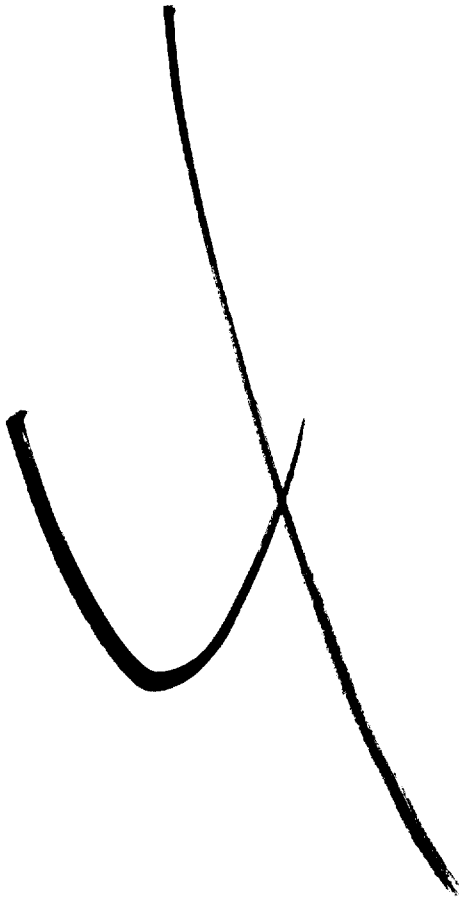
Nonclinical laboratory studies included testing at the component, hybrid and system level. All requirements were satisfied and the components and device-level testing performed according to specification. Results of animal testing demonstrated safe and reliable performance of the PCD Transvene System.

The indications for use of the PCD System include:

- Patients who have survived at least one episode of cardiac arrest due to ventricular arrhythmia not caused by an acute myocardial infarction; or
- Patients with recurrent sustained, ventricular tachycardia that remains inducible via programmed electrical stimuli or exercise, or occur spontaneously, despite the most effacious antiarrhythmic drug therapy that can be tolerated by the patient chronically.

The safety and efficacy of the PCD Transvene System in patients with VT and VF was evaluated in 317 patients with a mean implant duration of 4.5 months. The overall success rate in terminating spontaneous VT/VF episodes was 99.2%. The one year sudden cardiac death survival rate was 100% which was comparable to the reported sudden cardiac death rate of the PCD Epicardial System (98.8%) and Ventak-P Epicardial System (98.6%) patient populations. More importantly, the PCD Transvene System provided a significant improvement in overall one year survival (96.8%) when compared to the PCD Epicardial System (85.6%) and the Ventak-P Epicardial System (90.8%) patient populations. This improvement in overall survival was primarily due to the decreased perioperative mortality associated with the PCD Transvene System.

These data, in total, demonstrate the safe and effective performance of the PCD Transvene System in the indicated patient population. Therefore, the PCD Transvene System as reported in this PMA application is safe and effective for its intended use.



IV. Device Description and Manufacturing Section

A Device Description of all components of the Transvene/PCD System is provided in this section. This includes:

1. Description of the Model 6963, 6966 and 6999 Leads.

2. Description of the Model 7217B PCD Device.

3. Description of the Model 5355 ETCD Device.

First, however, a description of the Transvene Lead/Tachyarrhythmia Control System is presented.

Summary of System

A non-thoracotomy lead system is defined as one in which no electrode is placed in or on the pericardial sac. This system is designed to provide a minimally invasive alternative to an epicardial patch lead system for those patients who are candidates for an implantable tachyarrhythmia control device.

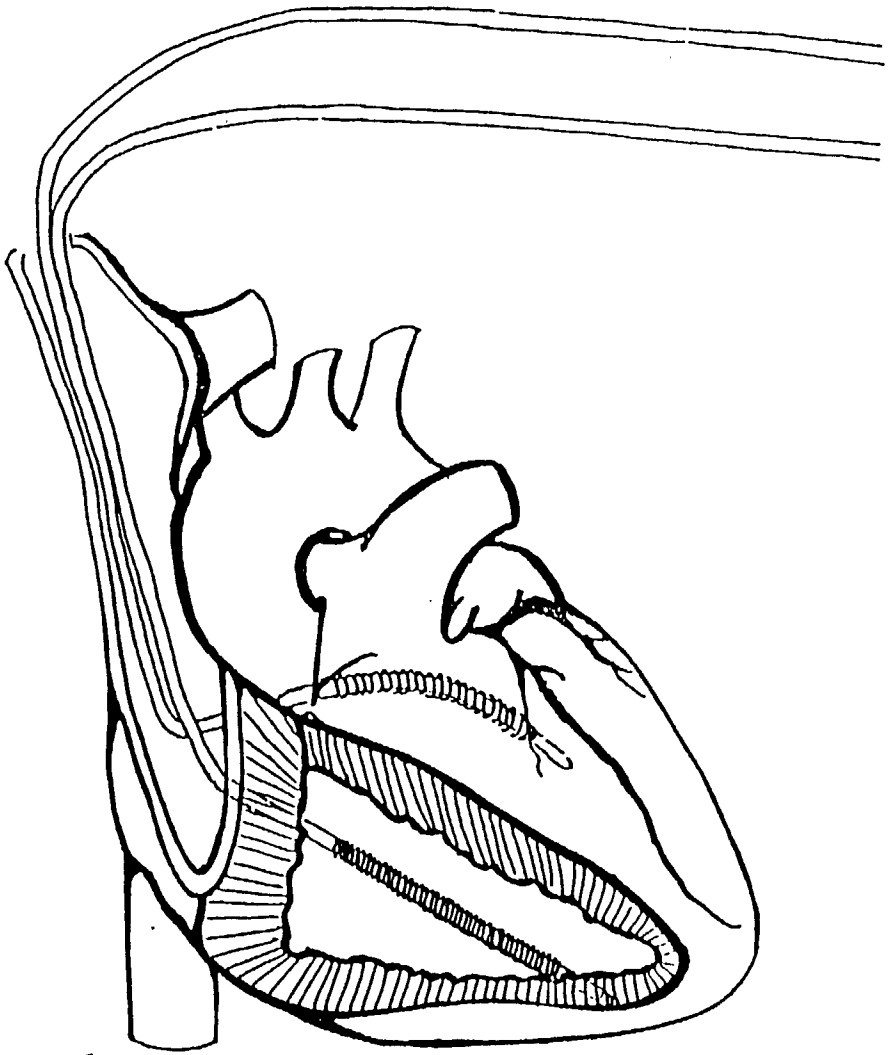
The non-thoracotomy lead system for the Model 7217B PCD device, called the Transvene lead system, consists of the following:

- Model 6963 Coronary Sinus/Superior Vena Cava Defibrillation Lead
- Model 6966 Right Ventricular Pacing, Sensing, and Defibrillation Lead
- Model 6999 Subcutaneous Patch Lead

Descriptions of these leads are contained in Section IV of this submission.

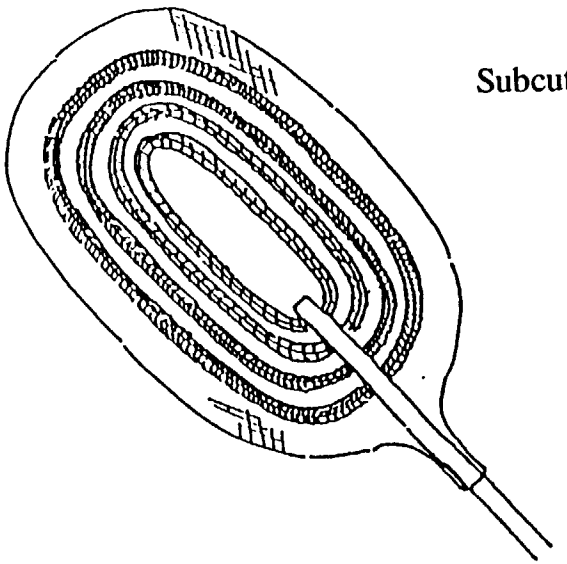
The figure on the following page is an illustration of the PCD Transvene lead system.

Non-Thoracotomy Lead System for PCD



Model 6963 Coronary Sinus or Superior Vena Cava

Model 6966 Right Ventricle



Subcutaneous Patch

Model 6999

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IV. Device Description

This section contains a general description of the Transvene lead system, which, in addition to the leads, includes the PCD and ETCD devices. This is then followed by more detailed device descriptions of the non-thoracotomy leads.

A. Description of the Transvene Lead/PCD System

The Medtronic Tachyarrhythmia Control System consists of two fundamental configurations: (1) the implantable configuration and (2) the external configuration. Both configurations use the Transvene lead system. See Figure IV-A-1.

The implantable configuration is composed of a Pacer-Cardioverter-Defibrillator (PCD) device, implantable leads, and a programmer. The PCD device is an implantable, multiprogrammable, automatic tachyarrhythmia control device.

The external configuration is composed of an External Tachyarrhythmia Control Device (ETCD), a patient cable, implantable leads, and a programmer. The ETCD is an externally-operated, multiprogrammable, tachyarrhythmia control device.

Intended Uses - Transvene Leads

Model 6963 Lead

The Medtronic Transvene Model 6963 Unipolar, Coronary Sinus or Superior Vena Cava, Tranvenous Lead features an electrode for the delivery of cardioversion and defibrillation therapies. It is intended for long-term use in the coronary sinus or superior vena cava and is designed to be used with an implantable tachyarrhythmia control device along with at least one other lead, such as the Model 6966 Tripolar, Right Ventricular, Transvenous Lead.

The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

Model 6966 Lead

The Medtronic Transvene Model 6966 Tripolar, Endocardial, Screw-In Lead is designed for pacing, sensing, and delivering cardioversion and defibrillation pulses in the ventricle. The lead has application where implantable tachyarrhythmia control systems are indicated.

The Model 6966 lead has a helical electrode made of platinum alloy that can be actively fixed in the endocardium. The helix can be extended or retracted by rotating the lead connector pin with a special fixation tool.

Active fixation leads are particularly beneficial for patients who have smooth or hypertrophic hearts where lead dislodgement may be potential a problem.

The three electrodes of this lead are the coil, ring, and helix:

> The defibrillating **coil electrode** is most proximal to the pulse generator and connects electrically to the connector pin of the unipolar leg of the bifurcation. This unipolar leg will not accept a stylet.
>
> The **ring electrode** is proximal to the helix and connects electrically to the connector ring of the bipolar leg of the bifurcation.
>
> The **helix tip electrode** is most distal to the pulse generator and provides active fixation in the endocardium. It can be extended or retracted by rotating the lead connector pin with a special fixation tool. The helix electrode connects electrically to the connector pin of the bipolar leg of the bifurcation. This bipolar leg is the only one that will accept a stylet.

The helix tip electrode and the ring electrode may be used for bipolar pacing and sensing; the coil electrode is intended to be used for delivery of cardioversion and defibrillation pulses.

The lead has application where implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

Model 6999 Lead

The Medtronic Model 6999 Unipolar, Subcutaneous, Oval, Patch Lead features an electrode for the delivery of cardioversion and defibrillation therapies. It is intended for long-term use and is designed to be used with an implantable tachyarrhytmia control device along with at least one complementary defibrillating electrode and a pacing/sensing lead; a third defibrillating electrode may also be used.

The lead has application for patients in whom implantable tachyarrhythmia cardioversion or defibrillation systems are indicated.

Intended Uses - PCD Device

The Model 7217B PCD device is intended for use in patients who are at high risk of sudden death due to ventricular tachyarrhythmia.

Current medical research indicates that such patients should:

- have survived at least one episode of a cardiac arrest, presumably due to a ventricular tachyarrhythmia as evidenced by resuscitation using a transthoracic defibrillator. The ventricular tachyarrhythmia should not be caused by an acute myocardial infarction; or

- in the absence of a prior cardiac arrest, have recurrent, sustained ventricular tachycardias that occur spontaneously or can be induced, despite the most efficacious antiarrhythmic drug therapy that can be tolerated chronically.

Extensive electrophysiologic evaluation and testing of the proposed pacing, cardioversion, or defibrillation therapies are recommended during and after the implantation of the Model 7217B PCD device. Before permanently programming the PCD device to the automatic detection and delivery of the VT and/or VF therapies, the patient should have demonstrated a satisfactory response to the proposed therapy.

Intended Uses - ETCD

The Model 5355 External Tachyarrhythmia Control Device is intended for use in conjunction with an antitachycardia/defibrillation lead system during diagnostic studies for implanting the Model 7217B PCD device.

Indications for use of the ETCD include

- Patients experiencing recurrent episodes of ventricular tachyarrhythmia,
- Patients who survived a cardiac arrest due to a ventricular tachyarrhythmia and are at risk for repeated episodes,
- Patients who are undergoing electrophysiologic studies and serial antitachycardia drug testing,
- Patients who have ventricular tachycardia and are being evaluated to assess the efficacy of pacing-level therapies on their arrhythmia, and
- Patients who are undergoing an assessment of the efficacy of antitachycardia pacing, cardioversion, or defibrillation therapies in anticipation of an implantable cardioverter-defibrillator.

Components of the System

A list of components used in the system is given below. It is separated into a listing of those components for which market approval is sought and those components that are now commercially available.

Seeking Approval:

Transvene Leads

Model 6963
Model 6966
Model 6999

Pacer-Cardioverter-Defibrillator (PCD) Device*
Model 7217B

External Tachyarrhythmia Control Device (ETCD)*

Model 5355 ETCD
Model 5418 Patient Cable
Model 5419 Patient Cable
Model 5414 Test Load
Model 5417 EGM Cable

Programmer Software Cartridge*

Model 9788 - Memory Module
for 7217B PCD Device and 5355 ETCD Devices

Lead Accessories*

Model 6701 Lead End Cap

Commercially Available:

Programmers
Model 9710 and accessories

Printers
Model 9751
Model 9712

* Indicates devices pending FDA approval, P900061

Components Used in the Implantable Configuration

The implantable configuration is composed of a PCD Device, lead system, and a 9710 Programmer with applicable software cartridge. The implantable device is a Model 7217B PCD Device. The PCD device requires an appropriate lead system consisting of up to three cardioversion/defibrillation electrodes. See Figure IV-A-2. The Transvene leads used with the Model 7217B PCD Device are the Models 6963, 6966, and 6999.

The Model 9710 Programmer is commercially available. Two printers are also commercially available. When higher printing speeds are desired, it is recommended that the programmer be used with the faster printer, the Model 9751. If slower printing speeds are acceptable, as may be the case in some follow-up situations, the Model 9710 Programmer can be used with the battery-powered Model 9712 Printer.

Components used in the External Configuration

The external tachyarrhythmia control system is composed of the Model 5355 ETCD, a Model 5418 Patient Cable, a Model 5419 cable, lead system, and a Model 9710 Programmer with applicable software cartridge, see Figures IV-A-3, 4. The ETCD uses replaceable batteries as its power source. The Model 5418 Patient Cable and Model 5419 Cable are designed to connect the Transvene leads to the ETCD. Like the impantable system, the ETCD uses the same Transvene leads (Models 6963, 6966, and 6999).

Purpose of the System

PCD System Configuration

The PCD Device is an implantable device designed to detect episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF), and upon detection, automatically deliver the appropriate therapy or a progression of therapies programmed by the physician for each patient. The available therapy types that can be programmed are overdrive pacing, cardioversion, and defibrillation. The PCD Device also has bradycardia pacing capability. The Transvene leads allow the PCD device to deliver these therapies to the heart.

ETCD System Configuration

The ETCD is an external tachyarrhythmia control device designed to deliver overdrive pacing, cardioversion, defibrillation, and bradycardia therapies in the same fashion as the PCD device. The ETCD can be programmed to automatically deliver overdrive pacing therapy upon detection of VT. When used as a component of a system that includes the appropriate Medtronic programmer and applicable software cartridge, the ETCD can deliver manually-initiated VT pacing, cardioversion, and defibrillation therapies. The ETCD allows the assessment of the Transvene lead system characteristics and aids in the assessment of lead system pacing and sensing characteristics.

Overview of System Features

General

The PCD device is designed to automatically detect episodes of VT or VF and, upon detection, deliver the appropriate programmed pacing, cardioversion, or defibrillation therapies. The device has two independently programmable detection and therapy procedures, one for VT and a second for VF.

When used as a component of a system that includes the appropriate Medtronic programmer and dedicated software, the ETCD is designed to deliver manually initiated cardioversion and defibrillation therapies. The ETCD is also designed to detect episodes of VT and VF. It can automatically deliver VT overdrive therapies (burst and ramp) upon detection of a VT.

VT Detection and Therapy

Both the PCD device and ETCD use a VT detection algorithm which can use up to three separately programmable criteria as it monitors the cardiac cycle length to identify the presence of a tachycardia. Upon detection, the devices deliver their first programmed VT therapy. If the VT episode persists and is again detected, up to three additional independently programmable VT therapies may be delivered to restore the patient's normal cardiac rhythm. This progression of four VT therapies can be tailored to each patient's need. For the PCD device the therapies may be selected from two methods of overdrive pacing (burst and ramp) and synchronized cardioversion.

For the ETCD the same overdrive pacing therapies can be automatically delivered, with cardioversion therapy being available as a manual therapy.

VF Detection and Therapy

The VF Detection algorithm monitors the cardiac cycle length to identify a VF episode. Upon detection, the PCD device provides a programmable high energy defibrillation pulse for VF therapy. Up to a maximum of four VF therapies may be delivered for ongoing detected VF episodes. Each defibrillation therapy consists of one (single pulse) or two (simultaneous or sequential) high voltage pulses designed to restore the normal cardiac rhythm.

For the ETCD, each cardioversion or defibrillation therapy, which must be initiated manually via the programmer, also consists of one high-voltage pulse or two (simultaneous or sequential) high-voltage pulses in the same fashion as the PCD devices.

Bradycardia Therapy

For both the ETCD and PCD devices, bradycardia pacing is delivered in the VVI mode. Asynchronous, (VOO), pacing is not available, and is avoided even with magnet application since this type of pacing has increased potential to initiate ventricular arrhythmias in patients receiving this system.

Lead Systems

The PCD Device and the ETCD perform pacing, sensing, cardioversion, and defibrillation through multiple electrodes in the lead system. Listed below are the electrodes and their function:

- The PACE/SENSE electrodes are incorporated in the right ventricular defibrillation lead. These electrodes function as the sensing circuit and deliver pacing pulses. The PACE/SENSE electrodes are used for sensing in conjunction with the SENSE2 electrode.

- The COMMON electrode is an electrode coil that serves as the cathode for cardioversion, defibrillation, and pacing.

- The PULSE2 electrode is an electrode coil that serves as the anode for cardioversion and defibrillation.

- The PULSE1 electrode is an optional electrode coil that serves as an additional anode for sequential and simultaneous cardioversion and defibrillation.

Cardioversion and defibrillation current pathways are between the PULSE2 and COMMON electrode coils and, if the additional lead is implanted, between the PULSE1 and COMMON electrode coils.

Other Capabilities

The physician may use the ETCD or the PCD devices to conduct noninvasive electrophysiologic studies (EPS) via the programmer with the appropriate software cartridge. The physician can also manually deliver various therapies via the programmer to manage an induced or spontaneous tachyarrhythmia.

The PCD device will provide the physician with information, via the Programmer, about its present programmed status and data on its operation accumulated between office visits. This information may be printed and retained in the patient's file.

The PCD Device and ETCD can also transmit an electrogram to the programmer. The electrogram is the electrical signal sensed on the leads.

A programmer-generated set of symbols, termed Marker Channel™, allows real-time visualization of sensing, pacing, detection, and therapy events occurring within the device.

In addition, the ETCD provides a display of measurements and other information related to delivered cardioversion and defibrillation pulses. With this information and other features, the ETCD can be used to assess the suitability of the lead system and its placement for individual patients.

PCD Battery Longevity Expectations

The longevity of the Model 7217B PCD Device depends upon several factors, including programmed bradycardia pacing parameters, the percentage of paced to sensed events, the pacing load, and on the frequency of high voltage capacitor charging. The longevity projections found in Table IV-A-1 apply under the following conditions:

- 65 ppm pacing rate,
- 5.4 V pacing pulse amplitude,
- 0.49 ms pacing pulse width, and
- 500 ohm pacing lead.

Projected Longevity[1]
Table IV-A-1

Pacing/Sensing	34 Joule Charging Frequency	Average Longevity Model 7217B
100% Sensing	Quarterly	5.0 years
15% Pacing	Monthly	4.2 years
100% Pacing	Monthly	3.4 years

The longevity of the device decreases with the following:

- An increase in pacing rate,
- An increase in pacing amplitude,
- A decrease in pacing impedance,
- An increase in pacing pulse width,
- An increase in the percentage of bradycardia paced to sensed events, or
- An increase in the charging frequency.

Each 34 Joule charging cycle will typically decrease the longevity of the device by approximately four to six days.

---

1 These preliminary longevity projections are based upon accelerated battery data and device modeling. With the stated condition, 100% pacing and monthly 34 Joule charging cycles, the minimum longevity of the device will be 2.5 years (7217B). Average refers to the projected mean longevity of the modeled run of PCD devices at the stated conditions. Minimum longevity means that virtually all (i.e., 99.9%) of all modeled production run of PCD devices will attain the value given.

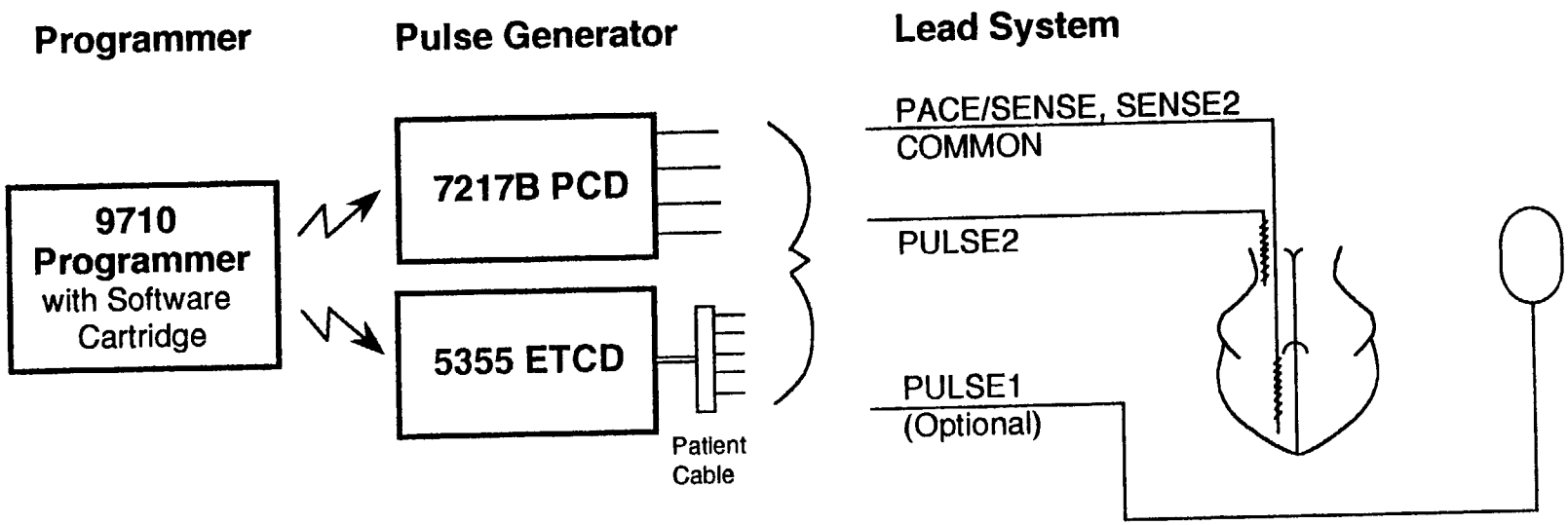

Figure IV-A-1. Tachyarrhythmia Control System Block Diagram

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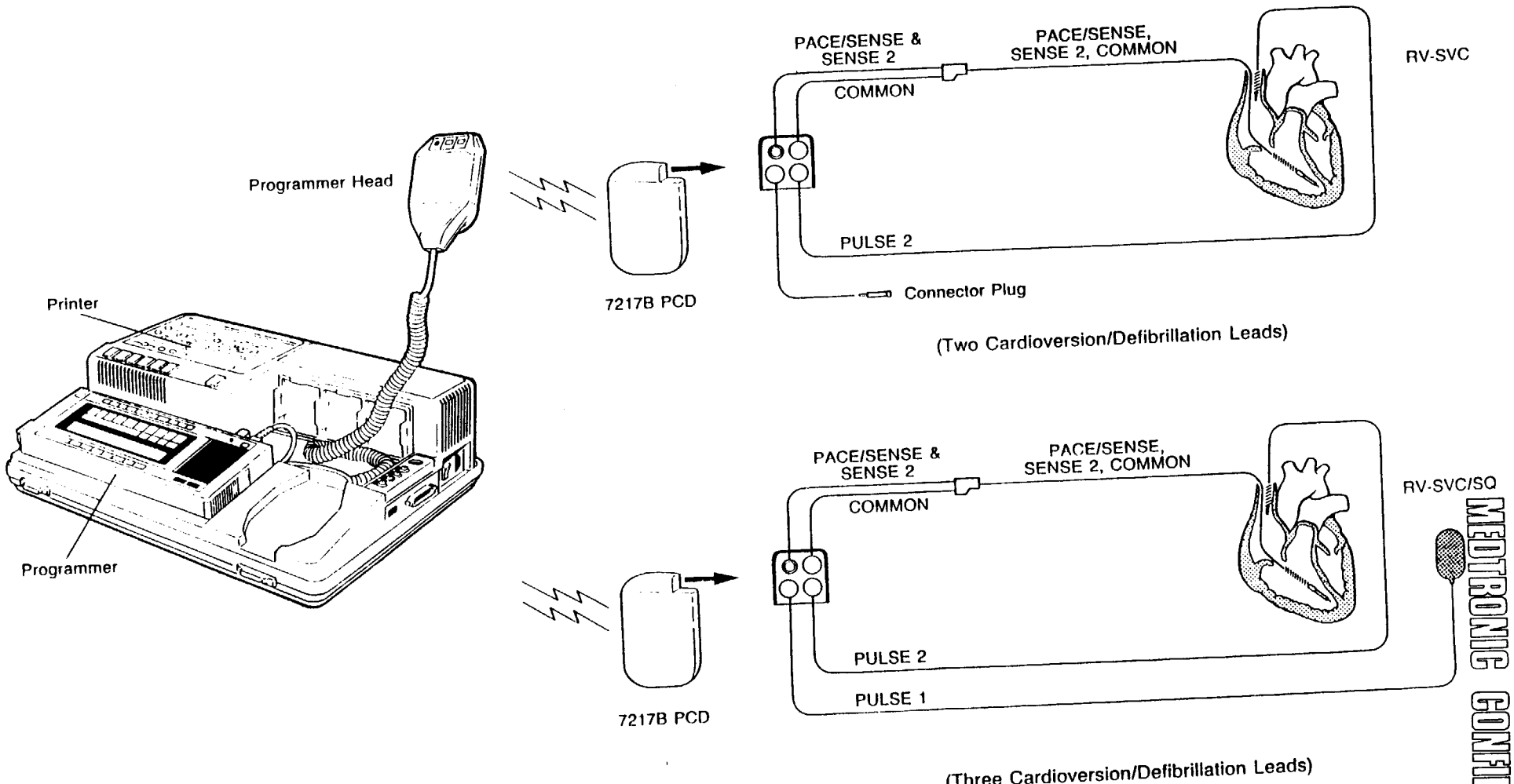
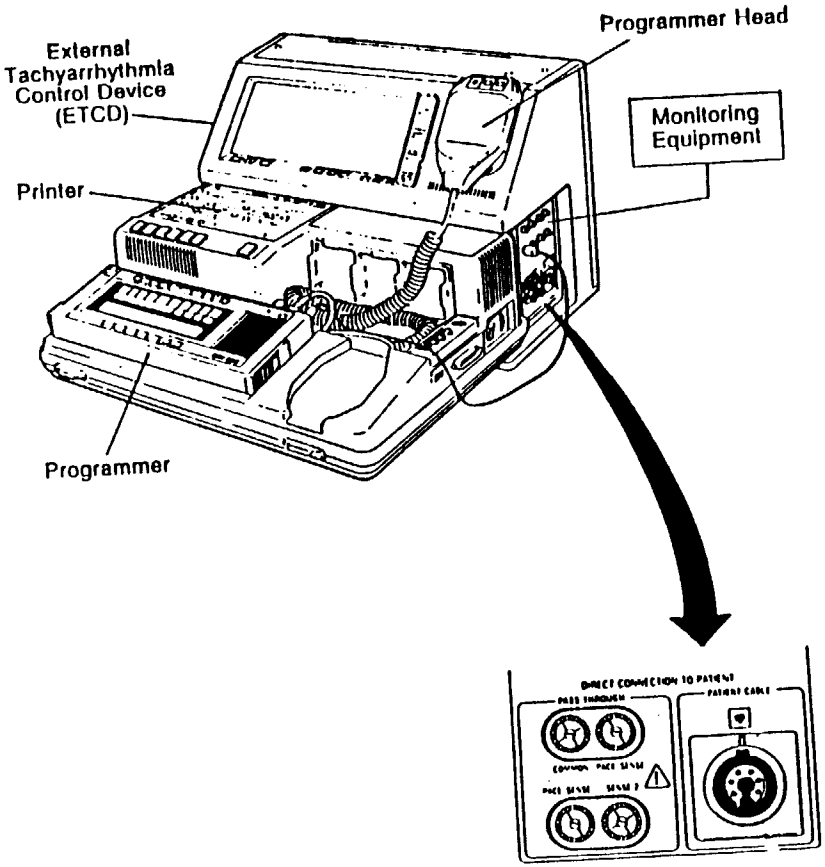
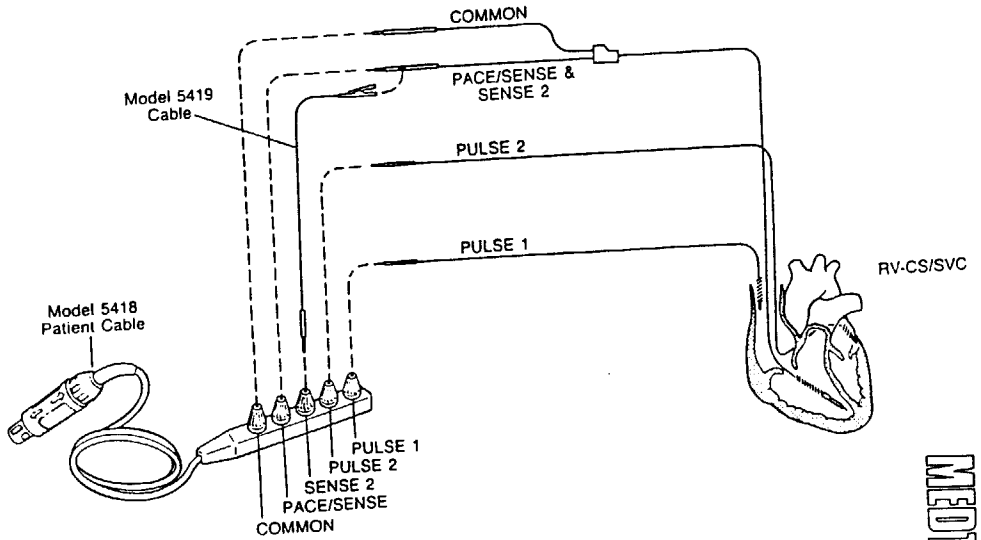


Figure IV-A-2

MEDTRONIC CONFIDENTIAL





Connections to Model 5418 Patient Cable for
Typical Simultaneous or Sequential Pathway (RV-CS/SVC).

Figure IV-A-3

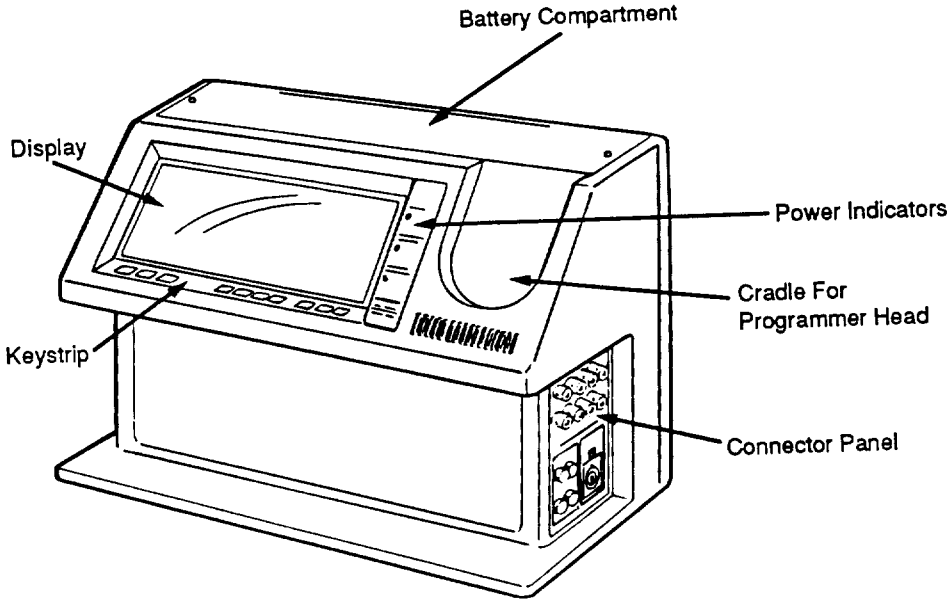


Figure IV-A-4. Model 5355 External Tachyarrhythmia Control Device

DESCR.

1. Description: Model 6963 Coronary Sinus/Superior Vena Cava, Model 6966 Right Ventricular and Model 6999 Subcutaneous Patch Leads

Illustrations of these leads are provided on the pages following this discussion.

The Medtronic Tachyarrhythmia Control System uses a tripolar, screw-in, right ventricular lead for (RV) pacing, sensing, cardioversion and defibrillation; a unipolar, coronary sinus/superior vena cava lead (CS/SVC); and a unipolar, subcutaneous oval patch electrode (SQ). The available models of the system are as follows:

- Model 6963 CS/SVC Lead
- Model 6966 RV Lead
- Model 6999 SQ Lead

The Model 6963, 6966 and 6999 leads are intended to be used with the Model 7217B PCD Device. The leads have a 6.5 mm connector intended for direct insertion into a 6.5 mm port of the 7217B PCD Device.

The Model 6963 lead is intended for use in the coronary sinus or superior vena cava. The lead features a platinum alloy electrode coil which provides the necessary surface area for cardioversion and defibrillation. Silicone insulation surrounds a low-resistance metal-alloy conductor coil.

The Model 6966 lead is designed for pacing, sensing, and delivering cardioversion and defibrillation pulses in the right ventricle. The lead features three metal-alloy conductors in (b)(4) surrounded by polyurethane insulation. The lead has a platinum alloy electrode coil which provides the necessary surface area for cardioversion and defibrillation. This electrode is most proximal (closest) to the pulse generator and connects to the unipolar (6.5 mm) leg of the bifurcated connector. This leg does not accept a stylet. The lead has a helical electrode made of platinum alloy that can be actively fixed in the endocardium. The helix can be extended or retracted by rotating the lead connector pin with a small tool. The helix tip electrode is most distal to the pulse generator and connects to the pin of the bipolar (3.2 mm) leg of the bifurcated connector. The ring electrode is made of a platinum alloy. It is proximal to the helix and connects to the ring of the bipolar (3.2 mm) leg of the bifurcated connector. Bipolar sensing occurs between the helix tip and the ring electrodes. Bipolar pacing occurs between the helix tip and the defibrillation coil electrode.

The Model 6999 lead is intended for use subcutaneously, submuscularly, or directly on the periosteum of the ribs. The lead features platinum alloy electrode coils and a low-resistance metal-alloy conductor surrounded by silicone insulation. Four helical coils are partially embedded into the silicone patch and provide the necessary surface area for cardioversion and defibrillation. A (b)(4) is molded into the patch and provides support for sutures. There are three nodes in the center and two nodes at the junction of the lead body and patch electrode of one side of the patch electrode. These nodes are intended to designate the insulated side of the patch electrode.

The following section describes the functional components, device properties, and principles of operation for the Model 6963, 6966 and 6999 leads.

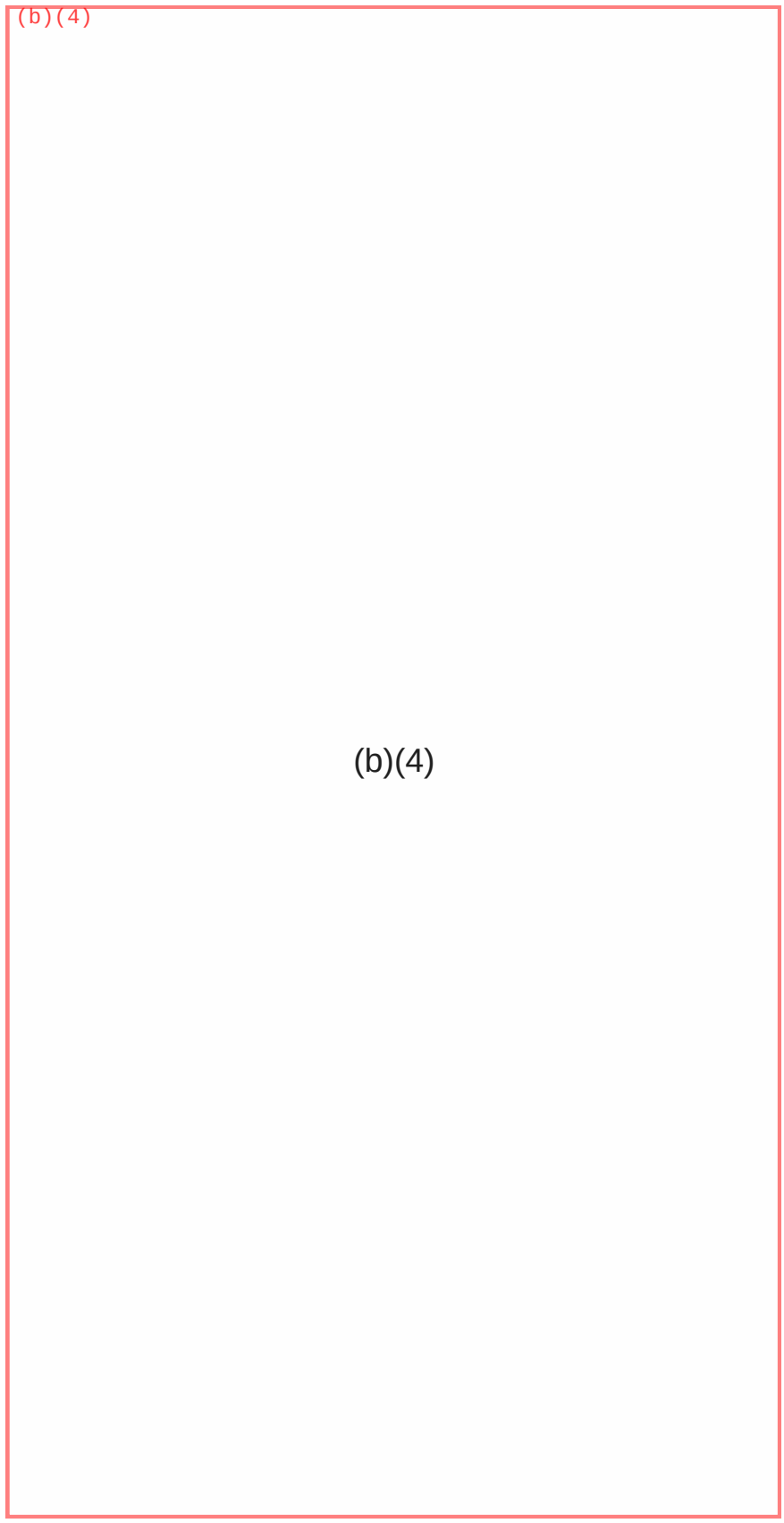
Illustrations of the Model 6963, 6966 and 6999 leads are provided on the following pages.

(b)(4)

(b)(4)

MODEL 6963 CS/SVC LEAD

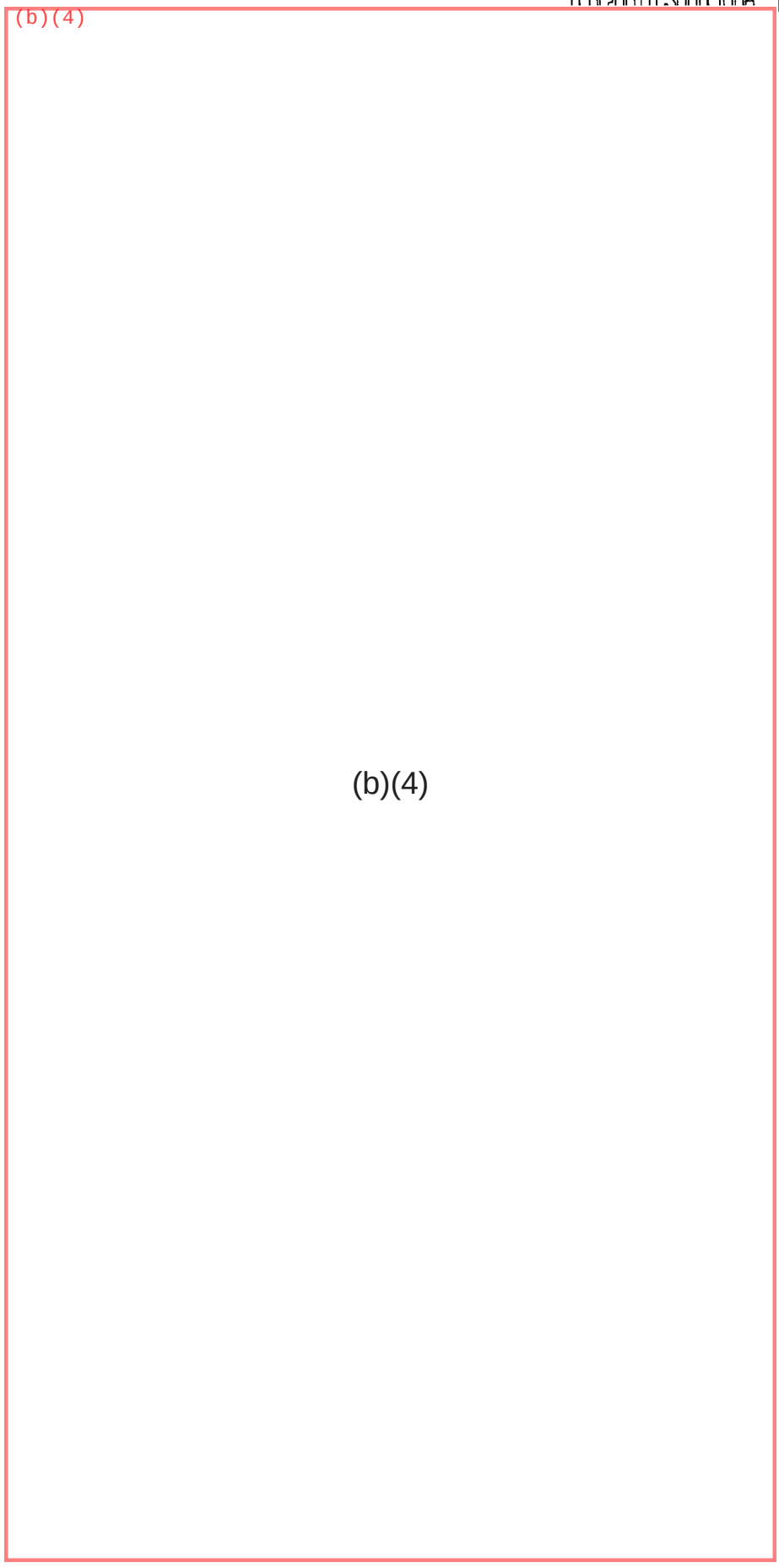
(b)(4)



MODEL 6966 RIGHT VENTRICULAR LEAD
DISTAL END

2/27

(b)(4)



MODEL 6966 RIGHT VENTRICULAR LEAD
PROXIMAL END

(b)(4)

(b)(4)

MODEL 6999 SUBCUTANEOUS
PATCH LEAD

a. Functional Components

1) Platinum Alloy Electrode Coil

The Model 6963 coronary sinus/superior vena cava lead and the Model 6966 right ventricular lead each feature a platinum alloy coil electrode that delivers cardioversion and defibrillation pulses to the heart. The Model 6963 lead uses silicone adhesive and the Model 6966 lead employs polyurethane tubing to help prevent tissue in-growth and aid in chronic lead removal.

The conductive surface of the Model 6999 subcutaneous patch electrode consists of four platinum helical coils partially embedded in molded silicone rubber. These coils serve as the electrodes that deliver cardioversion and defibrillation pulses to the heart. Inside the helical coils is silicone rubber to help prevent tissue in-growth and aid in chronic lead removal.

2) Low Resistance Metal Alloy Conductor Coil

This conductor coil consists of (b)(4) alloy that provides a low resistance pathway for delivery of cardioversion and defibrillation pulses from the tachyarrhythmia control device to the platinum alloy electrode coils. The (b)(4) was selected for use due to its proven long term reliability when used in implanted bradycardia lead systems. The use of (b)(4) coil provides the low resistance needed for the delivery of high voltage pulses. The coil used on the Model 6966 is (b)(4) The coils used on the Model 6963 and 6999 are not sputter coated.

3) Metal Alloy Conductor Coil (applicable only to the Model 6966 Lead)

The Model 6966 inner and middle conductor coils consist of several fine wires. The wires are (b)(4) in diameter for the inner coil and (b)(4) in diameter for the middle coil. The wires are made of (b)(4) alloy and (b)(4)

4) Helical Electrode (Model 6966 only)

The Model 6966 (b)(4) distal, helical electrode is extended into and retracted from the myocardium through a self-sealing electrode head by turning the connector terminal pin with a

140

pinch-on torquing tool. The stimulating surface area of the helical electrode is (b)(4) (nominal).

5) Ring Electrode (Model 6966 only)

The (b)(4) ring electrode for bipolar pacing and sensing is positioned just proximal to the distal, helical tip of the lead. The (nominal) surface area of the ring electrode is (b)(4)

6) Insulation

- Model 6963 and 6999 Leads

  These leads are comprised of (b)(4) insulation. This material has a long history (since 1962) of use on Medtronic pacing leads. Insulation wall thickness for both the 6963 and 6999 is (b)(4)

- Model 6966 Lead

  This lead is comprised of (b)(4) (b)(4)
  Insulation wall thicknesses are:

  inner (b)(4)
  middle (b)(4)
  outer

7) Anchoring Sleeve

There is an anchoring sleeve positioned on the lead body of the Model 6963 and 6966 leads. It is intended to be used for fixation of the lead body to soft tissues near the site of insertion of the lead into the vein at the time of the implant. It is designed to protect the lead from undue strains and stresses at the point of fixation.

8) (b)(4) Embedded into Silicone Rubber

(b)(4) is embedded into each subcutaneous patch and provides support when suturing the lead to the subcutaneous muscle.

9) Stylets

Stylets are (b)(4) which stiffen the lead and/or temporarily alter its shape during implant. This is accomplished through a controlled stiffness of the distal tip, allowing it to bend with the application of excessive force. Stylets are also designed to help minimize damage to the coil during insertion and removal. The Models 6963 and 6966 use stylets, the Model 6999 does not.

10) Connector Assembly

The Model 6963 and 6999 leads feature a (b)(4) terminal assembly consisting of a (b)(4) connector pin and (b)(4) rubber sleeve. The distal part of the sleeve provides a strain relief area.

The Model 6966 lead features a (b)(4) terminal assembly identical to that used on the 6963 and 6999 as described above. In addition, the lead connector is bifurcated and has an additional (b)(4) in-line, bipolar terminal assembly consisting of a (b)(4) connector pin, a cylindrical (b)(4) (ring) terminal just distal to the pin, and a (b)(4) rubber sleeve. This distal part of the sleeve provides a strain relief area.

b. Device Properties

The Model 6963, 6966 and 6999 non-thoracotomy leads are designed for sensing, pacing, cardioversion and defibrillation. These leads have application where implantable tachyarrhythmia control devices are indicated. Reference the technical manuals for the Model 6963, 6966 and 6999 leads for specific device features.

c. Principles of Operation

The PCD Transvene System uses leads which do not require open-chest surgery to implant. Multiple configurations involving either two or three different leads may be used to deliver cardioversion and defibrillation pulses. These configurations are comprised of a tripolar, right ventricular (RV) lead (Model 6966), and either a coronary sinus (CS) lead (Model 6963) or a subcutaneous (SQ) lead (Model 6999), or all three of these leads. The Model 6963 lead can be placed in either the coronary sinus/great cardiac vein or the superior vena cava (SVC).

In these systems, the helical tip and ring of the RV lead is used for sensing, thus providing standard, bipolar sensing. The tip electrode is termed PACE/SENSE and the ring electrode is termed SENSE 2. Bradycardia pacing takes place between the tip (PACE/SENSE) and the COMMON defibrillation electrode.

A system using two leads delivers cardioversion and defibrillation pulses between two coils (one on each lead). A system using three leads delivers cardioversion and defibrillation pulses either simultaneously or sequentially from the anode electrodes (PULSE 1 and PULSE 2) to the COMMON defibrillation electrode.

To detect VT/VF, the PCD device monitors the cardiac cycle length for fulfillment of the programmed VT/VF detection criteria. When the programmed criteria are fulfilled, the PCD device detects the VT or VF episode and delivers the first programmed therapy. If this therapy is ineffective and the VT/VF is again detected, the next programmed therapy is delivered. This progression continues until the PCD confirms episode termination or delivers all programmed therapies.

The performance of the Models 6966, 6963, and 6999 are evaluated at the following times:

1) At implant by the evaluation of the pacing and sensing thresholds and defibrillation efficacy when treating VT/VF

2) Chronically by evaluation of stability of chronic defibrillation efficacy in induced episodes of VT/VF and successful termination of spontaneous episodes of VT/VF.

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2. Description: Related Transvene Lead System Components

- Model 7217B PCD Device
- Model 5355 ETCD Device
- Model 9788 MemoryModule

These device descriptions are provided in Appendix 1, Features of Tachyarrhythmia Control System (Volume 7).

IV. Device Description and Manufacturing Section

B. A Manufacturing Description of the following devices is provided in this section:

- Lead Models 6963, 6966 and 6999
- Model 7217B PCD Device
- Model 5355 ETCD Device

1. Introduction

Manufacturing information for the three lead models comprising the Transvene Lead system is provided in this section.

(b)(4)

(b)(4)

6955

- Manufacture of the Model 6966 RV Lead

(b)(4)

(b)(4)

I. PMA Cover Letter

Medtronic

Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576
Telephone: (612) 574-4000
Cable: Medtronic Telex: 29-0598
Telecopy: (612) 574-4879

107

March 31, 1992

Office of Device Evaluation
PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

Re: Premarket Approval Application (PMA) for the Medtronic® Multiprogrammable Tachyarrhythmia Control System with Non-thoracotomy Cardioversion and Defibrillation Electrodes, i.e., the PCD™ Transvene System, Lead Models 6963, 6966 and 6999.

This submission is a PMA application for the Medtronic Transvene Lead System used in conjunction with the Model 7217B pacer-cardioverter-defibrillator (PCD), Model 5355 external tachyarrhythmia control device (ETCD) and Model 9788 MemoryMod Software Module.

The PCD and ETCD devices as used with an epicardial lead system were recommended for approval by the FDA Advisory Panel on February 3, 1992 (P900061). The purpose of this PMA application is to obtain approval for the use of the non-thoracotomy lead system for use with the Medtronic PCD and ETCD. The terms non-thoracotomy leads (NTL), transvenous leads and Transvene Lead System are synonymous and may be used interchangeably throughout this application.

The Transvene System, in conjunction with the PCD device, is intended to treat patients at risk of sudden cardiac death due to ventricular arrhythmias. Like the epicardial electrodes/PCD System, the primary benefits from the use of the Transvene/PCD System center on the detection and termination of these life-threatening ventricular arrhythmias. The incorporation of a non-thoracotomy lead system allows for a safer and effective implantation procedure, and improving both perioperative and long-term patient morbidity and mortality.

The Transvene/PCD System clinical study (IDE G870102) includes 319 Transvene lead implants with a mean implant duration of 4.5 months and a total of 1426 device months experience. There are 116 patients with lead system implant duration equal to or greater than six months. The data included in this submission is all data that was received by Medtronic and entered onto the clinical database as of November 27, 1991. The results from the clinical study are provided in Volume 5 of this application.

Market approval is not being sought for use of the Transvene/PCD System with other manufacturers' implantable-cardioverter-defibrillators, nor is it sought for use of the PCD device with other manufacturers' transvenous defibrillation lead systems.

Two manufacturing facilities are to be used in the assembly, sterilization and packaging of the Transvene leads. These are:

1. Medtronic, Inc.
   Rice Creek Facility
   7000 Central Avenue N.E.
   Minneapolis, MN 55432
   Tel: 612-574-4000
   Establishment Registration Number: 2182208
   Is presently prepared for inspection.
   Most recent FDA inspection: January 21-February 8, 1992.

2. Medtronic, B.V.
   Wenckebachstraat 10
   6466 NC Kerkrade West
   The Netherlands
   Tel: 31-45-43-85-85
   Is presently prepared for inspection.
   Most recent FDA inspection: January 6-9, 1992.

The existence of this PMA application and the data and other information it contains are confidential, and the protection afforded to such confidential information by 18 USC 1905 and other applicable laws is hereby claimed.

4

In accordance with 21 CFR 814.42(a), the FDA has 45 days from the date of receipt to notify Medtronic if this application is sufficiently complete for a substantive review and acceptable for filing.

Six copies of this application are enclosed. Should additional information be required by the Agency, please contact the undersigned.

Sincerely,

MEDTRONIC, INC.

Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
(612) 574-4688
(612) 574-6424 FAX

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B. Package Labeling

III. Device Description: Model 6966 Right Ventricular Lead

Illustrations of this lead are provided on the pages following this discussion.

The Medtronic Tachyarrhythmia Control System uses a tripolar, screw-in, right ventricular lead for (RV) pacing, sensing, cardioversion and defibrillation; a unipolar, coronary sinus/superior vena cava lead (CS/SVC); and a unipolar, subcutaneous oval patch electrode (SQ). The available models of the system are as follows:

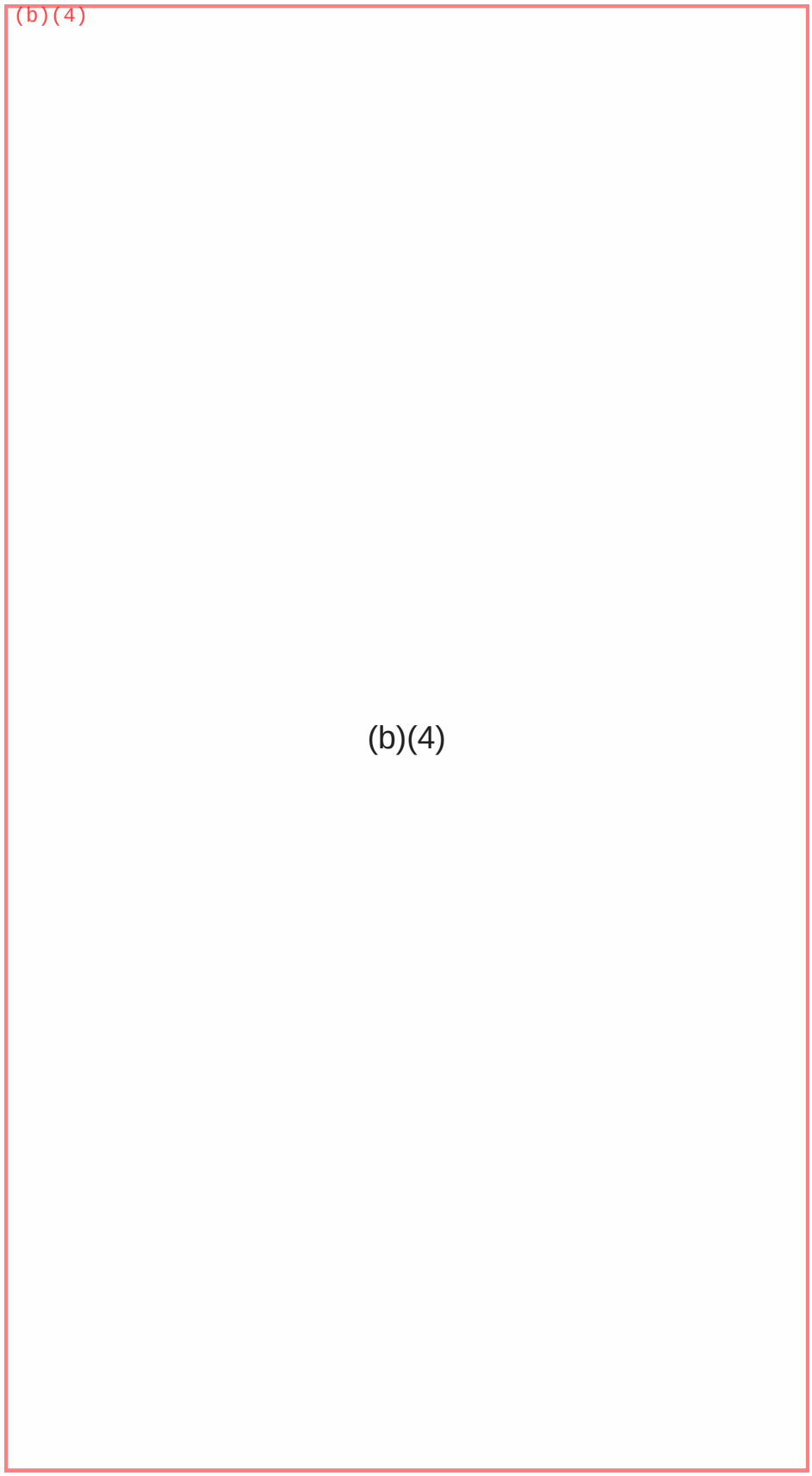
- Model 6963 CS/SVC Lead
- Model 6966 RV Lead
- Model 6999 SQ Lead

The Model 6966 lead is intended to be used with the Model 7217B PCD Device.

The Model 6966 lead is designed for pacing, sensing, and delivering cardioversion and defibrillation pulses in the right ventricle. The lead features three metal-alloy conductors in (b)(4) (b)(4) surrounded by polyurethane insulation. The lead has a platinum alloy electrode coil which provides the necessary surface area for cardioversion and defibrillation. This electrode is most proximal (closest) to the pulse generator and connects to the unipolar (6.5 mm) leg of the bifurcated connector. This leg does not accept a stylet. The lead has a helical electrode made of platinum alloy that can be actively fixed in the endocardium. The helix can be extended or retracted by rotating the lead connector pin with a small tool. The helix tip electrode is most distal to the pulse generator and connects to the pin of the bipolar (3.2 mm) leg of the bifurcated connector. The ring electrode is made of a platinum alloy. It is proximal to the helix and connects to the ring of the bipolar (3.2 mm) leg of the bifurcated connector. Bipolar sensing occurs between the helix tip and the ring electrodes. Bipolar pacing occurs between the helix tip and the defibrillation coil electrode.

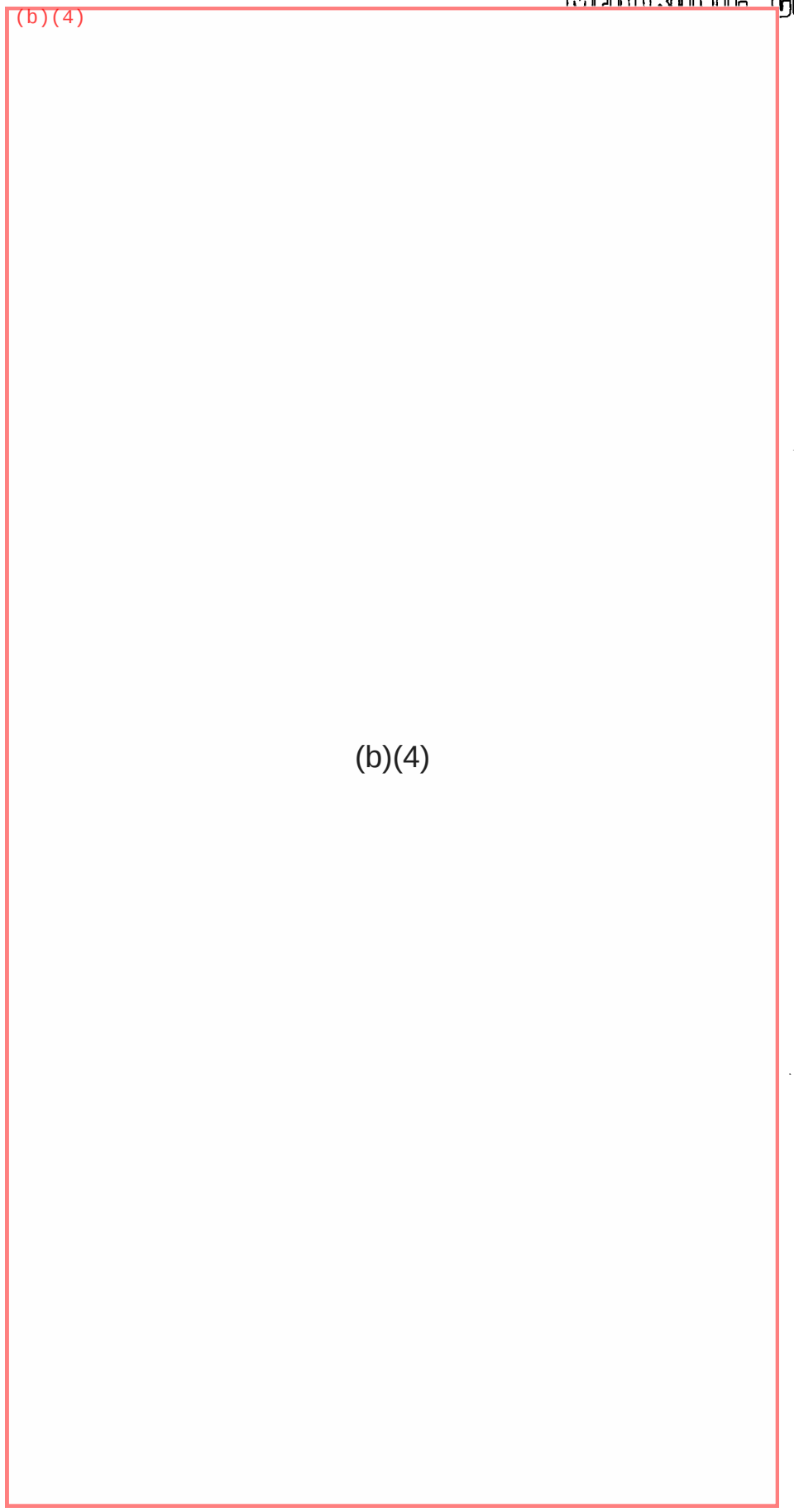
The following section describes the functional components, device properties, and principles of operation for the Model 6966 lead.

(b)(4)



MODEL 6966 RIGHT VENTRICULAR LEAD
DISTAL END

(b)(4)



MODEL 6966 RIGHT VENTRICULAR LEAD
PROXIMAL END

a. Functional Components

1) Platinum Alloy Electrode Coil

The Model 6966 right ventricular lead features a platinum alloy coil electrode that delivers cardioversion and defibrillation pulses to the heart. The Model 6966 lead employs polyurethane tubing to help prevent tissue in-growth and aid in chronic lead removal.

2) Low Resistance Metal Alloy Conductor Coil

This conductor coil consists of (b)(4) alloy that provides a low resistance pathway for delivery of cardioversion and defibrillation pulses from the tachyarrhythmia control device to the platinum alloy electrode coils. The (b)(4) was selected for use due to its proven long term reliability when used in implanted bradycardia lead systems. The use of (b)(4) coil provides the low resistance needed for the delivery of high voltage pulses. The coil used on the Model 6966 is (b)(4)

3) Metal Alloy Conductor Coil

The Model 6966 inner and middle conductor coils consist of several fine wires. The wires are (b)(4) in diameter for the inner coil and (b)(4) in diameter for the middle coil. The wires are made of (b)(4) alloy and (b)(4)

4) Helical Electrode

The Model 6966 (b)(4) distal, helical electrode is extended into and retracted from the myocardium through a self-sealing electrode head by turning the connector terminal pin with a pinch-on torquing tool. The stimulating surface area of the helical electrode is (b)(4) (nominal).

5) Ring Electrode

The (b)(4) ring electrode for bipolar pacing and sensing is positioned just proximal to the distal, helical tip of the lead. The (nominal) surface area of the ring electrode is (b)(4)

6) Insulation

The Model 6966 lead is comprised of (b)(4) and (b)(4). Insulation wall thicknesses are:

inner (b)(4)
middle
outer

7) Anchoring Sleeve

There is an anchoring sleeve positioned on the lead body of the Model 6966 lead. It is intended to be used for fixation of the lead body to soft tissues near the site of insertion of the lead into the vein at the time of the implant. It is designed to protect the lead from undue strains and stresses at the point of fixation.

8) Stylets

Stylets are (b)(4) which stiffen the lead and/or temporarily alter its shape during implant. This is accomplished through a controlled stiffness of the distal tip, allowing it to bend with the application of excessive force. Stylets are also designed to help minimize damage to the coil during insertion and removal.

9) Connector Assembly

The Model 6966 lead features a (b)(4) terminal assembly consisting of a (b)(4) connector pin and (b)(4) rubber sleeve. In addition, the lead connector is bifurcated and has an additional (b)(4), bipolar terminal assembly consisting of a (b)(4) connector pin, a cylindrical, (b)(4) (ring) terminal just distal to the pin, and a (b)(4) rubber sleeve. This distal part of the sleeve provides a strain relief area.

b. Device Properties

The Model 6966 non-thoracotomy lead is designed for sensing, pacing, cardioversion and defibrillation. This lead has application where implantable tachyarrhythmia control devices are indicated. Reference the technical manual for the Model 6966 lead for specific device features.

c. Principles of Operation

The PCD Transvene System uses leads which do not require open-chest surgery to implant. Multiple configurations involving either two or three different leads may be used to deliver cardioversion and defibrillation pulses. These configurations are comprised of a tripolar, right ventricular (RV) lead (Model 6966), and either a coronary sinus (CS) lead (Model 6963) or a subcutaneous (SQ) lead (Model 6999), or all three of these leads. The Model 6963 lead can be placed in either the coronary sinus/great cardiac vein or the superior vena cava (SVC).

In these systems, the helical tip and ring of the RV lead is used for sensing, thus providing standard, bipolar sensing. The tip electrode is termed PACE/SENSE and the ring electrode is termed SENSE 2. Bradycardia pacing takes place between the tip (PACE/SENSE) and the COMMON defibrillation electrode.

A system using two leads delivers cardioversion and defibrillation pulses between two coils (one on each lead). A system using three leads delivers cardioversion and defibrillation pulses either simultaneously or sequentially from the anode electrodes (PULSE 1 and PULSE 2) to the COMMON defibrillation electrode.

To detect VT/VF, the PCD device monitors the cardiac cycle length for fulfillment of the programmed VT/VF detection criteria. When the programmed criteria are fulfilled, the PCD device detects the VT or VF episode and delivers the first programmed therapy. If this therapy is ineffective and the VT/VF is again detected, the next programmed therapy is delivered. This progression continues until the PCD confirms episode termination or delivers all programmed therapies.

The performance of the Models 6966, 6963, and 6999 are evaluated at the following times:

1) At implant by the evaluation of the pacing and sensing thresholds and defibrillation efficacy when treating VT/VF

2) Chronically by evaluation of stability of chronic defibrillation efficacy in induced episodes of VT/VF and successful termination of spontaneous episodes of VT/VF.

Manufacturing Description: Model 6966 RV Lead, Rice Creek

The following Manufacturing Description has been prepared in conformance with the "Guidance for Preparation of PMA Manufacturing Information" made available by FDA August 21, 1991. Copies of the device description and labeling from other parts of the PMA have been included in the first part of this volume, as indicated in the cover letter.

This section contains a complete description of the methods used in, and the facilities and controls used for, the manufacture, processing, packaging, storage and distribution of the Model 6966 RV Lead. Process qualification testing and results are included in Section F.3. As requested, a summary describing how applicable GMP requirements are met has been provided for each area identified. In some cases copies of actual procedures are also provided.

The Model 6966 RV Lead meets the definition of a critical device; implantable leads are currently on the Critical Device List. We have thus addressed specifically additional controls that are in place to meet the critical device requirements.

A. Organization and Personnel

(1) Company policy and objectives for controlling quality and how they are made known to employees.

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(b)(4)

(b)(4)

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- (b)(4)
- (b)(4)
- (b)(4)
- (b)(4)

- (b)(4)
- (b)(4)

(b)(4)

(b)(4)

1. Production records review.

(b)(4)

(b)(4)

-

- (b)(4)

(b)(4)

2. Approval/rejection of components, materials, packaging, labeling, subassemblies and devices.

(b)(4)

(b)(4)

- (b)(4)

(b)(4)

3. Identifying and resolving quality assurance problems.

(b)(4)

(b)(4)

- (b)(4)

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- (b)(4)
- (b)(4)

(b)(4)

(b)(4)

4. Quality Assurance checks.

(b)(4)

(b)(4)

A. Organization and Personnel

(2) Organizational structure, including the quality system and the responsibilities and channels for identification, documentation and resolution of product quality problems, including responsibilities for assuring that corrective action is implemented.

(b)(4)

(b)(4)

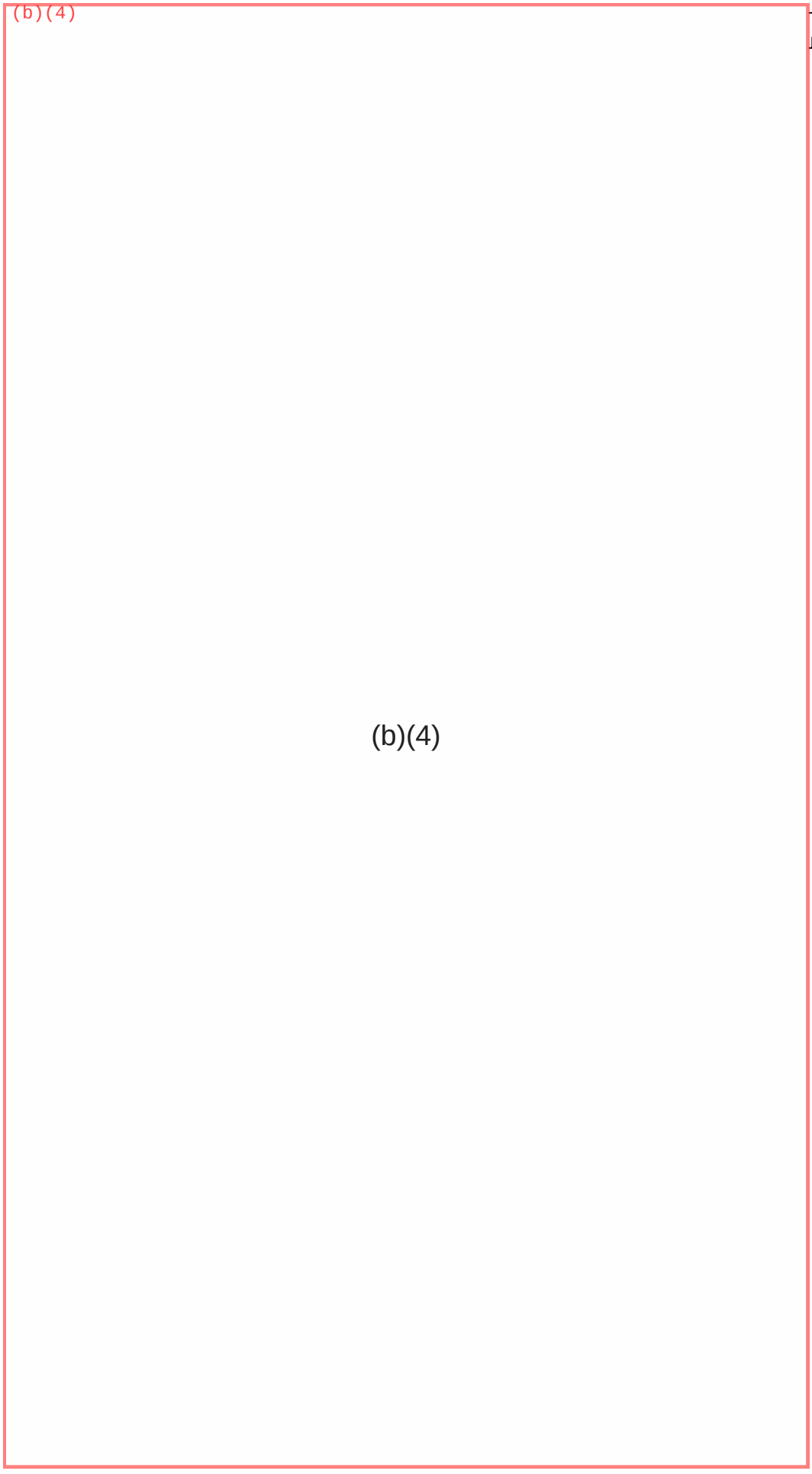


FIGURE 1. BUSINESS ORGANIZATION

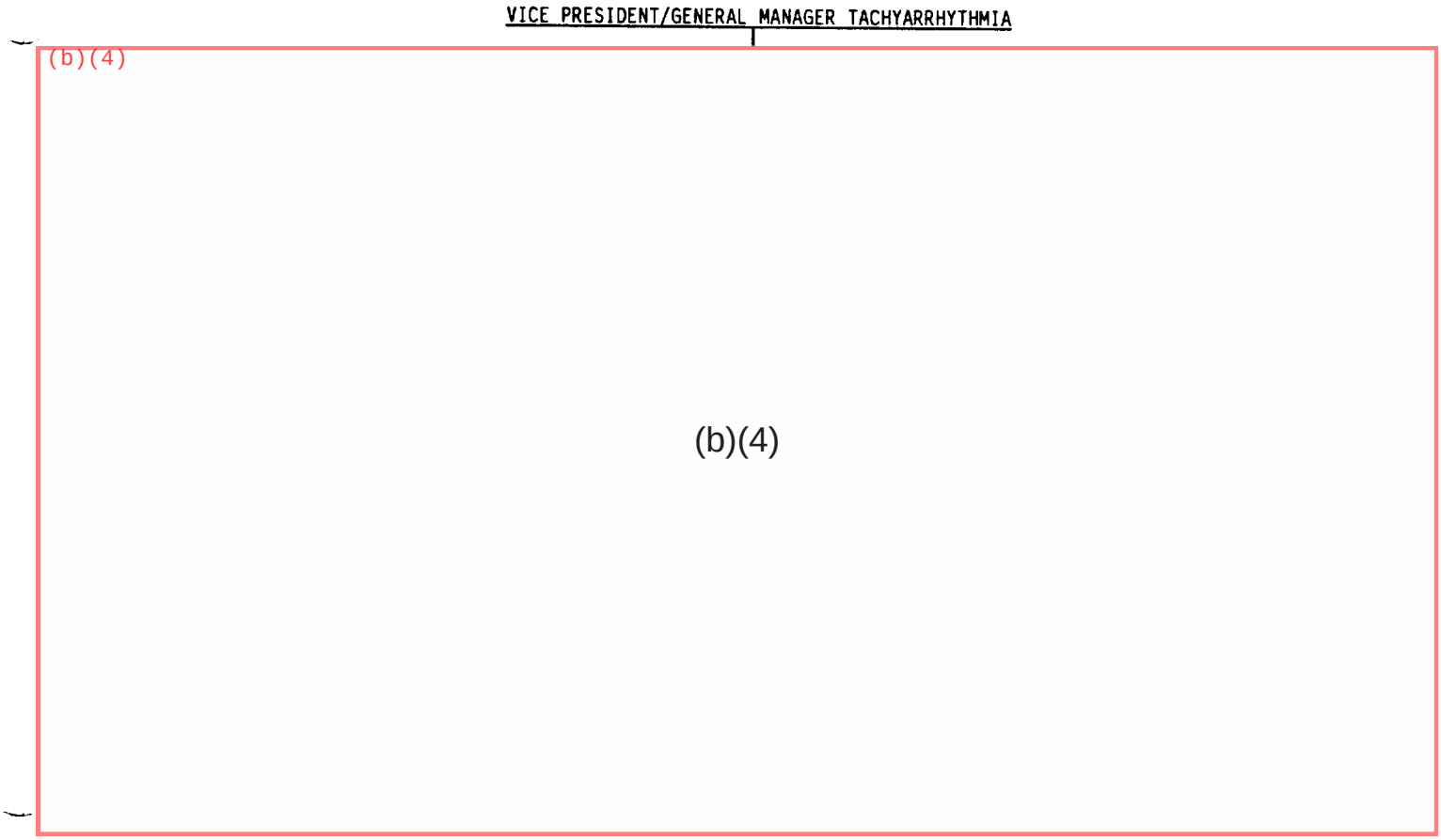


FIGURE 2. MANUFACTURING ORGANIZATION

A. Organization and Personnel

(3) Methods used to assure that personnel have proper training and experience for the operations performed.

(b)(4)

(b)(4)

A. Organization and Personnel

(4) Design and implementation of training programs, including methods for identifying training needs, qualification of personnel for special processes and operations, and documentation of training.

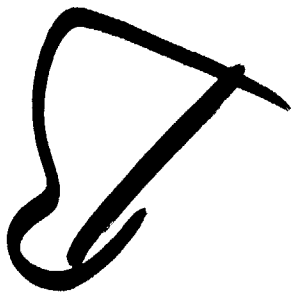
(b)(4)

(b)(4)

- (b)(4)

(b)(4)

(b)(4)



B. Quality Audit

(1) Design and implementation of the quality audit program including procedures for assessing that audits are reviewed by upper management, all appropriate areas are audited, corrective action is implemented, independence from functions audited is maintained, and auditors are qualified.

(b)(4)

(b)(4)

C. Buildings

(1) Methods and procedures used to assure orderly handling and to avoid mixups of components, finished devices, labeling, packaging and manufacturing materials during routine operations and storage.

(b)(4)

(b)(4)

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C. Buildings

(2) Methods and procedures used to control and monitor environmental conditions when environmental conditions could adversely affect a device's fitness for use.

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D. Equipment

D. Equipment

(1) Methods and procedures established to assure proper maintenance and calibration of equipment used for production and quality control including procedures used to assure the adequacy of automated equipment.

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POLICIES

(b)(4)

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Maintenance of Equipment: (b)(4)

(b)(4)

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Equipment History: (b)(4)

(b)(4)

(b)(4)

Maintenance Procedures: (b)(4)

(b)(4)

(b)(4)

PROCEDURES

Maintenance Procedures: (b)(4)

(b)(4)

(b)(4)

Use of Labels and ID Stamps: (b)(4)

(b)(4)

(b)(4)

Work Reports: (b)(4)

(b)(4)

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History File: (b)(4)

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Initial Certification of In-House Built Gauging: (b)(4)

(b)(4)

(b)(4)

Development and Control of Software: (b)(4)

(b)(4)

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E. Acceptance and Control of Components

(1) Methods and procedures used to define how purchased finished devices, components, packaging, labeling and manufacturing materials are to be inspected or verified as conforming to requirements.

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b)

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d)

e)

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g)

h)

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(b)(4)

E. Acceptance and Control of Components

(2) Methods and procedures used for the identification of released, rejected, quarantined, or unchecked incoming finished devices, components, packaging, labeling and manufacturing materials.

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E. Acceptance and Control of Components

(3) Methods/procedures used for identifying finished devices, components, labeling, packaging and manufacturing materials through all stages of production.

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E. Acceptance and Control of Components

(4) Methods/procedures used for identifying critical components for critical devices.

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F. Production and Process Controls

(1) Provide a flow diagram of the production process identifying all process steps.

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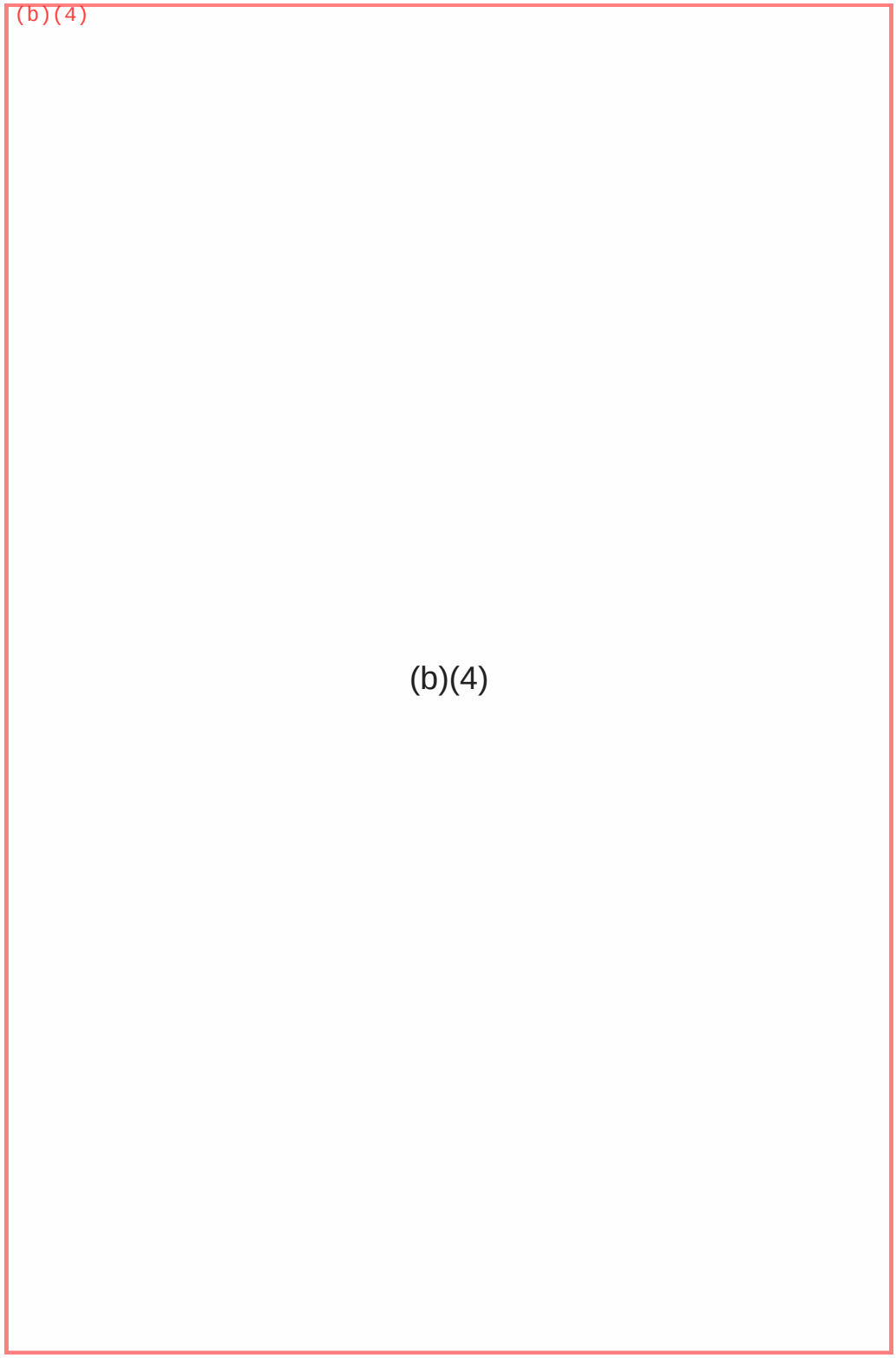

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MODEL 6966 WORKCELL FLOW CHART
WITH
CRITICAL OPERATIONS

(b)(4)

F. Production and Process Controls

(2) Methods/procedures that define and control the manner of production and installation, including work instructions and procedures for the review and control of these instructions.

(b)(4)

(b)(4)

F. Production and Process Controls

(3) Identify all significant manufacturing processes and the methods and procedures used to validate, or prove, the acceptability and stability of the processes, including validation of the methods and procedures used to monitor and control the processes after validation to assure they consistently operate within acceptable process parameters.

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TACHYARRHYTHMIA IMPLANTABLE LEAD MODEL 6966
CRITICAL AND SIGNIFICANT MANUFACTURING OPERATIONS

I. CRITICAL MANUFACTURING OPERATIONS

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II. SIGNIFICANT MANUFACTURING OPERATIONS

(b)(4)

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TACHYARRHYTHMIA IMPLANTABLE LEAD MODEL 6966
CRITICAL AND SIGNIFICANT MANUFACTURING OPERATIONS

Process	Qualification Plans	Qualification Reports
(b)(4)		

(b)(4)

* (b)(4) (b)(4)

Medtronic

DESIGN ASSURANCE PLAN

MEDTRONIC CONFIDENTIAL

Prepared By Brad Snyder

Date 02/01/91

Approved By

TITLE: Design/Process Qualification Plan for New Helix Electrode for Lead Models 6884/6966

KEY WORDS:

File Code (b)(4) (b)(4)

Project No.

Page 1 of 2

(b)(4)

(b)(4)

Medtronic

DESIGN ASSURANCE PLAN

MEDTRONIC CONFIDENTIAL (b)(4)

File Code (b)(4)

Page 2 of 2

(b)(4)

(b)(4)

MEDTRONIC CONFIDENTIAL

Medtronic PSG

DESIGN ASSURANCE REPORT

Prepared By Brad Snyder 4-18-91
Date 04/16/91
Approved By

TITLE: Reliability Assurance Report on the Qualification of the New Helix Electrode for Lead Models 6884/6966

KEY WORDS:

File Code (b)(4)
Project No. (b)(4)
Page 1 of 2

(b)(4)

(b)(4)

Medtronic PSG

DESIGN ASSURANCE REPORT

MEDTRONIC CONFIDENTIAL

File Code (b)(4)

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F. Production and Process Controls

(4) Procedures used to assure that process changes are properly reviewed, approved and validated.

(b)(4)

(b)(4)

(a) Process changes due to product specification changes:

- (b)(4)

(b)(4)

(b)(4)

- (b)(4)

(b) Process changes not related to product specification changes:

(b)(4)

- (b)(4)

F. Production and Process Controls

(5) Methods and procedures used to develop, identify, distribute and maintain manufacturing and quality assurance documentation including the procedures used to authorize and qualify documentation changes.

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The Summary Section (b)(4)

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The Detail Pages, (b)(4)

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The Method Sheets (b)(4)

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(b)(4)

Manufacturing Documentation (b)(4)

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Distribution and Disposal (b)(4) (b)(4)

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Documentation Disposal

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Damaged Document

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Additional Copies

(b)(4)

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The Manufacturing Document Variance QAI covers the following:

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(b)(4)

F. Production and Process Controls

(6) Methods/procedures used to identify and control non-conforming finished devices, components, packaging and labeling. The description should include reprocessing procedures and controls, and procedures used to investigate, identify, and correct causes of non-conformance.

(b)(4)

(b)(4)

Reprocessing Procedures and Controls

(b)(4)

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(b)(4)

(b)(4)

F. Production and Process Controls

(7) Methods/procedures used to identify critical operations for critical devices.

(b)(4)

(b)(4)

Factors that are considered when critical operations are identified are as follows:

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- (b)(4)
-
-

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- (b)(4)
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G. Packaging/Labeling Control

4

G. Packaging and Labeling Control

(1) Methods/procedures used to assure that labeling received and used in production is acceptable for its intended use and to assure that there are no labeling mixups during storage and labeling operations.

(b)(4)

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G. Packaging and Label Control

(2) Methods/procedures used to assure that packaging will protect the device during normal processing, handling, storage and distribution.

(b)(4)

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& Installation

H. Holding, Distribution and Installation

(1) Methods/procedures used to assure that only devices approved for release are released for distribution and that finished devices held for distribution are not adversely affected by storage conditions such as the environment or time.

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H. Holding, Distribution and Installation

(2) Methods/procedures used for critical device distribution records.

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H. Holding, Distribution and Installation

(3) Methods/procedures used for installing the device, including any inspections and instructions provided.

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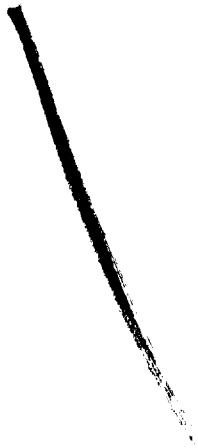

I. Device Evaluation

(1) Methods/procedures used for establishing acceptance criteria and assuring that finished devices meet approved specifications before release.

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Finished Device Inspection Procedures

(b)(4)

I. Electrical

A.
B.

(b)(4)

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II. Functional

A.
B.
C.

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III. Dimensional

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IV. Visual

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V. Package Inspection

(b)(4) (b)(4)

- (b)(4)
- (b)(4)
- (b)(4)

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I. Device Evaluation

(2) Methods/procedures used to investigate product that fails to meet acceptance criteria, including assuring that corrective action is implemented and the records are maintained.

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Positive Identification - (b)(4)

(b)(4)

Disposition - (b)(4)

(b)(4)

- (b)(4)

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I. Device Evaluation

(3) Methods/procedures used to identify, evaluate and investigate the causes of failure of devices that fail to meet requirements after distribution, including the methods/procedures used to assure that corrective action is implemented.

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Implantable Leads

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2.
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5.

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Specialized testing may include:

1.
2.
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4.

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J. Records

(1) Methods/procedures used for the establishment, use and maintenance of the Device History Record. Provide copies of the records which make up the Device History Record, e.g., routing forms, data sheets, and batch records.

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Medtronic

Page 1 of 4

TRACEABILITY CARD

JOB

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TRACEABILITY CARD

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TRACEABILITY CARD

DATA

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TRACEABILITY CARD
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TRACEABILITY CARD

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TRACEABILITY CARD

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Medtronic

Page 1 of 1

TRACEABILITY CARD

BATCH

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J. Records

(2) Methods/procedures used to establish and maintain the Device Master Record (DMR) and to control changes to the DMR.

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Device Records

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J. Records

(3) Complaint receiving and processing procedures, including the methods/procedures used to assure that all complaints received are properly reviewed, evaluated and, when necessary, investigated. Provide copies of records used in the complaint processing program and the complaint processing procedures used.

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Definitions

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Complaints are defined as such by Medtronic as follows:

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7.

Procedure

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10. (b)(4)

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11.

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(Report from field) MEDTRONIC CONFIDENTIAL

Medtronic

MEDTRONIC COMPLAINT REPORT

Date:

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(Report via phone - internal)

MEDTRONIC COMPLAINT REPORT

MEDTRONIC CONFIDENTIAL

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Medtronic

Consumer Affairs Contact Report

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REMOVED PRODUCT INFORMATION REPORT

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(Cover sheet for all complaints)

COMPLAINT SUMMARY INPUT

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MEDTRONIC CONFIDENTIAL 204

PRODUCT INFORMATION REPORT
MEDTRONIC® CARDIOVASCULAR INSTRUMENT

Return instrument along with this
form for evaluation

(PLEASE PRINT OR TYPE)

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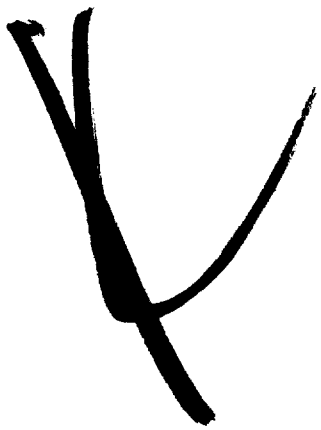
Medtronic

Medtronic, Inc.
6970 Old Central Ave
P O Box 1453
Minneapolis, MN 55440
Telephone (612) 574-4000



K. Sterile Devices

(1) Methods/procedures for release for distribution, e.g., sterility testing, parametric release, and process control release. Provide copies of all finished device testing procedures.

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a) Sterilization Equipment Qualification

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b) Biological Qualification: D-Value Testing

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Test No.	Product Sample	Inoculation Level	D-Value
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c) Bioburden

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d) Sterilization Parameters

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Table I

Nominal Sterilization Process Parameters (b)(4)

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K. Sterile Devices

(2) Methods/procedures to indicate whether the packaging materials have been challenged to assure they are microbially retentive, and that the seal(s) maintains sterility.

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K. Sterile Devices

(3) Pyrogenicity studies which have been conducted on the device, if applicable. Also, indicate whether each lot will be tested, and provide a copy of the test procedure.

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DETECTION OF SAMPLE ENDOTOXIN

Page_____of_____ Date_____ Employee #_____

MEDTRONIC CONFIDENTIAL

Temperature In_____Out_____

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K. Sterile Devices

(4) If ethylene oxide is used as the sterilization method, methods/procedures for the aeration time, the test method to detect EO residues, the frequency of testing, and the release criteria. Provide copies of all procedures and data.

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ETHYLENE OXIDE RESIDUE WORKSHEET

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STERILANT RE JE MONITORING LOG

07/91

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Medtronic QUALITY ASSURANCE INSTRUCTION Number: (b)(4)

uction Type CHEMICAL QUALITY ASSURANCE ENGINEERING

Residue EtO in Sterilized Product

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Medtronic QUALITY ASSURANCE INSTRUCTION Numbe (b)(4)

Instruction Type	Chemical Quality Assurance Engineering
Instruction Title	Residue ETO In Sterilized Product

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MEDTRONIC CONFIDENTIAL 264

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ATTACHMENT 1

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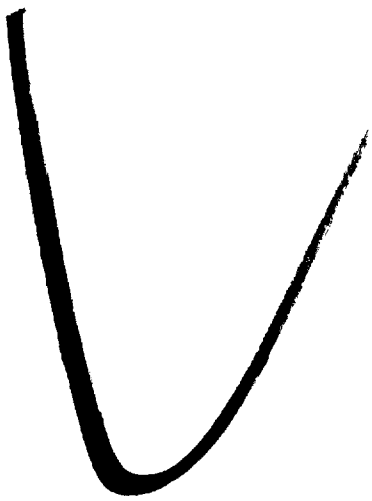


L. Devices Containing Software

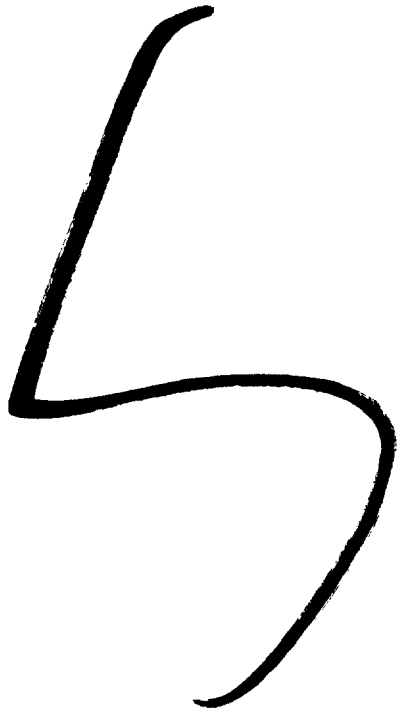
(1) Methods/procedures for the acceptance of software, and the specifications for the software.

This item is not applicable to the Model 6966 RV lead.

L. Devices Containing Software

(2) Provide the following information with respect to the reproduction of the software: identify the type of medium used to store software and the rationale for its selection; the environmental controls under which the media are programmed, handled and sorted; the procedure used for software duplication; and the method used to assure the program is accurately copied.

This item is not applicable to the Model 6966 RV lead.



TECHNICAL MANUAL

The TRANSVENE™-RV Tripolar, Endocardial, Screw-in Lead for Ventricular Pacing, Sensing, Cardioversion and Defibrillation

MODEL 6966

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Printed In The Netherlands

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DESCRIPTION AND INTENDED USE

The Medtronic® Model 6966 Tripolar, Endocardial, Screw-In Lead is designed for pacing, sensing, and delivering cardioversion and defibrillation pulses in the ventricle. It is intended for long-term use and is designed to be used only a Medtronic implantable tachyarrhythmia control device, such as the Medtronic Model 7217B PCD Device along with at least one other complementary lead, such as TRANSVENE™ - RV Model 6963 Coronary Sinus or Superior Vena Cava lead, or the TRANSVENE™ - SQ Model 6999 Unipolar, Subcutaneous, Oval Patch Lead.

The TRANSVENE™-SVC lead has a helical electrode made of platinum alloy that can be actively fixed in the endocardium. The helix can be extended or retracted by rotating the lead connector pin with a special fixation tool. Active fixation leads are particularly beneficial for patients who have smooth or hypertrophic hearts where lead dislodgement may be a potential problem.

The three electrodes of this lead are: coil, ring, and helix (Figure 1).

The defibrillating coil electrode is most proximal to the pulse generator and connects electrically to the connector PIN of the UNIPOLAR leg of the bifurcation. This UNIPOLAR leg will not accept a stylet.

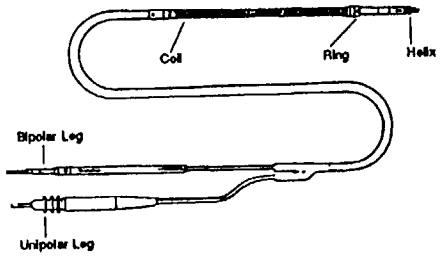


Figure 1. The three electrodes and two connector legs.

The ring electrode is proximal to the helix and connects electrically to the connector RING of the BIPOLAR leg of the bifurcation.

The helix tip electrode is most distal to the pulse generator and provides active fixation in the endocardium. It can be extended or retracted by rotating the lead connector PIN with a special fixation tool. The helix electrode connects electrically to the connector PIN of the BIPOLAR leg of the bifurcation. This BIPOLAR leg is the only one that will accept a stylet.

The coil electrode is intended to be used for delivery of cardioversion and defibrillation pulses. The helix tip electrode and the ring electrode may be used for bipolar pacing and sensing; however, when used with standard bipolar PCD™ pulse generators, pacing occurs between the helix tip electrode and the coil electrode.

The lead's conductors are in a multifilar configuration and are insulated with polyurethane.

CONTENTS OF PACKAGE

The leads are supplied sterile. Each package contains:

- 1 TRANSVENE™-RV lead with anchoring sleeve, stylet, and stylet guide
- 2 fixation tools
- 1 vein lifter
- Extra stylets
- Product literature

CONTRAINDICATIONS

When tricuspid valvular disease or a mechanical heart valve is present, use of a ventricular endocardial lead is contraindicated.

WARNINGS

The safety, efficacy, and procedures for using the Model 6966 Tripolar, Endocardial, Screw-in Ventricular Lead are being evaluated under an investigational protocol. Patients must be advised that this lead is investigational. **Do not attempt to use this lead with a non-Medtronic Implantable Cardioverter/Defibrillator device.** Do not use only battery-powered equipment during lead implantation and testing to protect against fibrillation that may be caused by alternating currents. Line-powered equipment used in the vicinity of the patient must be properly grounded. Lead connector pins must be insulated from any leakage currents that may arise from line-powered equipment.

PRECAUTIONS

Necessary Hospital Equipment

External defibrillating equipment should be kept nearby for immediate use during the acute lead system testing, implanta-

tion procedure, and whenever arrhythmias are possible or intentionally induced during post-implant testing.

Inspecting the Package

Carefully inspect the package before opening. If the container, the package, or the lead appear to have been damaged, do not use the lead. Return the damaged lead to your Medtronic representative.

Before Inserting the Lead

Use an anchoring sleeve with all leads. Ensure that the anchoring sleeve is positioned close to the lead's bifurcation sleeve. This will prevent inadvertent passage of the anchoring sleeve into the vein.

Handling the Lead

Leads should be handled with great care at all times. **Any severe bending, kinking, stretching, or handling with surgical instruments may cause permanent damage to the lead.**

Lead insulators attract small particles such as lint and dust. Therefore, to minimize contamination, protect the lead from materials shedding these substances. Handle the lead with sterile surgical gloves that have been rinsed in sterile water or equivalent.

Do not immerse leads in mineral oil, silicone oil, or any other liquid.

The maximum number of revolutions of the electrode fixation tool needed to extend or retract the helix is 20. **Exceeding the maximum revolutions may damage the lead.**

Chronic Repositioning

Chronic repositioning or removal of screw-in leads may not be possible because of blood or fibrotic tissue development into the helix mechanism. Removal of the lead could result in avulsion of the endocardium, valve, or vein. In addition, the lead junctions may separate, leaving the lead tip and bare wire in the heart or vein. In most clinical situations, it is preferable to abandon unused leads in place.

However, if a lead must be removed or repositioned, proceed with extreme caution. If a helix does not disengage from the endocardium by rotating the connector pin, rotating the lead body counterclockwise may withdraw the helix and decrease the possibility of damage to the cardiovascular structures during removal. If a lead is removed, inspect it carefully for insulator or conductor coil damage. (Medtronic requests that all removed or unused leads or portions thereof be returned for analysis.)

If a lead is abandoned, it should be capped to avoid transmitting electrical signals from the pin to the heart. A lead that

has been cut off should have the remaining lead end sealed and it should be sutured to adjacent tissue to avoid migration into the heart.

See additional cautions in the section "Suggested Implantation Procedure."

POTENTIAL COMPLICATIONS

The potential complications related to the use of endocardial leads include, but are not limited to, the following patient-related conditions: fibrillation, air embolism, cardiac perforation, heart wall rupture, cardiac tamponade, pericardial rub, infection, myocarditis, constrictive pericarditis, pneumothorax, and hemothorax.

Other potential complications related to the lead system and the programmed parameters of a pulse generator include, but are not limited to the following:

Complication	Possible Effects
Displacement, lead insulation or conductor fracture, poor connection to the tachyarrhythmia control device	Intermittent or continuous loss of sensing; oversensing; intermittent or continuous loss of defibrillation, cardioversion, or pacing therapy; and possible muscle or nerve stimulation in the pocket area*
Electrode fracture	Intermittent or continuous loss of defibrillation, cardioversion therapy, sensing, or pacing therapies*
Threshold elevation or exit block sion,	Loss of defibrillation, cardiover- or pacing therapy efficacy*

*Loss of detection, defibrillation, cardioversion, or pacing therapies may occur due to lead dislodgement, fracture, or threshold elevation. Therefore, the patient's ECG should be monitored during the hospital stay. If such a loss occurs, check sensing thresholds or X rays for lead dislodgement or conductor fracture.

ENSURING PRODUCT INTEGRITY

Carefully inspect the package before opening. It is not recommended that you use the product after its expiration date.

If the integrity of the package has been compromised prior to the product expiration date, place the contents in a gas-permeable package and resterilize it with ethylene oxide as described below.

CAUTION: Use ethylene oxide only.

The process should not exceed temperatures of 55° C (125° F). Allow proper aeration of ethylene oxide residues prior to implantation. Use some acceptable method to determine sterilizer effectiveness, such as a biological indicator.

Due to the variability between sterilizers, precise sterilization instructions cannot be provided. Contact your sterilizer manufacturer for more information regarding sterilization procedures.

SUGGESTED IMPLANTATION PROCEDURE

The implantation procedure generally includes checking the mechanical functioning of the lead electrode before it is inserted; using a stylet guide, stylets, and vein lifter; selecting an insertion site; positioning the lead; securing the lead; taking electrical and defibrillation efficacy measurements; anchoring the lead; and connecting the lead to the pulse generator.

Some implantation techniques vary according to physician preference and the patient's anatomy or physical condition. As described below, the techniques for selecting an insertion site, using a stylet guide or a stylet, positioning a lead, and anchoring a lead suggest one or two possible versions, while more may exist.

Verifying the Mechanical Functioning of the Helix Electrode

Before implantation, verify the mechanical functioning of the electrode, as described below.

1. Within the sterile field, remove the lead and the accompanying stylets from the sterile packaging. The lead is packaged with a stylet guide attached and a stylet already inserted. The connector pin that accepts the stylet controls the helix mechanism.

2. To attach the fixation tool, first remove the stylet guide. Press both legs of the fixation tool together and place the most distal hole of the fixation tool on the connector pin that accepts the stylet (Figure 2).

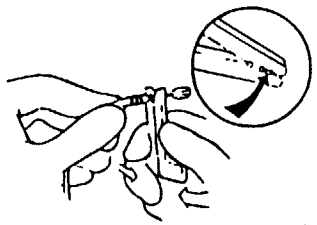


Figure 2. Attachment of the fixation tool to the connector pin.

3. Rotate the tool clockwise until the coiled electrode is completely exposed (Figure 3). Maximum electrode exposure reveals 2 coils.

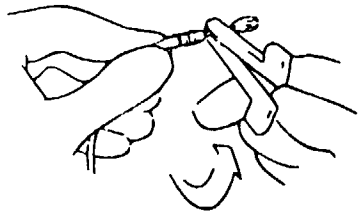


Figure 3. Rotating the fixation tool.

The maximum number of revolutions of the fixation tool needed to extend or retract the helix is 20.

CAUTION: Exceeding the maximum number of revolutions may damage the lead.

4. Disconnect the fixation tool from the connector pin and release the proximal end of the lead body. Allow several seconds for the lead and its conductor coil to unwind.

5. After allowing the lead and its conductor coil to unwind, reattach the fixation tool and turn it counterclockwise until the helix tip is retracted in the sheath.

Using the Stylet Guide and Stylets

The lead is packaged with a stylet guide attached and a stylet already inserted. The connector pin with the stylet in it controls the helix mechanism. Use of the stylet guide is optional. An attached stylet guide may be removed by gently pulling it off. To attach a stylet guide, gently push it as far as possible onto the connector pin that accepts the stylet (Figure 4).

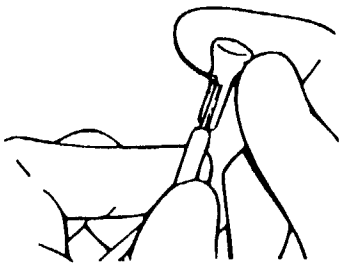


Figure 4. Stylet guide attachment.

A stylet provides additional stiffness and controlled flexibility for maneuvering the lead into position. Stylets vary in stiffness to accommodate a physician's preference for lead and stylet flexibility.

CAUTION: To avoid damage to the lead or body tissue, do not use excessive force or surgical instruments to insert a stylet into the lead. When handling a stylet, avoid overbending, kinking, or blood contact.

CAUTION: Repeated insertions of a stylet increase the chance that blood may accumulate on it, which may cause difficulty in passing the stylet through the lead and may cause damage to the lead.

After the stylet is inserted, gently remove the stylet guide so that it rests alongside the stylet knob.

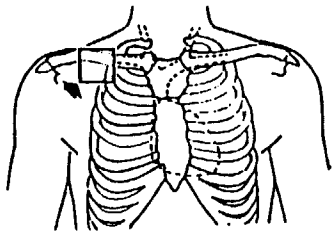
Selecting an Insertion Site

The lead may be inserted by venotomy through several different venous routes, including the right or left cephalic vein or the external or internal jugular vein.

CAUTION: If insertion is done via a subclavian approach, the lead should be positioned far laterally to avoid clamping the lead body between the clavicle and the first rib. Clamping the lead may eventually cause the conductor to fractur, may cause damage to the insulation, or may cause other damage to the lead. This may result in complications such as loss of detection, loss of pacing therapies, or loss of cardioversion/defibrillation therapy. Certain anatomical abnormalities, such as thoracic outlet syndrome, may also precipitate pinching and subsequent fracture of the lead. If significant resis-

tance is encountered during a subclavian stick implant procedure, do not force the lead by adjucting patient's posture (i.e., raising the arm or putting a towel behind the person's back) to facilitate the passage of the lead. In such cases it is recommended that an alternate venous entry site be used.

Use fluoroscopy to facilitate accurate lead placement.



Using the Vein Lifter

A vein lifter facilitates lead introduction. Insert its tapered end into the incised vein and gently push the lead tip underneath and into the vein (Figure 5).

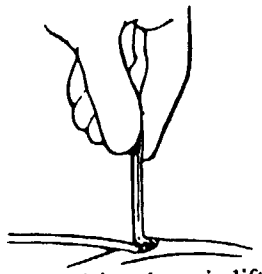


Figure 5. Using the vein lifter.

CAUTION: Avoid placing the lead under extreme tension or angulation to prevent lead dislodgement and possible lead fracture. **Do not grip the lead with surgical instruments.**

Positioning a Ventricular Lead

Advance the lead into the right atrium. For added control in maneuvering the lead tip through the tricuspid valve, the distal end of the lead may be slightly curved by inserting a gently curved stylet (Figure 6). After the lead tip is passed into the ventricle, the curved stylet may be replaced with a straight stylet. Then the lead tip may be advanced to the right ventricular apex while taking care to avoid perforation of the ventricular wall.

CAUTION: To avoid damage to the stylet, do not use a sharp object to impart a curve to the distal end (Figure 6).

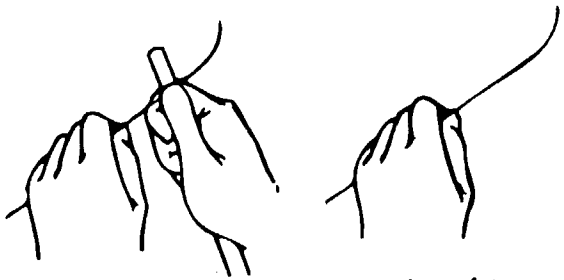


Figure 6. Imparting a curve to the stylet.

Accurate positioning of the electrode is essential for stable endocardial pacing. A satisfactory position is usually achieved when the lead tip points straight toward the apex, or when the distal end dips or bends slightly.

Use fluoroscopy (lateral position) to ensure that the tip is not in a retrograde position or is not lodged in the coronary sinus.

The patient should have x-rays taken every six months to verify the integrity of the PCD™ system.

After placing the lead in a satisfactory position, secure the lead by extending the helix into the endocardium.

Securing the Electrode Into the Endocardium

The following procedure is recommended for electrode fixation:

1. Press both legs of the fixation tool together and place the most distal hole of the fixation tool on the connector pin that accepts the stylet (Figure 2).
2. Gently press the lead tip against the endocardium by pushing the stylet and the lead at the vein entry site. Then, rotate the tool clockwise until the coiled electrode is completely exposed (Figure 3). Maximum electrode exposure reveals 2 coils.

The maximum number of revolutions of the fixation tool needed to extend or retract the helix is 20.

CAUTION: Exceeding the maximum number of revolutions to extend or retract the helix may damage the lead.

3. Use fluoroscopy to verify helix electrode exposure. Closing of the space between the conductor (A) and the indicator ring (B) implies complete exposure of the helix electrode (Figure 7).

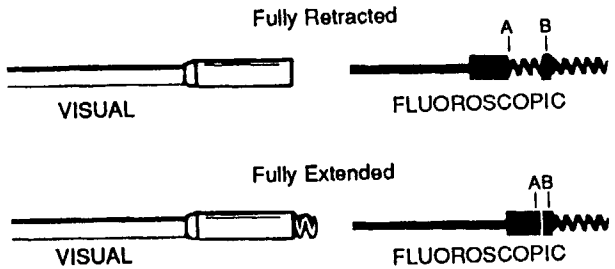


Figure 7. Possible views of the electrode.

4. Disconnect the fixation tool from the connector pin and release the proximal end of the lead body. Allow several seconds for the residual torque in the lead to be relieved.
5. After allowing the residual torque in the lead to be relieved, rotate the whole lead body clockwise approximately one revolution to ensure that the helical electrode is secured to the endocardium.
6. Carefully withdraw the stylet part way.
7. Obtain electrical measurements to verify satisfactory placement and electrode fixation. Refer to the following section, Taking Electrical and Defibrillation Efficacy Measurements, for recommended procedures and values.
8. Verify that the helix is affixed by gently pulling back on the lead and checking for resistance. A properly affixed helix will remain in position. If the helix is not properly affixed, the lead tip may become loose in the right ventricle.
9. If repositioning is required, reattach and rotate the fixation tool counterclockwise until the electrode is withdrawn. Use fluoroscopy to verify withdrawal. Repeat the procedure above.

CAUTION: When retracting the helix, do not rotate the fixation tool more than 20 revolutions. When the electrode is fully retracted, 2 coils of the helix will be visible between the indicator ring and the conductor.

10. Remove the stylet guide and stylet completely. When removing the stylet guide, grip the lead firmly just below the connector pin; this will help prevent possible lead dislodgement.
11. Obtain final electrical measurements. The lead may be repositioned, if necessary, to meet the implant defibrillation efficacy criteria outlined in the following section.

Taking Electrical Measurements and Defibrillation Efficacy Measurements

In order to demonstrate reliable defibrillation efficacy, it is recommended that ventricular fibrillation be initiated and successfully terminated three out of four times at a stored output energy of 18 joules or less.

Recommended Pacing/Sensing Measurements at Implant
(when using a pacing system analyzer)

Measurements Required	Acute Lead System	Chronic Lead System
Capture threshold	≤ 1.5 V - epicardial	≤ 3.0 V
(at 0.5 ms pulse width)	≤ 1.0 V - endocardial	≤ 3.0 V
Impedance	200 - 800 ohms	200 - 800 ohms
Filtered R-wave amplitude	≥ 5 mV (during sinus rhythm)	≥ 3 mV (during sinus rhythm)
Slew rate	≥ 0.75 V/s	≥ 0.45 V/s

200

Initial electrical measurements may deviate from the recommendations because of acute cellular trauma. If this occurs, wait five to fifteen minutes and repeat the testing procedure. Values may vary depending upon lead type, pulse generator settings, cardiac tissue condition, and drug interactions. If electrical measurements do not stabilize to acceptable levels, it may be necessary to reposition the lead and repeat the testing procedure.

For more information on obtaining electrical measurements, consult the technical manual supplied with the testing device.

Anchoring the Lead

Use the anchoring sleeve to secure the lead from moving and to protect the lead insulation and conductor coil from damage caused by tight ligatures.

Anchor the lead with nonabsorbable sutures.

TRANSVENE™-RV uses a triple groove anchoring sleeve illustrated in Figure 8.

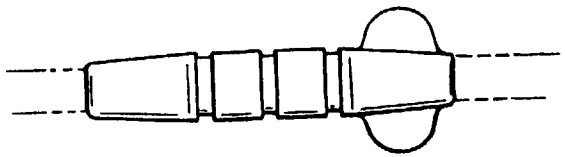


Figure 8. The triple groove anchoring sleeve.

With a triple groove anchoring sleeve, generally two or three of the grooves may be used with the following procedure (Figure 9 or 10):

The triple groove anchoring sleeve is situated at the connector end of the lead. Partially insert the anchoring sleeve into the vein.

Use the most distal suture groove to secure the anchoring sleeve to the vein.

Use the middle groove to secure the anchoring sleeve to the fascia and lead. First, create a base by looping a suture through the fascia underneath the middle groove and tying a knot. Continue by firmly wrapping the suture around the middle groove and tying a second knot.

Use the third and most proximal groove to secure the anchoring sleeve to the lead body.

Alternatively, only two of the three grooves may be used on the anchoring sleeve to tie down the lead. In that case, follow the anchoring procedure for the distal and middle groove (Figure 10).

CAUTION: Do not use the anchoring sleeve tabs for suturing.

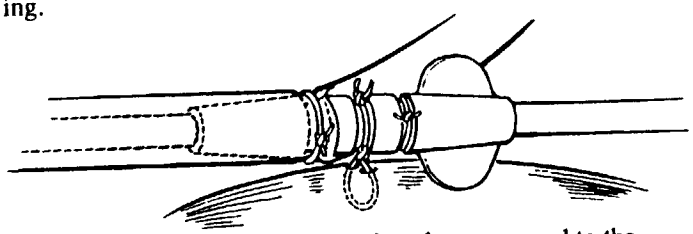


Figure 9. Triple groove anchoring sleeve secured to the lead and fascia using three grooves.

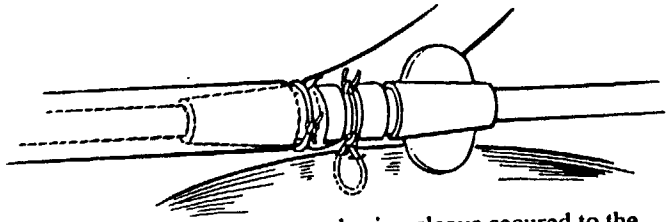


Figure 10. Triple groove anchoring sleeve secured to the lead and fascia using two grooves.

Tie the sutures securely but gently to prevent damage to the anchoring sleeve.

CAUTION: Do not secure the ligatures so tightly that they damage the vein or lead. **Do not tie a ligature directly to the lead body** (Figure 11). During anchoring, take care to avoid dislodging the lead tip.

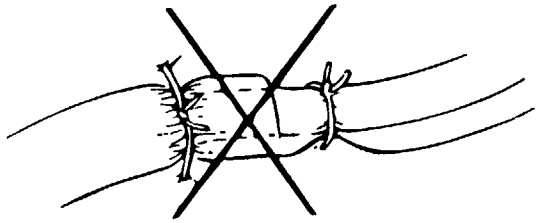


Figure 11. Do NOT secure the sutures too tightly and do NOT tie a suture to the lead body.

Connecting the Lead to a Tachyarrhythmia Device

Before tunneling the lead connector, record each lead's serial number along with the function of the lead. Tunnel the lead subcutaneously to the pulse generator pocket. A tunneling tool may be used to pull all the leads through to the pocket area. Use of a chest tube is suggested in tunneling the lead connector to the pulse generator to prevent damage to the lead.

Refer to Figures 12a and 12b for instructions and illustrations showing lead connections to the Medtronic® PCD™ Tachyarrhythmia Control Device Model 7217B.

Insert the lead connector into the connector block. Refer to the tachyarrhythmia control device technical manual for the use of setscrews and setscrew tools.

Before closing the pocket, verify sensing, pacing and defibrillation efficacy.

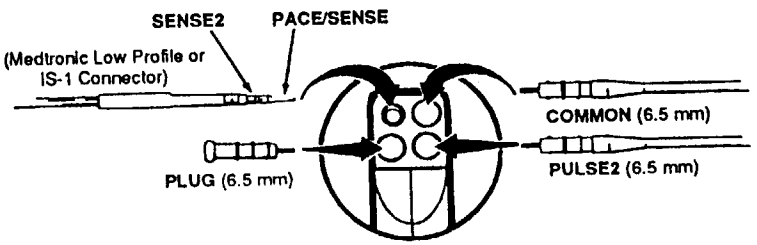
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillating Electrodes	Endocardial Two-Electrode System Connection Diagram
Medtronic® Model 7217B PCD™ Device	2	**PACE/SENSE, SENSE2** Insert the Pace/Sense lead connector of the TRANSVENE™-RV into the PACE/SENSE, SENSE2 port. **COMMON** Insert the unipolar lead connector of the TRANSVENE™-RV, -SVC, or -SQ into the COMMON port.  **PULSE1** Insert the connector plug packaged with the pulse generator into the PULSE1 port. **PULSE2** Insert the lead connector of either the TRANSVENE™-RV, -SVC, or -SQ lead into the PULSE2 port.

Figure 12a. Connections for endocardial and subcutaneous leads (single pulse) into the Medtronic® PCD™ Tachyarrhythmia Control Device 7217B.

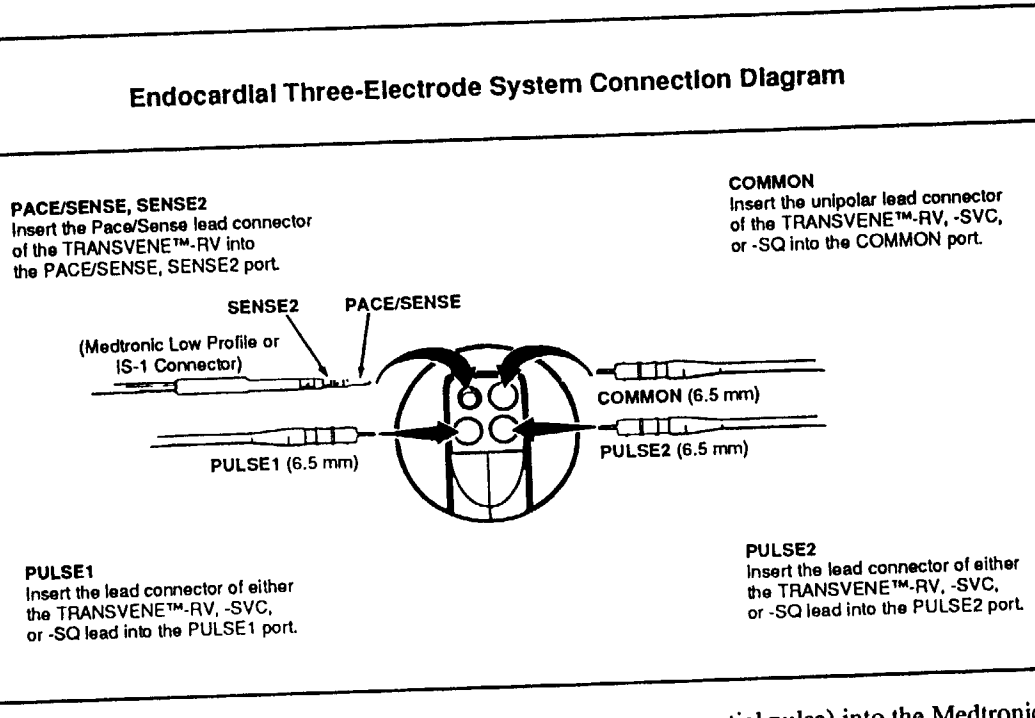
Tachyarrhythmia Control Device Model	Number of Implanted Defibrillating Electrodes	Endocardial Three-Electrode System Connection Diagram
Medtronic® Model 7217B PCD™ Device	3	

Figure 12b. Connections for endocardial and subcutaneous leads (simultaneous or sequential pulse) into the Medtronic® PCD™ Tachyarrhythmia Control Device 7217B.

CAUTION: Always remove the stylet before connecting the lead to the pulse generator. Failure to remove the stylet may result in lead failure.

CAUTION: To prevent undesirable twisting of the lead body, wrap the excess lead length loosely under the pulse generator and place both into the subcutaneous pocket (Figure 13). Ensure that the leads do not leave the pulse generator at an acute angle. Sharp angles place undue stress on the lead conductor and insulation.

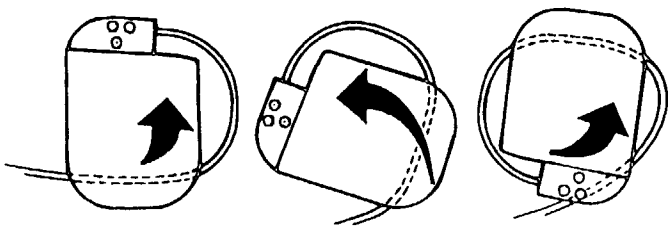


Figure 13. While rotating the pulse generator, loosely wrap the excess lead length and place it under the pulse generator.

CAUTION: When placing the pulse generator and leads into the subcutaneous pocket:

- Do NOT coil the lead. Coiling the lead can twist the lead body and may result in lead dislodgement (Figure 14).
- Do NOT grip the lead or pulse generator with surgical instruments.

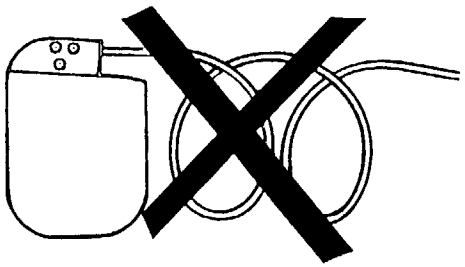


Figure 14. Do not coil the lead body.

After implantation, monitor the patient's electrocardiogram continuously. If a lead dislodges, it usually occurs during the immediate postoperative period.

TECHNICAL SPECIFICATIONS (Nominal)

PARAMETER		MODEL 6966
Type		Tripolar
Chamber		Ventricle
Fixation		Screw-In
Length		110 cm
Connectors	Unipolar:	6.5 mm
	Bipolar:	3.2 mm
Materials	Conductors:	MP35N Alloy
	Insulator:	Polyurethane
Electrode Surface (tip, ring, and coil)		Platinum Alloy
Electrode Surface Area	Helix:	10 mm2
	Ring:	37 mm2
	Coil:	290 mm2 (5 cm length)

PARAMETER		MODEL 6966
Lead Introducer (recommended size)		11 French
Diameters (circumference)	Body:	3.3 mm
	Helix:	1.6 mm
	Maximum Head:	3.5 mm
Helix Length (fully extended)		2 mm
Conductor Resistances	Pacing:	45 ohms (unipolar) 190 ohms (bipolar)
	Difibrillation:	3.5 ohms
Anchoring Sleeve (white, non-radiopaque)		Triple Groove
Maximum Revolutions that can be used to extend or retract the helix when using a straight stylet		20

GENERAL WARNING

Medtronic® implantable leads are implanted in the extremely hostile environment of the human body. Leads are necessarily very small in diameter and must still be very flexible, which unavoidably reduces their potential performance or longevity. Leads may fail to function for a variety of causes, including, but not limited to: medical complications, body rejection phenomena, allergic reaction, fibrotic tissue, or failure of leads by breakage or by breach of their insulation covering. In addition, despite the exercise of all due care in design, component selection, manufacture, and testing prior to sale, leads may be easily damaged before, during, or after insertion by improper handling or other intervening acts. Consequently, no representation or warranty is made that failure or cessation of function of leads will not occur or that the body will not react adversely to the implantation of leads or that medical complications (including perforation of the heart) will not follow the implantation of leads or that the lead will, in all cases, restore adequate cardiac function.

MEDTRONIC® DEFIBRILLATION LEAD DISCLAIMER OF WARRANTIES

THIS MEDTRONIC® TRANSVENE™-RV MODEL 6966 PERMANENT IMPLANTABLE DEFIBRILLATION LEAD (THE "LEAD") HAS BEEN MANUFACTURED UNDER CAREFULLY CONTROLLED CONDITIONS TO ASSURE ITS QUALITY AND RELIABILITY. HOWEVER, BECAUSE MEDTRONIC HAS NO CONTROL OVER CONDITIONS UNDER WHICH THE LEAD IS USED, MEDTRONIC PROVIDES THE FOLLOWING DISCLAIMER:

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EUROPE/AFRICA/MIDDLE EAST
Medtronic Europe
Immeuble Myron
6, avenue E. van Nieuwenhuyse
B-1160, Brussels
Belgium
Telephone: (32) 2-676 08 11

ASIA/PACIFIC
Australia
Medtronic Australasia Pty. Ltd.
22 Clarke Street
Crows Nest, Sydney, N.S.W., 2065
Australia
Telephone: (61) 2-437-6066

Asia
Metronic International Ltd.
2002 CC Wu Building
308 Hennessey Road, Wanchai
Hong Kong, B.C.C.
Telephone: (852-5) 891-4068

Japan
Medtronic Japan Co. Ltd.
Shuwa Kioi-Cho Park Bldg, 5F
3-6, Kioi-cho, Chiyoda-ku
Tokyo 102
Japan
Telephone: (81) 3-3230-2919

LATIN AMERICA
Medtronic, Inc.
450 Fairway Drive**United States**
Suite 205
Deerfield Beach, FL 33441
U.S.A.
Telephone: (305) 428-8556

NORTH AMERICA
Canada
Medtronic of Canada Ltd.
6733 Kitimat Road
Mississauga, Ontario L5N 1W3
Canada
Telephone: (416) 826-6020
Toll-free: 1-800-268-5346
(24-hour consultation service)

Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432
U.S.A.
Telephone: 1-800-328-2518
(24-hour consultation service)

Medtronic

March 1992
UC9002414aEN 195434-002

Medtronic

TRANSVENE™-RV 6966

HIGH VOLTAGE UNIPOLAR CONNECTOR (6.5 mm)
CONNECTEUR UNIPOLAIRE HAUTE TENSION (6,5 mm)
UNIPOLARER KONNEKTOR FÜR HOCHSPANNUNG (6,5 mm)
CONECTOR MONOPOLAR PARA VOLTAJE ALTO (6.5 mm)
CONETTORE MONOPOLARE PER ALTA TENSIONE (6,5 mm)

PACE/SENSE BIPOLAR CONNECTOR (3.2 mm)
CONNECTEUR BIPOLAIRE PACE/SENSE (3,2 mm)
BIPOLARER KONNEKTOR FÜR STIMULATION/WAHRNEHMUNG (3,2 mm)
CONECTOR BIPOLAR PACE/SENSE (3,2 mm)
CONETTORE BIPOLARE PER STIMOLAZIONE/RIVELAMENTO (3,2 mm)

Serial Number
Numéro de Série
Seriennummer
Número de Serie
Numero di Serie

Use Before
Utiliser Avant
Zu Implantieren vor dem
Fecha de Caducidad
Data di Scadenza

Sterile Lot Number
Lot de Stérilisation No.
Sterilisationsnummer
Lote Estéril Número
Numero di Lotto Sterile

Sterilization Date
Date de Stérilisation
Sterilisationsdatum
Fecha de Esterilización
Data di Sterilizzazione

Non Reusable
Usage Unique
Nicht wiederverwendbar
Interior Desechable
Non Riusabile

Lead Length:
Longueur de la Sonde:
Länge der Elektrode:
Longitud del Electrodo:
Lunghezza dell'Elettrocatetere:

Contents: One lead with Polyurethane Insulation.
Contenu: Une sonde avec Isolation de Polyuréthane.
Inhalt: Eine Elektrode mit Polyurethan Isolation.
Contenido: Un cable con Material Aislante de Poliuretano.
Contenuto: Un catetere con Materiale Isolante in Poliuretano.

Sterilization: Ethylene oxide gas
Stérilisation: Gaz d'oxyde d'éthylène
Sterilisation: Äthylenoxydgas
Esterilización: Gas óxido de etileno
Sterilizzazione: Gas ossido di etilene

CAUTION: Federal Law (U.S.A.) restricts this device to sale by or on the order of a physician.
ATTENTION: La règlementation américaine (FDA) n'autorise la vente de ce produit que sur prescription médicale.
ACHTUNG: Ein US-Bundesgesetz schränkt den Verkauf dieses Produkts an Ärzte oder auf Anordnung durch einen Arzt ein.
PRECAUCION: Las Leyes Federales (EE.UU) restringen la venta de este dispositivo únicamente a médicos o por prescripción médica.
ATTENZIONE: La legge Federale (U.S.A.) limita la vendita di questo prodotto esclusivamente ai medici o su richiesta d'un medico.

The contents of this package is **STERILE.**
Le contenu de ce paquet est **STERILE.**
Der Inhalt dieser Packung ist **STERIL.**
El contenido de este envoltorio está **ESTERIL.**
Il contenuto de questa confezione è **STERILE.**

If the package is damaged or opened see the Technical Manual for Information.
Si l'emballage est endommagé ou ouvert voir le manuel technique pour information.
Im Falle einer beschädigten oder geöffneten Packung Gebrauchsanweisung beachten.
Si el paquete ha sido dañado o abierto, ver el Manual Técnico para información.
Se la confezione è danneggiata o aperta vedere il Manuale Tecnico per le informazione relative.

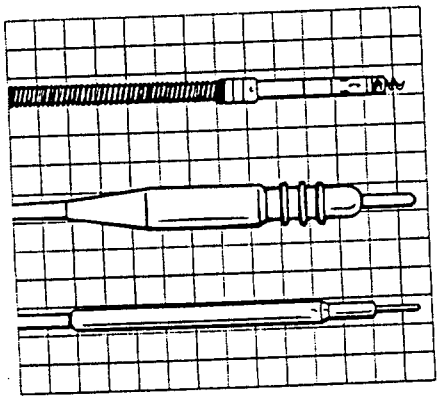
Sterile Pack Label for Model 6966 Lead

Medtronic

TRANSVENE™-RV 6966

HIGH VOLTAGE UNIPOLAR CONNECTOR (6.5 mm)
CONNECTEUR UNIPOLAIRE HAUTE TENSION (6,5 mm)
UNIPOLARER KONNEKTOR FÜR HOCHSPANNUNG (6,5 mm)
CONECTOR MONOPOLAR PARA VOLTAJE ALTO (6,5 mm)
CONETTORE MONOPOLARE PER ALTA TENSIONE (6,5 mm)

PACE/SENSE BIPOLAR CONNECTOR (3.2 mm)
CONNECTEUR BIPOLAIRE PACE/SENSE (3,2 mm)
BIPOLARER KONNEKTOR FÜR STIMULATION/WAHRNEHMUNG (3,2 mm)
CONECTOR BIPOLAR PACE/SENSE (3,2 mm)
CONNETTORE BIPOLARE PER STIMOLAZIONE/RIVELAMENTO (3,2 mm)



Serial Number
Numéro de Série
Seriennummer
Número de Serie
Numero di Serie

Use Before
Utiliser Avant
Zu Implantieren vor dem
Fecha de Caducidad
Data di Scadenza

Sterile Lot Number
Lot de Stérilisation No.
Sterilisationsnummer
Lote Estéril Número
Numero di Lotto Sterile

Sterilization Date
Date de Stérilisation
Sterilisationsdatum
Fecha de Esterilización
Data di Sterilizzazione

Lead Length:
Longueur de la Sonde:
Länge der Elektrode:
Longitud del Electrodo:
Lunghezza dell'Elettrocatetere:

Sterilization Validity Period: 4 Years
Durée de Validité de Stérilisation: 4 Ans
Wirksamkeit der Sterilisation: 4 Jahre
Periodo de Validez de la Esterilización: 4 Años
Periodo di Validità della Sterilizzazione: 4 Anni

Contents: One lead with Polyurethane Insulation, Accessories and Product Literature.
Contenu: Une sonde avec Isolation de Polyuréthane, Accessoires et Documentation.
Inhalt: Eine Elektrode mit Polyurethan Isolation, Zubehör und Dokumentation.
Contenido: Un cable con Material Aislante de Poliuretano, Accesorios y Documentacion.
Contiene: Un catetere con Materiale Isolante in Poliuretano, Accessori e Documentazione.

CAUTION: Federal Law (U.S.A.) restricts this device to sale by or on the order of a physician.
ATTENTION: La règlementation américaine (FDA) n'autorise la vente de ce produit que sur prescription médicale.
ACHTUNG: Ein US-Bundesgesetz schränkt den Verkauf dieses Produkts an Ärzte oder auf Anordnung durch einen Arzt ein.
PRECAUCION: Las Leyes Federales (EE,UU) restringen la venta de este dispositivo únicamente a médicos o por prescripción médica.
ATTENZIONE: La legge Federale (U.S.A.) limita la vendita di questo prodotto esclusivamente ai medici o su richiesta d'un medico.

The contents (**STERILE**) of the inner package have been sterilized by ethylene oxide gas.
Le contenu (**STERILE**) du paquet interne a été stérilisé au gaz d'oxyde d'éthylène.
Der Inhalt (**STERIL**) der inneren Verpackung ist in Äthylenoxydgas sterilisiert.
El contenido (**ESTERILE**) del paquete interior ha sido esterilizado con gas óxido de etileno.
Il contenuto (**STERILE**) della confezione interna è stato sottoposto a sterilizzazione con gas ossido di etilene.

STORAGE: Store below 40° C/104° F
STOCKAGE: Au-dessous de 40° C/104° F
LAGERUNG: Unter 40° C/104° F
ALMACENAMIENTO: Por debajo de 40° C/104° F
IMMAGAZZINAGGIO: Al di sottodi 40° C/104° F

Shelf Box Label for Model 6966 Lead

6963

Intr. 6963, 6999

p920015/c1v3

- Manufacture of the Model 6963 CS/SVC Lead and Model 6999 SQ Patch

- Medtronic, Kerkrade, The Netherlands

5

Medtronic

Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576
Telephone: (612) 574-4000
Cable: Medtronic Telex: 29-0598
Telecopy: (612) 574-4879

March 31, 1992

Office of Device Evaluation
PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

Re: Premarket Approval Application (PMA) for the Medtronic® Multiprogrammable Tachyarrhythmia Control System with Non-thoracotomy Cardioversion and Defibrillation Electrodes, i.e., the PCD™ Transvene System, Lead Models 6963, 6966 and 6999.

This submission is a PMA application for the Medtronic Transvene Lead System used in conjunction with the Model 7217B pacer-cardioverter-defibrillator (PCD), Model 5355 external tachyarrhythmia control device (ETCD) and Model 9788 MemoryMod Software Module.

The PCD and ETCD devices as used with an epicardial lead system were recommended for approval by the FDA Advisory Panel on February 3, 1992 (P900061). The purpose of this PMA application is to obtain approval for the use of the non-thoracotomy lead system for use with the Medtronic PCD and ETCD. The terms non-thoracotomy leads (NTL), transvenous leads and Transvene Lead System are synonymous and may be used interchangeably throughout this application.

The Transvene System, in conjunction with the PCD device, is intended to treat patients at risk of sudden cardiac death due to ventricular arrhythmias. Like the epicardial electrodes/PCD System, the primary benefits from the use of the Transvene/PCD System center on the detection and termination of these life-threatening ventricular arrhythmias. The incorporation of a non-thoracotomy lead system allows for a safer and effective implantation procedure, and improving both perioperative and long-term patient morbidity and mortality.

The Transvene/PCD System clinical study (IDE G870102) includes (b)(4) Transvene lead implants with a mean implant duration of 4.5 months and a total of 1426 device months experience. There are (b)(4) with lead system implant duration equal to or greater than six months. The data included in this submission is all data that was received by Medtronic and entered onto the clinical database as of November 27, 1991. The results from the clinical study are provided in Volume 5 of this application.

Market approval is not being sought for use of the Transvene/PCD System with other manufacturers' implantable-cardioverter-defibrillators, nor is it sought for use of the PCD device with other manufacturers' transvenous defibrillation lead systems.

Two manufacturing facilities are to be used in the assembly, sterilization and packaging of the Transvene leads. These are:

1. Medtronic, Inc.
   Rice Creek Facility
   7000 Central Avenue N.E.
   Minneapolis, MN 55432
   Tel: 612-574-4000
   Establishment Registration Number: 2182208
   Is presently prepared for inspection.
   Most recent FDA inspection: January 21-February 8, 1992.

2. Medtronic, B.V.
   Wenckebachstraat 10
   6466 NC Kerkrade West
   The Netherlands
   Tel: 31-45-43-85-85
   Is presently prepared for inspection.
   Most recent FDA inspection: January 6-9, 1992.

The existence of this PMA application and the data and other information it contains are confidential, and the protection afforded to such confidential information by 18 USC 1905 and other applicable laws is hereby claimed.

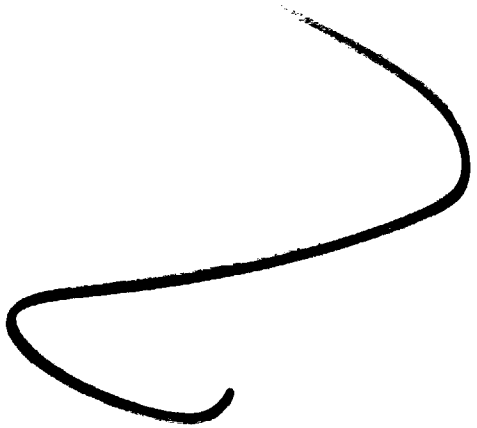
In accordance with 21 CFR 814.42(a), the FDA has 45 days from the date of receipt to notify Medtronic if this application is sufficiently complete for a substantive review and acceptable for filing.

Six copies of this application are enclosed. Should additional information be required by the Agency, please contact the undersigned.

Sincerely,

MEDTRONIC, INC.

Jennifer M. Marrone
Manager, Regulatory Affairs
Cardiac Pacing Business
(612) 574-4688
(612) 574-6424 FAX



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III. Device Description: Model 6963 Coronary Sinus/Superior Vena Cava and Model 6999 Subcutaneous Patch Leads

Illustrations of these leads are provided on the pages following this discussion.

The Medtronic Tachyarrhythmia Control System uses a tripolar, screw-in, right ventricular lead for (RV) pacing, sensing, cardioversion and defibrillation; a unipolar, coronary sinus/superior vena cava lead (CS/SVC); and a unipolar, subcutaneous oval patch electrode (SQ). The available models of the system are as follows:

- Model 6963 CS/SVC Lead
- Model 6966 RV Lead
- Model 6999 SQ Lead

The Model 6963 and 6999 leads are intended to be used with the Model 7217B PCD Device. The leads have a 6.5 mm connector intended for direct insertion into a 6.5 mm port of the 7217B PCD Device.

The Model 6963 lead is intended for use in the coronary sinus or superior vena cava. The lead features a platinum alloy electrode coil which provides the necessary surface area for cardioversion and defibrillation. Silicone insulation surrounds a low-resistance metal-alloy conductor coil.

The Model 6999 lead is intended for use subcutaneously, submuscularly, or directly on the periosteum of the ribs. The lead features platinum alloy electrode coils and a low-resistance metal-alloy conductor surrounded by silicone insulation. Four helical coils are partially embedded into the silicone patch and provide the necessary surface area for cardioversion and defibrillation. A (b)(4) (b)(4) is molded into the patch and provides support for sutures. There are three nodes in the center and two nodes at the junction of the lead body and patch electrode of one side of the patch electrode. These nodes are intended to designate the insulated side of the patch electrode.

The following section describes the functional components, device properties, and principles of operation for the Model 6963 and 6999 leads.

(b)(4)

(b)(4)

MODEL 6963 CS/SVC LEAD

(b)(4)

(b)(4)

MODEL 6999 SUBCUTANEOUS
PATCH LEAD

a. Functional Components

1) Platinum Alloy Electrode Coil

The Model 6963 coronary sinus/superior vena cava lead features a platinum alloy coil electrode that delivers cardioversion and defibrillation pulses to the heart. The Model 6963 lead uses silicone adhesive to help prevent tissue in-growth and aid in chronic lead removal.

The conductive surface of the Model 6999 subcutaneous patch electrode consists of four platinum helical coils partially embedded in molded silicone rubber. These coils serve as the electrodes that deliver cardioversion and defibrillation pulses to the heart. Inside the helical coils is silicone rubber to help prevent tissue in-growth and aid in chronic lead removal.

2) Low Resistance Metal Alloy Conductor Coil

This conductor coil consists of (b)(4) alloy that provides a low resistance pathway for delivery of cardioversion and defibrillation pulses from the tachyarrhythmia control device to the platinum alloy electrode coils. The (b)(4) was selected for use due to its proven long term reliability when used in implanted bradycardia lead systems. The use of (b)(4) coil provides the low resistance needed for the delivery of high voltage pulses. The coils used on the Model 6963 and 6999 are not (b)(4)

3) Insulation

The Model 6963 and 6999 leads are comprised of silicone rubber insulation. This material has a long history (since 1962) of use on Medtronic pacing leads. Insulation wall thickness for both the 6963 and 6999 is (b)(4)

4) Anchoring Sleeve

There is an anchoring sleeve positioned on the lead body of the Model 6963. It is intended to be used for fixation of the lead body to soft tissues near the site of insertion of the lead into the vein at the time of the implant. It is designed to protect the lead from undue strains and stresses at the point of fixation.

5) (b)(4) Embedded into (b)(4) Rubber

(b)(4) is embedded into the Model 6999 subcutaneous patch and provides support when suturing the lead to the subcutaneous muscle.

6) Stylets

Stylets are (b)(4) which stiffen the lead and/or temporarily alter its shape during implant. This is accomplished through a controlled stiffness of the distal tip, allowing it to bend with the application of excessive force. Stylets are also designed to help minimize damage to the coil during insertion and removal. The Model 6963 uses a stylet, the Model 6999 does not.

7) Connector Assembly

The Model 6963 and 6999 leads feature a 6.5 mm terminal assembly consisting of a (b)(4) connector pin and silicone rubber sleeve. The distal part of the sleeve provides a strain relief area.

b. Device Properties

The Model 6963 and 6999 non-thoracotomy leads are designed for sensing, pacing, cardioversion and defibrillation. These leads have application where implantable tachyarrhythmia control devices are indicated. Reference the technical manuals for the Model 6963 and 6999 leads for specific device features.

c. Principles of Operation

The PCD Transvene System uses leads which do not require open-chest surgery to implant. Multiple configurations involving either two or three different leads may be used to deliver cardioversion and defibrillation pulses. These configurations are comprised of a tripolar, right ventricular (RV) lead (Model 6966), and either a coronary sinus (CS) lead (Model 6963) or a subcutaneous (SQ) lead (Model 6999), or all three of these leads. The Model 6963 lead can be placed in either the coronary sinus/great cardiac vein or the superior vena cava (SVC).

In these systems, the helical tip and ring of the RV lead is used for sensing, thus providing standard, bipolar sensing. The tip electrode is termed PACE/SENSE and the ring electrode is termed SENSE 2. Bradycardia pacing takes place between the tip (PACE/SENSE) and the COMMON defibrillation electrode.

A system using two leads delivers cardioversion and defibrillation pulses between two coils (one on each lead). A system using three leads delivers cardioversion and defibrillation pulses either simultaneously or sequentially from the anode electrodes (PULSE 1 and PULSE 2) to the COMMON defibrillation electrode.

To detect VT/VF, the PCD device monitors the cardiac cycle length for fulfillment of the programmed VT/VF detection criteria. When the programmed criteria are fulfilled, the PCD device detects the VT or VF episode and delivers the first programmed therapy. If this therapy is ineffective and the VT/VF is again detected, the next programmed therapy is delivered. This progression continues until the PCD confirms episode termination or delivers all programmed therapies.

The performance of the Models 6966, 6963, and 6999 are evaluated at the following times:

1) At implant by the evaluation of the pacing and sensing thresholds and defibrillation efficacy when treating VT/VF

2) Chronically by evaluation of stability of chronic defibrillation efficacy in induced episodes of VT/VF and successful termination of spontaneous episodes of VT/VF.

Manufacturing Description:

Model 6999 Subcutaneous Lead
Model 6963 Coronary Sinus Lead

Medtronic European Service and Technology Center (ESTC), Kerkrade, The Netherlands

The following Manufacturing Description has been prepared in conformance with the "Guidance for Preparation of PMA Manufacturing Information" made available by FDA August 21, 1991. Copies of the device description and labeling from other parts of the PMA have been included in the first part of this volume, as indicated in the cover letter.

This section contains a complete description of the methods used in, and the facilities and controls used for, the manufacture, processing, packaging, storage and distribution of the Models 6999 and 6963 Nonthoracotomy (NTL) Leads. Process qualification testing and results are included in Section F.3. As requested, a summary describing how applicable GMP requirements are met has been provided for each area identified. Copies of actual procedures are provided when specifically requested by the Guidance.

The Models 6999 and 6963 Leads meet the definition of a critical device; implantable leads are currently on the Critical Device List. We have thus addressed specifically additional controls that are in place to meet the critical device requirements.

A. Organization and Personnel

(1) Company policy and objectives for controlling quality and how they are made known to employees.

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(b)(4)

A. Organization and Personnel

(2) Organizational structure, including the quality system and the responsibilities and channels for identification, documentation and resolution of product quality problems, including responsibilities for assuring that corrective action is implemented.

(b)(4)

(b)(4)

Manufacturing

(b)(4)

(b)(4)

Engineering & Services

(b)(4)

(b)(4)

Customer Services

(b)(4)

(b)(4)

Supply Planning & Distribution

(b)(4)

(b)(4)

EUROPEAN SERVICE AND TECHNOLOGY CENTER
ORGANIZATIONAL STRUCTURE

(b)(4)

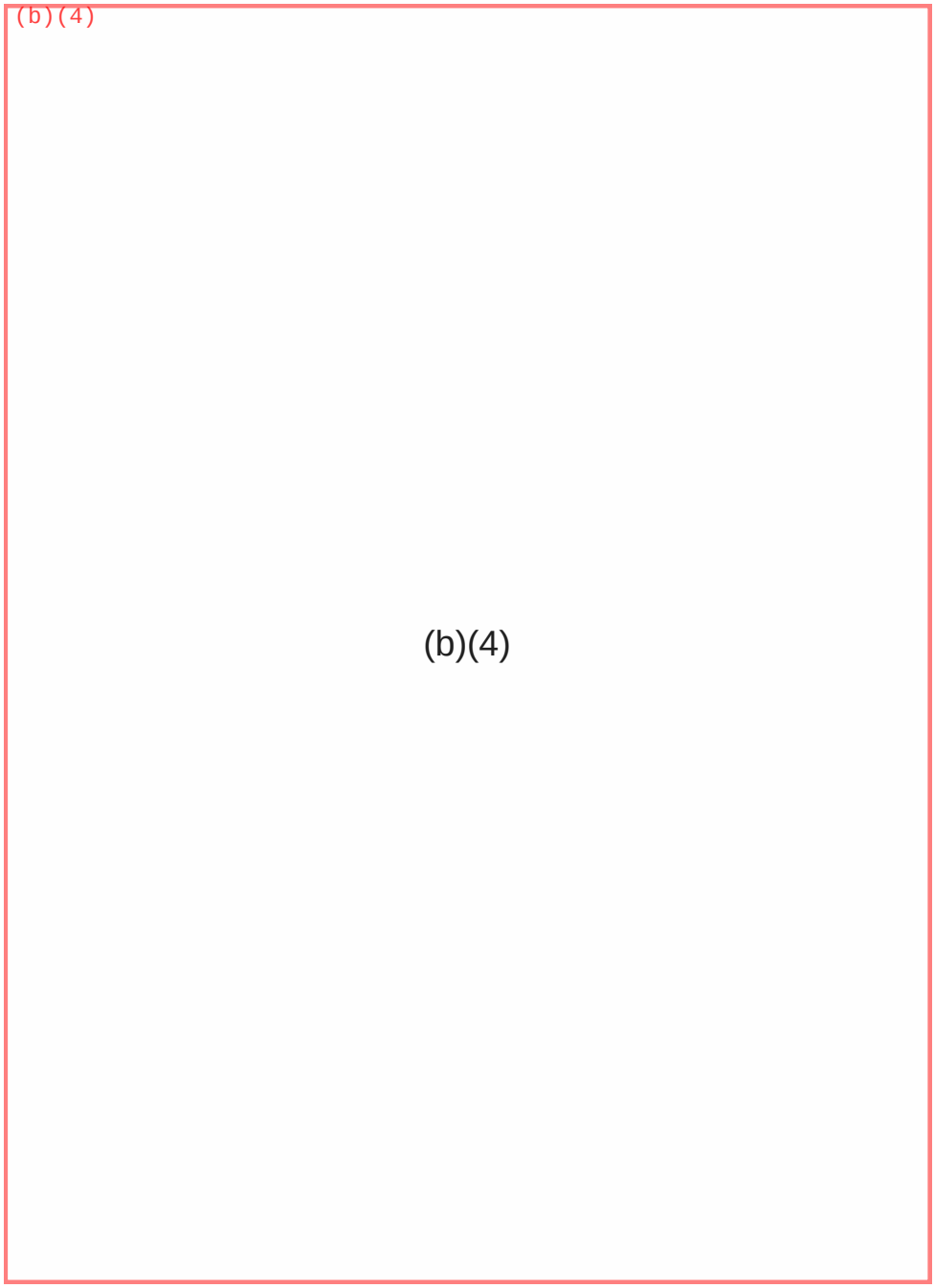
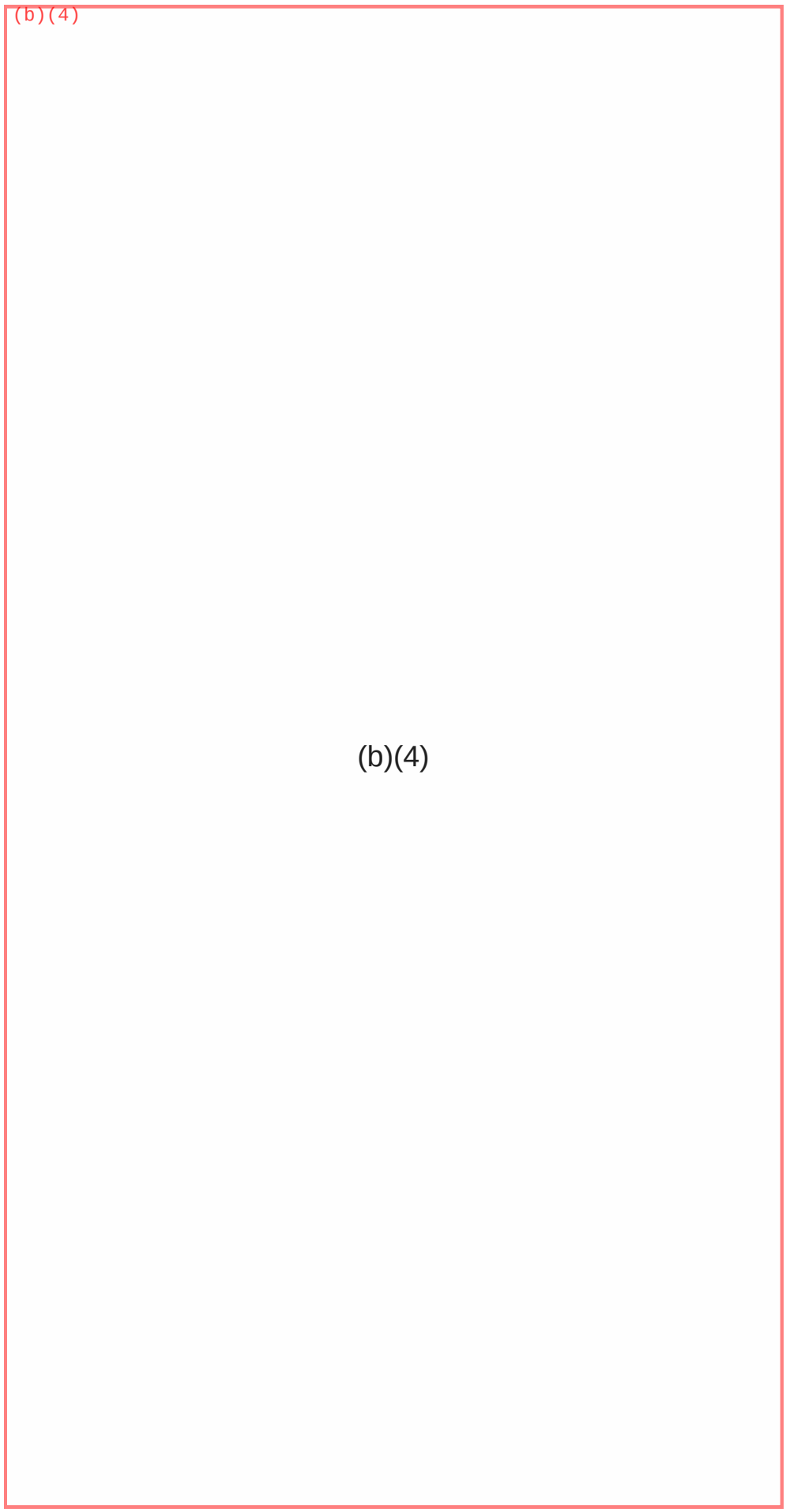


Figure 1.

MEDTRONIC CONFIDENTIAL



A. Organization and Personnel

(3) Methods used to assure that personnel have proper training and experience for the operations performed.

(b)(4)

(b)(4)

A. Organization and Personnel

(4) Design and implementation of training programs, including methods for identifying training needs, qualification of personnel for special processes and operations, and documentation of training.

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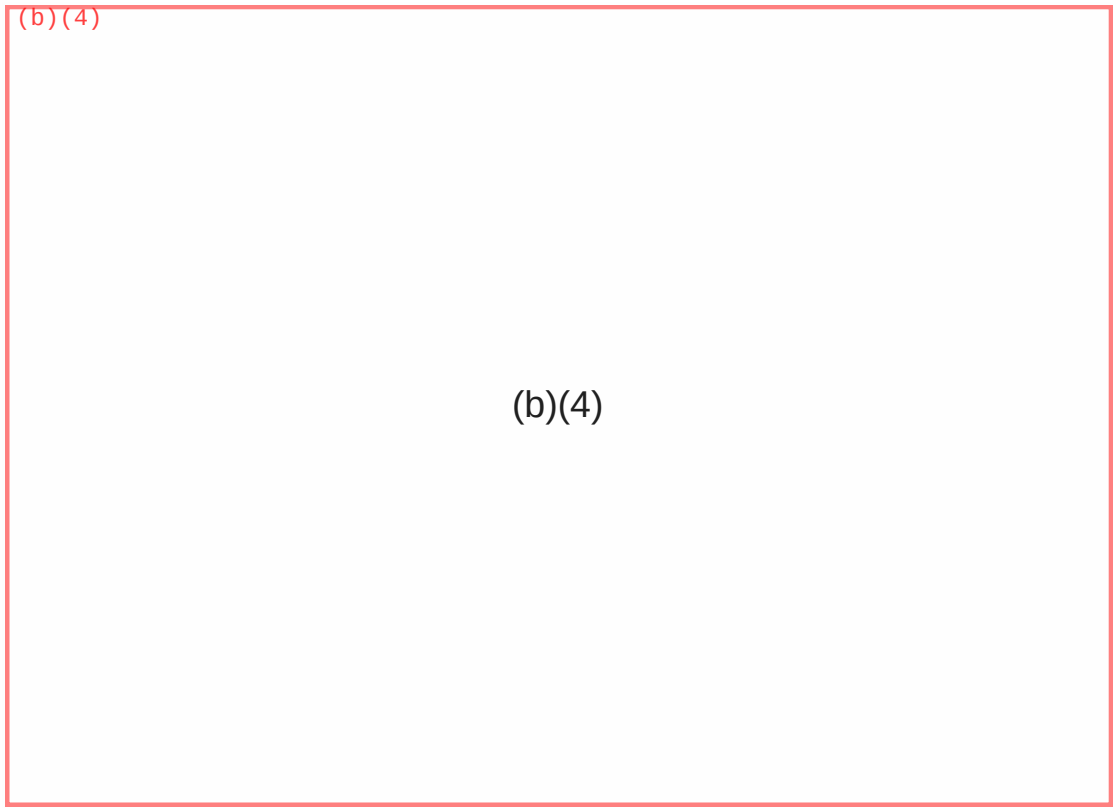

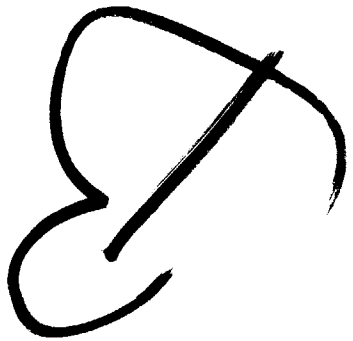

B. Quality Audit

(1) Design and implementation of the quality audit program including procedures for assessing that audits are reviewed by upper management, all appropriate areas are audited, corrective action is implemented, independence from functions audited is maintained, and auditors are qualified.

(b)(4)

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C. Buildings

(1) Methods and procedures used to assure orderly handling and to avoid mixups of components, finished devices, labeling, packaging and manufacturing materials during routine operations and storage.

(b)(4)

(b)(4)

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(b)(4)

C. Buildings

(2) Methods and procedures used to control and monitor environmental conditions when environmental conditions could adversely affect a device's fitness for use.

(b)(4)

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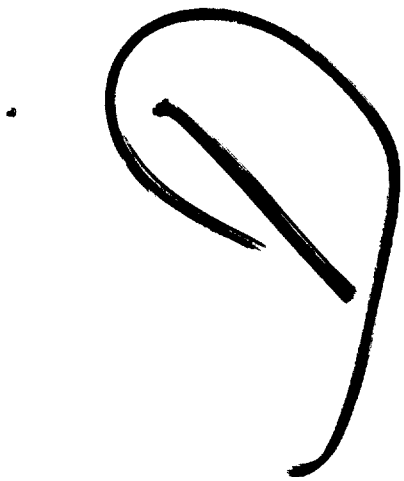
(b)(4)



D. Equipment

(1) Methods and procedures established to assure proper maintenance and calibration of equipment used for production and quality control including procedures used to assure the adequacy of automated equipment.

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E. Acceptance and Control of Components

(1) Methods and procedures used to define how purchased finished devices, components, packaging, labeling and manufacturing materials are to be inspected or verified as conforming to requirements.

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a) (b)(4)

b)

c) (b)(4)

d)

e)

f)

g) (b)(4)

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h) (b)(4)

(b)(4)

E. Acceptance and Control of Components

(2) Methods and procedures used for the identification of released, rejected, quarantined, or unchecked incoming finished devices, components, packaging, labeling and manufacturing materials.

(b)(4)

(b)(4)

E. Acceptance and Control of Components

(3) Methods/procedures used for identifying finished devices, components, labeling, packaging and manufacturing materials through all stages of production.

(b)(4)

(b)(4)

E. Acceptance and Control of Components

(4) Methods/procedures used for identifying critical components for critical devices.

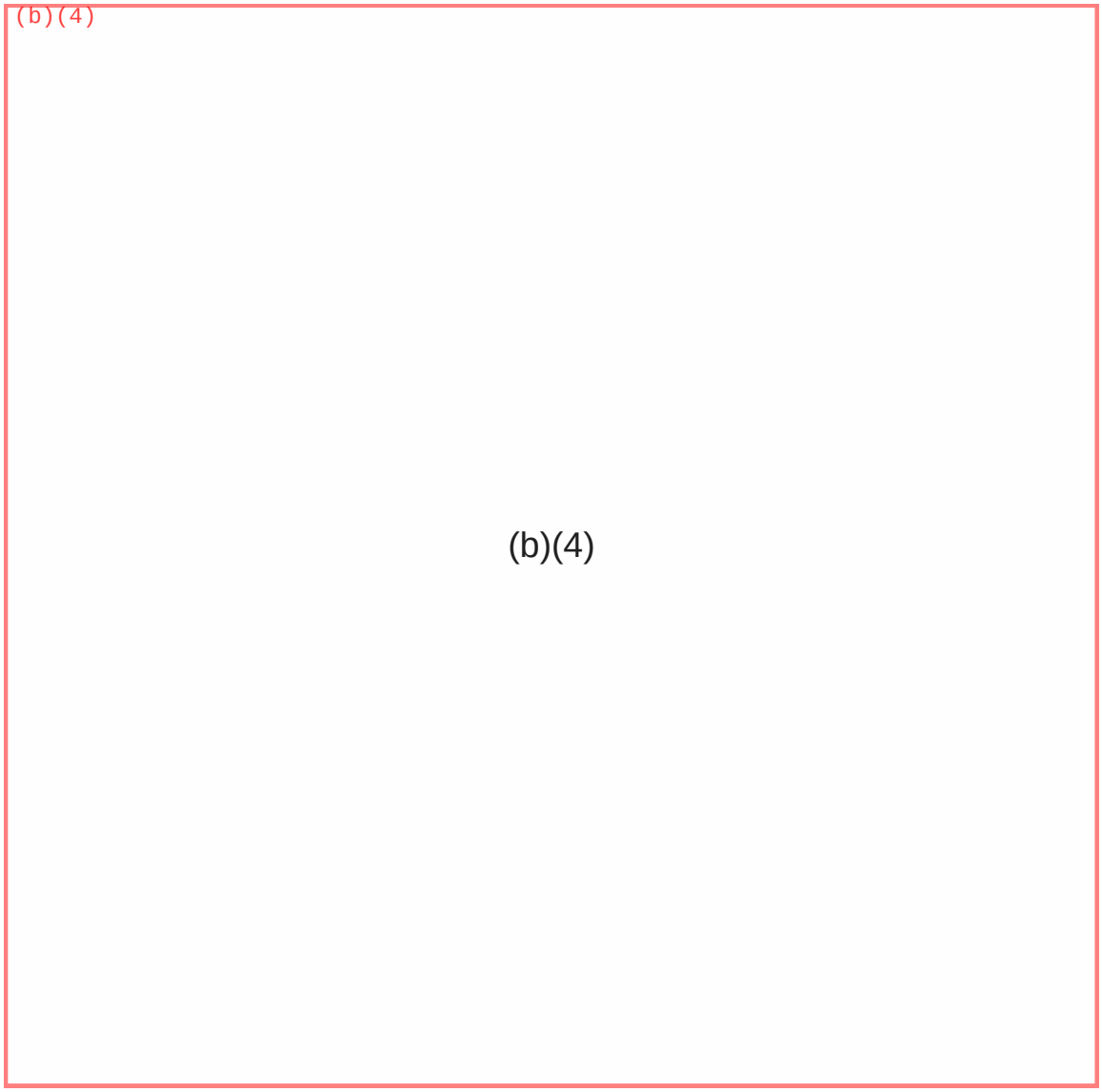
(b)(4)

(b)(4)

F. Production and Process Controls

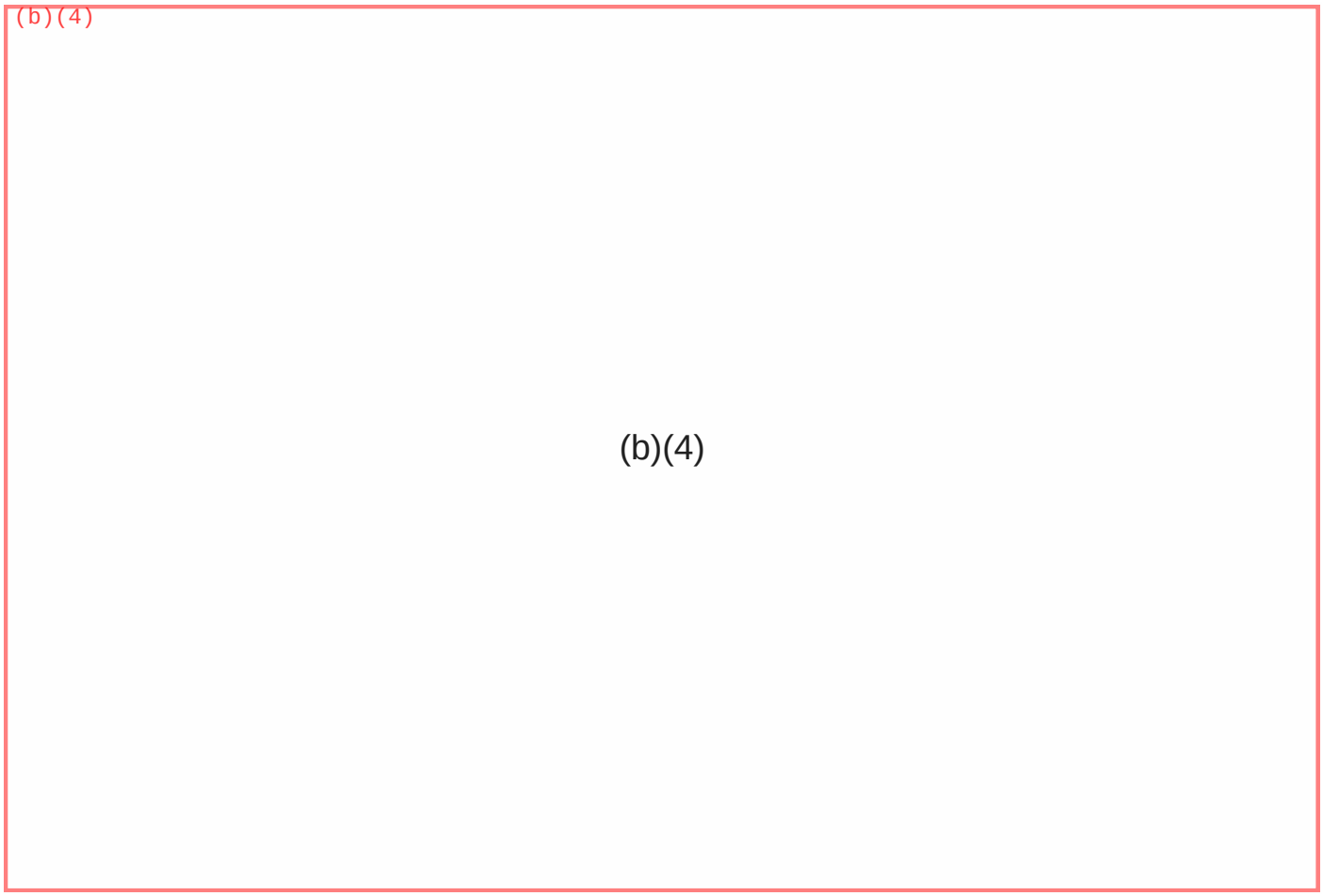
(1) Provide a flow diagram of the production process identifying all process steps.

(b)(4)



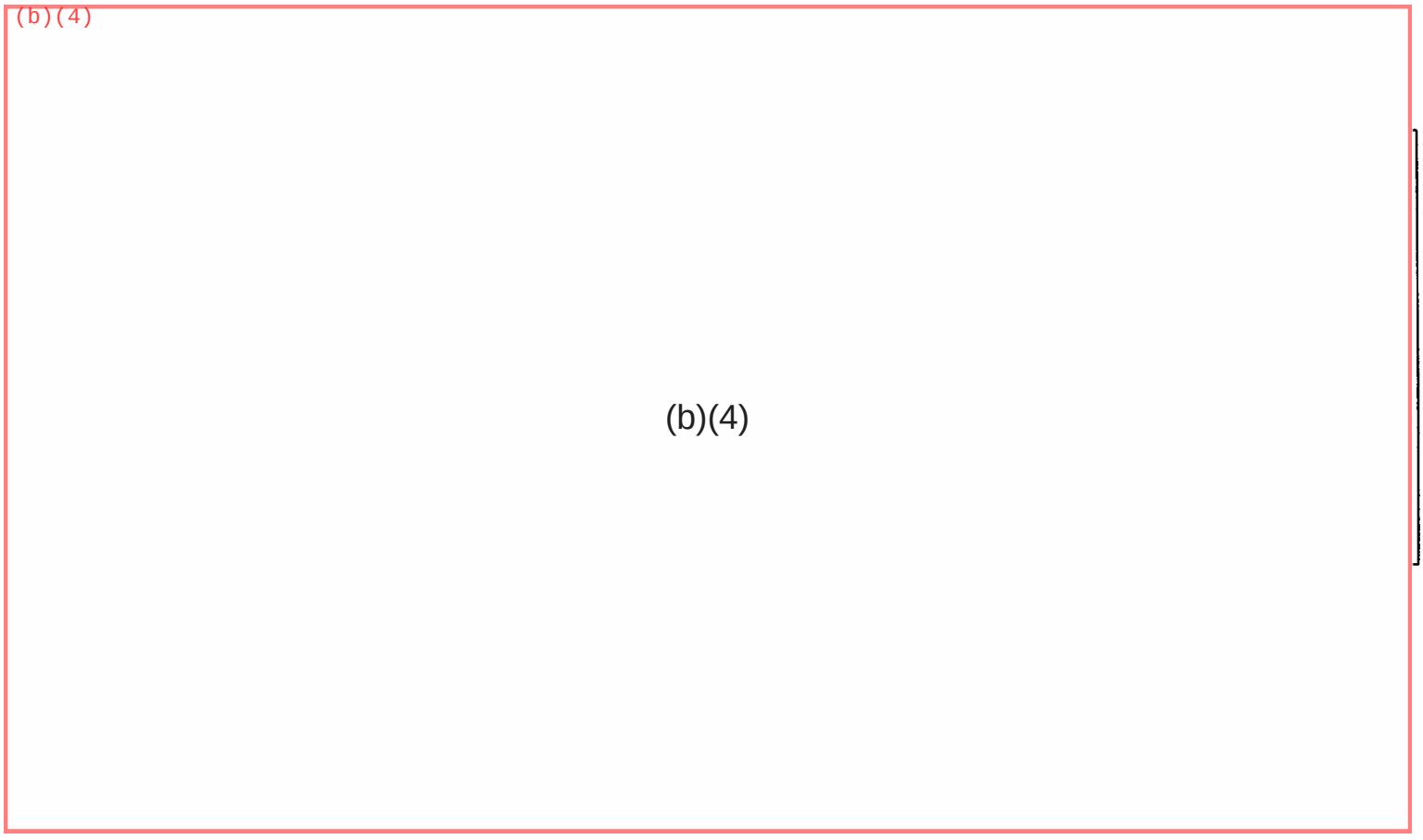
MODEL 6963 WORKCELL FLOW-CHART

(b)(4)



MODEL 6999 WORKCELL FLOW-CHART

(b)(4)



F. Production and Process Controls

(2) Methods/procedures that define and control the manner of production and installation, including work instructions and procedures for the review and control of these instructions.

(b)(4)

(b)(4)

F. Production and Process Controls

(3) Identify all significant manufacturing processes and the methods and procedures used to validate, or prove, the acceptability and stability of the processes, including validation of the methods and procedures used to monitor and control the processes after validation to assure they consistently operate within acceptable process parameters.

(b)(4)

(b)(4)

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(b)(4)

Table 1. Lead model 6963 critical and principal processes.

(b)(4)

(b)(4)

Table 1. Lead model 6999 critical and principal processes.

(b)(4)

(b)(4)

MEDTRONIC B.V. PRODUCT ASSURANCE DOCUMENT	Doc. no. : (b)(4) 3_5 Issue : A Date : (b)(4)
Title: Qualification plan of lead **Model 6963** built at ESTC	Prepared by: (b)(4) Approved by: (b)(4)

MEDTRONIC CONFIDENTIAL

(b)(4)

(b)(4) MEDTRONIC CONFIDENTIAL

1.0 PURPOSE

(b)(4)

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MEDTRONIC CONFIDENTIAL

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Attachment 2: Flow charts 6921, 6999

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F. Production and Process Controls

(4) Procedures used to assure that process changes are properly reviewed, approved and validated.

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(a) Production operation changes due to product specification changes:

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(b) Process changes not related to specification changes:

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F. Production and Process Controls

(5) Methods and procedures used to develop, identify, distribute and maintain manufacturing and quality assurance documentation including the procedures used to authorize and qualify documentation changes.

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Manufacturing Documentation (b)(4) (b)(4)

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Distribution and Disposal (b)(4) (b)(4)

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Documentation Disposal

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Additional Copies

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Rush Changes

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F. Production and Process Controls

(6) Methods/procedures used to identify and control non-conforming finished devices, components, packaging and labeling. The description should include reprocessing procedures and controls, and procedures used to investigate, identify, and correct causes of non-conformance.

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Rework Procedures and Controls

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F. Production and Process Controls

(7) Methods/procedures used to identify critical operations for critical devices.

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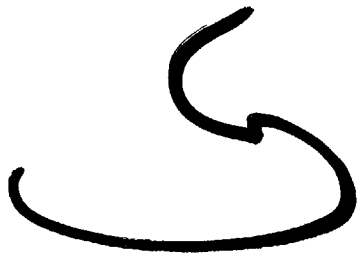
Control



G. Packaging and Labeling Control

(1) Methods/procedures used to assure that labeling received and used in production is acceptable for its intended use and to assure that there are no labeling mixups during storage and labeling operations.

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G. Packaging and Label Control

(2) Methods/procedures used to assure that packaging will protect the device during normal processing, handling, storage and distribution.

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Information Classified

H. Holding, Distribution and Installation

(1) Methods/procedures used to assure that only devices approved for release are released for distribution and that finished devices held for distribution are not adversely affected by storage conditions such as the environment or time.

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H. Holding, Distribution and Installation

(2) Methods/procedures used for critical device distribution records.

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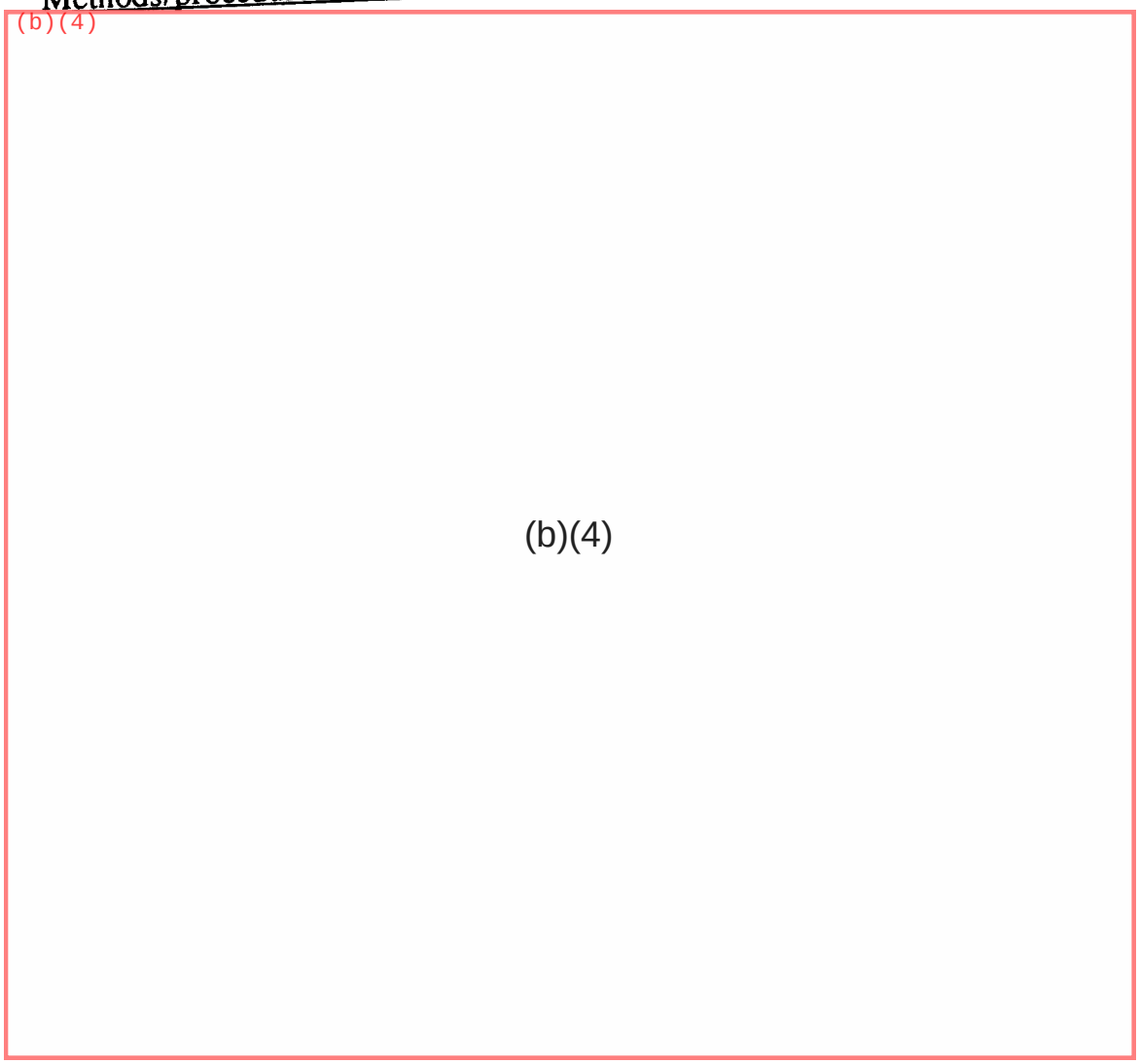

H. Holding, Distribution and Installation

(3) Methods/procedures used for installing the device, including any inspections and instructions provided.

Installation controls do not apply to the Model 6963 and 6999 leads.

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I. Device Evaluation

(1) Methods/procedures used for establishing acceptance criteria and assuring that finished devices meet approved specifications before release.

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Finished Device Inspection Procedures

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I. Device Evaluation

(2) Methods/procedures used to investigate product that fails to meet acceptance criteria, including assuring that corrective action is implemented and the records are maintained.

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I. Device Evaluation

(3) Methods/procedures used to identify, evaluate and investigate the causes of failure of devices that fail to meet requirements after distribution, including the methods/procedures used to assure that corrective action is implemented.

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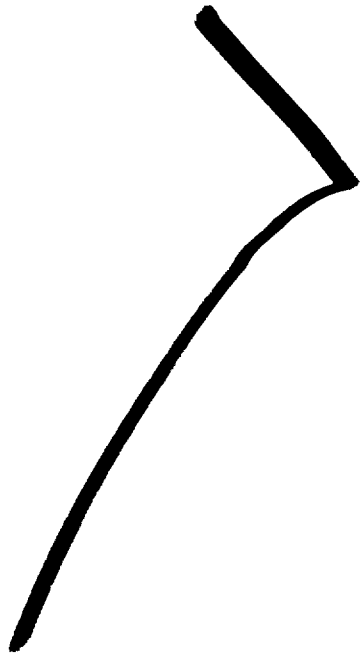

J. Records

(1) Methods/procedures used for the establishment, use and maintenance of the Device History Record. Provide copies of the records which make up the Device History Record, e.g., routing forms, data sheets, and batch records.

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Following is an example of the Product Batch Card for the Model 6963 and 6999 leads.

INITIAL BATCH QTY:
FINAL BATCH QUANTITY:

SERIAL NUMBER FROM:
TO INCLUDING: TAF . . . . . K

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