Establishment Inspection Report	FEI:	**2649622**
Medtronic Puerto Rico Operations Co.	EI Start:	10/29/2007
Villalba, PR 00766	EI End:	12/14/2007

SUMMARY

Inspection of this manufacturer of cardiac pacing leads, spinal cord stimulation systems, and cardiac electrophysiology catheters (medical devices) was conducted as part of SJN-DO FY'08 work plan and as a request from CDRH to conduct a PMA inspection for product P060039 (Medtronic Attain StarFix model 4195 lead) under assignment ID 891086 and a Post-market inspection for product P970004/S33 (InterStim Sacral Nerve Stimulator). Coverage was followed in accordance with CP 7383.001 "Medical Device Premarket and Postmarket Inspections", and CP 7382.845 "Inspection of Medical Device Manufacturers". In addition, a QSIT Level 1 (abbreviated) inspection was conducted which covered the CAPA (corrective and preventive actions) and P & PC (production and process controls) subsystems. Additional coverage was provided to evaluate voluntary class I recall Z-0067-2008 for Sprint Fidelis Leads.

Previous surveillance, Post-PMA and PMA inspection dated 3/9/06 was classified NAI and disclosed no objectionable conditions. No form FDA-483, Inspectional Observations, was issued and PMA P970004/S33 was recommended for approval.

Current inspection disclosed no significance deviations from the QSR. Two observations, which were not included in a form FDA-483, were discussed with the firm's management. These are: (1) not all the equipments involved in an out-of-specifications sterilization non-conformance were included within the scope of the corrective and preventive actions implemented; and (2) written procedure for non-conformance analysis and report is not clear as for the timeframe to log, open and/or initiate an investigation for sterilization failures after any given defect is noticed and reported as a non-conformance. Corrections were promised by the plant manager. No form FDA-483, Inspectional Observations, was issued. Inspection of PMA P060039 (Medtronic Attain StarFix model 4195 lead) found no objectionable conditions. Approval recommendation was send to SJN-DO pre-approval manager (PAM).

No refusals were encountered and no samples were collected during the inspection.

ADMINISTRATIVE DATA

Inspected firm:	Medtronic Puerto Rico Operations Co.
Location:	Carr # 149 Km 56.3 Villalba, PR 00766
Phone:	787-847-3500
FAX:	
Mailing address:	P.O. Box 6001

Villalba, PR 00766

Dates of inspection:	10/29/2007, 10/30/2007, 10/31/2007, 11/1/2007, 11/2/2007, 11/28/2007, 11/29/2007, 12/5/2007, 12/6/2007, 12/7/2007, 12/12/2007, 12/13/2007, 12/14/2007
Days in the facility:	13
Participants:	Hector J Colon Torres, Investigator

HISTORY

History of this firm remains as reported during previous inspection. Medtronic Puerto Rico Operations Co. (MPROC), located in Villalba, PR, is comprised of Medtronic Cardiac Rhythm Management (CRDM) and Medtronic Neuromodulation (Neuro and Gastro/Urology) businesses. The firm manufactures cardiac pacing leads, spinal cord stimulation systems, and cardiac electrophysiology catheters (please refer to **Exhibit #1, pages 1-2,** for a list of product families manufactured at MPROC Villalba). All the products manufactured at the Villalba plant are sterilized on-site by ethylene oxide (EtO), except for the diagnostic catheters which are sterilized by gamma radiation at (b) (4) and the urology (b) (4) products which are sterilized by EtO at (b) (4) in (b) (4) Medtronic Villalba is part of MPROC which also comprise the Juncos, PR and Humacao, PR facilities. However, each site has its own and independent Quality System.

MPROC Villalba most responsible individual is Mr. Gerardo Mari-Roca, Sr. Manufacturing Director/Plant Manager. Mr. Mari-Roca reports directly to MPROC Vice President, Mr. Manuel Santiago, who in turn reports to Mr. Brian Urke, VP CRDM Operations. **Exhibit #2, pages 1-5** includes the current organization structure for both MPROC Villalba CRDM & Neuro, and corporate.

Any official correspondence from the Agency to MPROC Villalba should be addressed to:

Medtronic Puerto Rico Operations Co.
Attn: Mr. Gerardo Mari-Roca, Plant manager
Rd. 149, Km. 56.3
Call Box 6001
Villalba, PR 00766

This firm is currently registered with FDA for 2007 under number 2649622. Please refer to **Exhibit #3, pages 1-2,** for copies of the annual registration submission dated 1/10/2007.

INTERSTATE COMMERCE

All the products manufactured at Medtronic Villalba are shipped to several distribution centers located throughout United States, Europe, and Asia. The main distribution centers are Heerlen, Netherlands, EOC Dist in Netherlands; Moundsview, MN, East Distributor in Minneapolis, MN; and San Juan, PR, Medtronic Sales Office in PR. In addition, most major components used for the manufacture of finished products come from external sources in interstate commerce.

JURISDICTION

The products manufactured at Medtronic Villalba are medical devices intended for human use. In addition, the finished devices are shipped to the United States, Europe, and Asia, though entering in interstate movement. **Exhibit #1** is a list of product families manufactured by this firm.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

On 10/29/07, I met, presented my credentials, and issued a form FDA-482, Notice of Inspection, to Mr. Gerardo Mari-Roca, who identified himself as the Sr. Manufacturing Director CRDM/Plant Manager of Medtronic Puerto Rico Operations Co., located at Villalba, PR Mr. Mari-Roca's authority was evidenced as described on the firm's Quality Manual. He also accepted the forms FDA-482, Notice of Inspection (on 10/29/07 and 11/28/07), and expressed his commitment for the voluntary corrections of the verbal observations issued during the inspection. I also observed several official documents signed by him throughout the inspection to include memorandums and notifications posted at bulletin boards.

I also met and presented my credentials to Mrs. Betsy Rosario Rivera, Sr. QA/QS Manager and Medtronic Villalba Management Representative. In addition to Mrs. Rosario I met Mr. Rafael Berly-Torres, Regulatory Compliance Manager, Mr. Miguel O. Beltrán-Delgado, Sr. QA/QS Manager for MPROC Neuromodulation business, Mr. Ricardo J. Lugo, Sr. Manufacturing Director

for MPROC Neuromodulation, and Mr. Norman Ganion, Sr. Principal Auditor (Minneapolis, MN). Mrs. Rosario, Mr. Berly, Mr. Ganion and Mr. Beltrán accompanied me throughout the inspection.

The following people were also interviewed and provided valuable information and support during the inspection:

- Mr. Norberto Rivera, Sr. Manufacturing Engineer – He explained the manufacturing process for the Medtronic Attain StarFix model 4195 lead (4195 lead).
- Mr. Roberto Murillo, QA/QS Manager – He provided information in reference to trends, non-conformances, and investigations. He also explained the Product Transfer process for the 4195 lead.
- Mrs. Wanda Alvarez, Principal Engineer – She explained the activities related to Left Heart 4195 transfer implementation, and Blue Push Tubing components qualification and visual inspection.
- Mrs. Eileen Ruiz, Laboratory Supervisor – She provided information in reference to the activities conducted at MPROC for the sterilization of the 4195 lead to include loading patterns, bioburden, endotoxin, and EtO residual testing. In addition, she explained sterilization records and charts.
- Mrs. Mayte Acevedo, Sr. Quality Engineer – She explained the activities related to CAPA 000806.
- Mr. Craig Meadows, CRDM Engineering Services Manager – He provided information in reference to sterilization.
- Mr. Erick Cuvillier, Clinical Research Director Latin America – He explained the implanting process and functioning of leads to both right and left sides of the heart.
- Mr. José Muñoz, Sr. Quality Assurance Engineer – Provided requested copies of labeling.
- Mr. Joe Dupay, Sr. Program Director – Provided information about the 4195 OUS events.
- Mrs. Vicki Bjorklund, Designer – She provided information related to designing and functional aspects of the 4195 lead.
- Mr. James Roche, Reliability Engineer – He provided information about the validated lobe deployment test, clinical studies, and statistical rationale for the acceptability of the test.

- Mr. Miguel Galarza, Quality Engineer Sterilization and Catheters – He explained sterilization issues, DPM's and investigations.

- Mrs. María Vega, Quality Control Engineer Sterilization and Final Pack – She explained the defect of "damage strain relief" on the 3830 model.

- Mrs. Gisela González, Sr. Quality Engineer, Neuromodulation – She provided information related to non-conformance investigation 07NR.042 and all related events.

- Mr. Alexis Tomassini, Manufacturing Engineer Sterilization (CRDM) – He provided information in reference to the sterilization chambers, preventive maintenance and calibration.

- Mrs. Diane Wolf, Complaint Handling Manager (Minneapolis, MN) – She provided information related to complaint reports and acronyms.

- Mrs. Iris Hernández, Sr. Manufacturing Engineer – She provided information related to the manufacturing flow of the sprint fidelis lead and the fracture defect.

FIRM'S TRAINING PROGRAM

This area was not evaluated in detail during this inspection. However, during the review of corrective and preventive actions documents it was evident that a training program is implemented as some of the corrective actions that I reviewed include training given to employees.

MANUFACTURING/DESIGN OPERATIONS

The product subject to this PMA inspection was the P060039 (Medtronic Attain StarFix model 4195 lead). I did a tour of the room where the 4195 lead is manufactured. Mr. Norberto Rivera explained in detail all manufacturing steps. The manufacturing steps for the 4195 lead are described in **Exhibit #4,** flowchart of Manufacturing Document Procedure document no. 502992-JIT, titled "4195 Lead Assembly". Design operations are conducted at the Minneapolis, MN facility of Medtronic.

COMPLAINTS

The complaints information was evaluated throughout the inspection. Samples of complaints were requested and reviewed for the evaluation of the CAPA subsystem, the PMA, and the Post-PMA portions of the inspection. Please refer to the "CAPA", "PMA", and "Post-PMA" headings of this report for details.

CORRECTIVE AND PREVENTIVE ACTIONS (CAPA)

The CAPA subsystem was evaluated as part of a QSIT Level I (Abbreviated) inspection. I requested the firm's CAPA procedures for review and found that the requirements of the quality system regulation are defined and documented. The firm identifies and analyses several sources of product and quality problems such as consumer complaints, product non-conformances, distributors' quality feedback, and internal audits among others. Upon questioning and reviewing of documents, the firm showed me that the quality data is analyzed, trends are identified and if needed CAPA's are generated and implemented. The firm uses statistical techniques such as pareto charts, spread sheets, and other non statistical techniques for data analysis. This analysis includes comparisons between data sources to establish global view of quality problems. I also requested and reviewed several written procedures related to the firm's Quality System and Quality Data Analysis (complaints, NCR's, PRR's, etc.) during the inspection.

I challenged the quality data information system by selecting several quality data sources: MDR's, NCR's (non-conformance report/investigations), consumer complaints, PRR's (Product Review Request) and process deviations. I requested a listing in electronic format of all the events from the selected sources from April 2006 through October 2007. I used the table #2 of the *Binomial Staged Sampling Plans, Row "A", Column "0 out of"* to select a (b) (4) record sample for each source. MDR activities are conducted at the headquarters located in Minneapolis, MN. In addition, I requested a total of (b) (4) GCAPA's (global CAPA's) generated and implemented since April 2006, thus increasing the sample to (b) (4) investigation records. No objectionable conditions were found.

In addition, and as part of the CAPA subsystem inspection I requested and reviewed the trending reports for all three Medtronic business (CRDM, Neuro, and Catheters) from October 2007 and going back one year.

For the sterilization level DPM (defects per million) summary, I requested the 3:1 chart for May-Sep 07; the major offenders leading to high DPM's on each of those months; and the equivalent of defect units in relation to the DPM value.

I also requested:

- NCR 07NR.074
- OCT 2007 Trend Report for cell no. 211 (Select Secure 3830 model)

I reviewed the Oct 2007 (FY 08) MPROC CRDM DPM Trend Report dated 11/12/07. A negative trend is observed on sterilization level DPM's from May-Oct 2007 for the Select Secure 3830 model in which the major contributors are "collapse accessory cavity" and "stain in outer tray". I also reviewed NCR 07NR.012 in reference to mix-up units in sterilization chambers.

Mr. Galarza explained the two defects leading to high DPM's in sterilization. He added that both defects are cosmetic and that there is no impact to the quality and functionality of the product. He showed an actual example of each defect. Product is repacked and re-sterilized. NCR 07NR.074 was opened for the investigation of the collapse defect. Corrective and preventive actions were implemented in the inner tray design. Defects reported after the implemented actions are statistically non significant compared to the expected values as per CAPA 000179.

Mr. Murillo explained the defects related to the Select Secure 3830 model that caused a DPM increase from May-Oct 2007 (b) (4) Mrs. Maria Vega explained the defect of "damage strain relief" on the 3830 model.

The evaluation of this subsystem (CAPA) resulted in the discussion of two verbal observations which are discussed in more detail in the **"Objectionable Conditions and Management Response"** section of this report.

PRODUCTION AND PROCESS CONTROLS

I choose the manufacturing process of the Attain Starfix™ 4195 for the evaluation of this subsystem. This product is also the subject for the PMA part of this inspection. I evaluated the process transfer, equipment qualifications, process validations, component qualifications, non-conformances investigations, sterilization, and training of personnel. Please refer to the "PMA Evaluation" section of this report for details.

PMA EVALUATION

The product subject to this PMA P060039 inspection was the Medtronic Attain StarFix model 4195 lead. The model 4195 is a (b) (4) (b) (4) This lead features deployable lobes for stable fixation.

On 10/29/07, I did a tour of the room where the 4195 lead is manufactured. Mr. Norberto Rivera explained in detail all manufacturing steps. I also requested the following documentation:

- Manufacturing Flowchart
- Volume of product manufactured so far for OUS (non-US markets) and since when.
- Separate complaints list for the 4195 model.
- Distribution for the 4195 in OUS.
- Product Transfer SOP
- Implementation Plan/Report
- List of trained employees
- Process Validation Plan/Report

The general qualification and validation requirements for MPROC Villalba are detailed and defined in written SOP (b) (4) The validation requirements, as defined in **Exhibit #5** are, in chronological order, the Installation Qualification, Operational Qualification, Process Qualification, and Process Validation.

I reviewed Procedure (b) (4) titled *"Product/Process/Technology Introduction"* (**Exhibit #6**) to include the implementation plan and report, documents no. (b) (4) and (b) (4) (**Exhibits #7 and #8**). (b) (6) explained the activities for the Process Validation Plan and Report. She indicated that the 4195 lead is designed to be used with any left heart device. (b) (6) (b) (6) explained all the activities related to the transfer of the product from Rice Creek, MN to the Villalba, PR facility. The Transfer Implementation Phase 1 Report (**Exhibit #8**) dated "10 JUL 06", indicates that "after completion of the activities related to the Training, Qualification Builds, Validation Builds, and Special Processes Validations at MPROC for lead model 4195, the manufacturing process (b) (4) **Exhibit #9,** titled 4195 Lead assembly) is considered qualified and can be released to production". It also indicates that the "4195 Interfacility Transfer Implementation Phase 1 is considered completed". This report also enumerates a series of manufacturing issues that occurred during the process of implementation. I informed to those present that I would require clarification on those issues during the course of the inspection as I request its pertinent documentation.

I requested and reviewed the plan and report titled "Process Qualification for Lead Model 4195 Transferred to MPROC Facility" (Please refer to **Exhibits #10 and #11**). The report dated "03 AUG 05"indicates in the conclusion section that "although the results taken from the qualification activities performed during the (b) (4) operational at MPRI showed that all units met the manufacturing processes requirement for the lead model 4195, a lead failing the reliability test (b) (4) made this process qualification failed". I requested the information in reference to the failing test.

Mr. Berly provided document no. (b) (4) titled "Product Spec – Lead, Cardiac Vein, Unipolar, Curved, Over-The-Wire, Deployable Lobes" (**Exhibit #12**). Section (b) (4) of the document describes the lobe deployment requirements (**Exhibit #12, page 6**). The (b) (4) is a reliability test conducted at Medtronic, Inc. Minneapolis, MN, to verify that the lobes can meet the (b) (4) requirements. The test requirements indicate (b) (4) the (b) (4) and (b) (4) (*note: the firm uses this word to describe the return of the lobes to their original position before deployment*) when positioned in a left heart path model

(b) (4) or (b) (4) equivalent using the following method". It also indicates that "the lead shall not be damaged after (b) (4) of full deployment and undeployment within the (b) (4) (approximately (b) (4) of the left heart path model ((b) (4) or (b) (4). This test was only conducted for qualification/validation purposes and it is not a finished product release criteria. Mr. Murillo indicated that in the manufacturing side there is indeed a (b) (4) required for product release. He indicated that the manufacturing (b) (4) is applied to all leads manufactured (100%) and consist in the (b) (4) and (b) (4) This functionality is visually confirmed by the operator in charge of conducting the test (please refer to **Exhibit #9, page 19**) .

The firm identified the root cause of the failure as "lack of adhesive over the indicator rings". The investigation, corrective and preventive actions are documented on non-conformance report (b) (4) (**Exhibit #13**). Mr. Miguel A. Galarza explained the document and provided the evidence for the corrective actions.

I requested and reviewed the documents no. (b) (4) and (b) (4) titled *"Process* (b) (4) (b) (4) *plan/report for lead model 4195 transferred to MPROC facility"* (**Exhibits #14 and #15**). After all pertinent activities were finished, the report concludes that "based on the results of the qualification and reliability testing activities performed for the lead model 4195, the manufacturing process 502992-JIT is considered qualified at MPROC facility".

I requested and reviewed the documents no. (b) (4) and (b) (4) titled, *"Process Validation Plan/Report for 4195 Lead Model –MPROC Facility"* (**Exhibits #16 and #17**). The report indicates that on "Lot (b) (4) of the (b) (4) failed the (b) (4) The lead samples did not deploy in the tortuous path model". In addition, the report concludes that (b) (4) lots will have to repeat all of the validation testing and a third lot with corrective measures in place will have to repeat the (b) (4) to meet the validation (b) (4) requirement". This is the same test that failed during the process qualification activities.

I requested the following:

- (b) (4) plan and report.
- All related information and reports in reference to the validation failures and the (b) (4) vendor corrective actions and process (b) (4)
- CAPA's and NCR's related to the 4195 model.

The firm found that engineering analysis of passed and failed validation test samples showed the deployment failures were related to non-uniformity in the coating along the length of the push tubing in the failed samples compared to uniform coating on passed samples, as stated by (b) (6) (b) (6) in her memo dated (b) (4) and titled "(b) (4) (b) (4) (**Exhibit #18**). This document number (b) (4) was created upon my request on (b) (4) as an aid to (b) (4) issue and all related activities. This document indicates the problem extension, background, root cause, corrective and preventive actions, risk assessment, and conclusions.

As a result of this finding, a corrective action was implemented at the inspection level of the component at the supplier (Medtronic Energy and Component Center – MECC) facility in Rice Creek, MN. I reviewed document number (b) (4) titled *"Inspection of* (b) (4) *Coated Tubing"* (**Exhibit #19**). This document explains in detail all the inspectional steps for the tubing component which will be further used in the manufacture of the 4195 lead at MPROC, Villalba.

I requested and reviewed documents number (b) (4) and (b) (4) titled *"Process* (b) (4) (b) (4) *Plan/Report for 4195 Lead Model – MPROC Facility"* (**Exhibit #20 and #21**). When the firm found that the root cause of the (b) (4) failures was at the component level, a (b) (4) (b) (4) of the process was performed at the manufacturing level in MPROC, Villalba. The (b) (4) (b) (4) report indicates that "based on the validation results, the 4195 lead model assembly process is considered validated at MPROC manufacturing facility". In addition, it indicates that "further qualification of the addition of the visual inspection control measure for the blue push tubing will be completed per the test plan (b) (4). This is in reference to the qualification conducted for the verification of the corrective action recommended and implemented at the vendor (MECC).

I requested and reviewed documents number (b) (4) and (b) (4) titled *"Qualification Plan/Report for Visual Inspection for Push Tubing Coating – Model 4195"* (**Exhibit #22 and #23**). After all the activities were conducted the report concludes that "the addition of the visual inspection method is not qualified based on the failure to meet the acceptance requirements for (b) (4) cycles and required (b) (4) sets". In addition, the report mentions that "in the case of qualification run (b) (4) of the (b) (4) failed the lobe deployment test. For qualification run (b) (4) of the (b) (4) samples did not pass the lobe deployment test. In some instances, the lead sample did not meet the requirement that all (b) (4) must (b) (4) For other samples, (b) (4) (b) (4) occurred, but failed to meet the (b) (4) This was the third time the samples failed to pass the (b) (4) even after corrective actions were implemented.

I requested the following:

- Investigation reports from rice creek (Medtronic Energy and Component Center – MECC) internal supplier addressing the failures, root cause and corrective and preventive actions implemented.
- Product specifications (Doc. No. (b) (4) revisions effective at the moment of both validation failures.

The push tubing vendor investigated the coating process (reference document no. (b) (4) (b) (4) please refer to **Exhibit #24**) and through an iterative process described in the project plan, improved the uniformity of the push tubing coating. The compilation of the process adjustments was re-qualified and validated at the component level at the vendor (reference document no. (b) (4) – Process Qualification of (b) (4)

and (b) (4) – 4195 Plan, **Exhibit #25,** and document no. (b) (4) – 4195 (b) (4) and (b) (4) Qualification Report – Overall Length Feature, **Exhibit #26/** document no. (b) (4) Process Qualification of (b) (4) and (b) (4) – 4195 Report, **Exhibit #27**). The tubing manufactured with the revalidated manufacturing process was subsequently qualified in the final assembly configuration to confirm that the vendor process improvements successfully resolved the functional requirement for lobe deployment on (b) (4) (reference document no. (b) (4) tubing component qualification report). I reviewed Doc. No. (b) (4) (b) (4) (b) (4) (b) (6) explained the document and indicated that it explains the root cause of the failure and the activities set as deliverables and exception for the project.

I requested and reviewed the (b) (4) documents no. (b) (4) and (b) (4) **Exhibits #28 and #29**). (b) (6) explained the activities related to these documents. The report indicates that "based on the component qualification results, the (b) (4) component from the updated component manufacturing process is considered qualified for use on the 4195 lead model". The report also indicates that "all samples passed the (b) (4) requirement. Leads passed the requirement with no anomalies noted during the testing. No additional anomalies were seen on the samples after the (b) (4) (b) (4)

After reviewing these reports I asked (b) (6) and all those present to explain why the (b) (4) (b) (4) requirement was changed from (b) (4) of (b) (4) and (b) (4) (b) (4) I indicated that during the qualification/validation activities, the lobe deployment test failed three times with a requirement of (b) (4) and then passed when the requirement was reduced to (b) (4) (b) (4) I requested copy of the product specifications version at the time of the qualifications/validation. I reviewed the 4195 product specifications, revisions G (**Exhibit #30**) and H (**Exhibit #31**). A change in the lobe deployment requirements was implemented between both revisions. Revision (b) (4) section (b) (4) indicates (b) (4) of (b) (4) and (b) (4) while Revision (b) (4) section (b) (4) indicates (b) (4) This test was the one that failed in the process validation and then in the (b) (4) qualification after corrective actions were implemented. I requested a written justification explaining the change of the test specifications/requirements from (b) (4)

I also requested the following:

- Indications for use (labeling) for the 4195 lead.
- Specifics about the (b) (4) reliability testing to include the conditions under which the test is performed.
- Specifics in terms of corrective and preventive actions as well as health risk assessment for the particular failure of (b) (4) and (b) (4)

I evaluated three NCR's (non-conformance investigations), one CAPA and several (b) (4) – US) consumer complaints, referred by the firm as "events". I reviewed NCR's no. (b) (4) (b) (4) and (b) (4) Mrs. Mayte Acevedo, Sr. Quality Engineer explained the activities

related to CAPA 000806. In addition, from the (b) (4) complaint list I selected a total of (b) (4) "events" for review. The events numbers are: (b) (4) for device ID (b) (4) (for ID (b) (4) (b) (4) (b) (4) and (b) (4) All the selected events are associated to lobe deployment issues and are from already OUS marketed devices or from US clinical studies.

Mr. Jose Muñoz provided a copy of the Attain Starfix™ 4195 directions manual (**Exhibit #32**). The directions for use section of this manual (section 6, pages 8-17) do not indicate a maximum for deployment/undeployment of the lobes of the lead when implanted or relocated. He added that the directions for use for the subject PMA will be similar to those on the OUS product.

Mr. Ganion provided a copy of document number (b) (4) titled "FMEA for Lead Model 4195" (**Exhibit #33**). This document shows the Failure Modes and Effects Analysis for the 4195 model. Product FMEA demonstrates high RPN's for each failure mode referencing (b) (4) or (b) (4)

I expressed my concerns with the effectiveness of the corrective actions. I indicated to all present that "events" related to problems with the deployment/undeployment keep reporting for the already distributed 4195 OUS leads. In addition, the directions for use are not clear in terms of how many times or cycles could be applied to (b) (4) the (b) (4) of the lead when implanted and/or relocated. Mr. Ganion indicated that a component characterization project was conducted to support the final component qualification and process validation. He provided copies of document number (b) (4) titled (b) (4) (b) (4) (**Exhibit #34**) and number (b) (4) titled (b) (4) (b) (4) (**Exhibit #35**).

Mr. James Roche provided, via e-mail, the specifics about the lobe deployment reliability testing to include the conditions under which the test is performed (please refer to **Exhibit #36**).

In reference to the complaints or "events" Mr. Ganion indicated that all product returns are reported as events even if the device was not used. He mentioned that sometimes the whole system is returned and all components of the system are also reported within the event complaint. Mr. Joe Dupay explained that the OUS events for the 4195 lead in reference to (b) (4) are not related to the blue tubing coating which was the main corrective action implemented during process validation. He mentioned that the returns and deployment events have been decreasing and none have been reported since 5/07. He indicated that the OUS experiences have show the importance of good physician training. He added that for the US lead there will be a mandatory training for representatives prior to receiving the product for sale and a required physician training that will be completed prior to a first implant. Mr. Dupay provided a written summary of "experiences" on 4195 (b) (4) In this report he explains the reported events, the no relation between the events and the coating issues, and the next steps for US release. He concludes that "there is no data to suggest that the field experiences seen to date (up-to-date) are related to the original coating

validation issues" and that "the corrective actions and subsequent passing validation appears effective". (Please refer to **Exhibit #37**).

In terms of the justification to change the lobe deployment test requirements from (b) (4) (b) (4) Mr. James Roche indicated that there is a (b) (4) of probability that a Physician will not exceed (b) (4) This was determined by clinical studies that showed that the mean for the number of times the (b) (4) were (b) (4) for each unique model 4195 lead was (b) (4) Based on the mean plus (b) (4) standard deviations the (b) (4) cycles was calculated and set to (b) (4) He added, in reference to my concern about the directions for use, that due to the high probability for the physicians to (b) (4) of (b) (4) during an implant and/or relocation of the lead, there is no need to indicate a maximum number in the directions for use of this product. Mr. Roche provided a written rationale describing the above (**Exhibit #38**).

Sterilization

I requested the following:

- Sterilization activities and related documentation for the 4195 model.
- Specifics on the equivalency of sterilization for Qualification processes at Rice Creek vs Villalba plus equivalency between the 4195 and the 4193 model that was used as comparison.

I reviewed the Microbial Qualification for lead model 4195 manufactured at Medtronic Villalba Plan/Report (b) (4) I also requested and reviewed the Sterilization Qualification Protocol and Report for the 4195 (Rice Creeek). Mr. Craig Meadows and Mrs. Eileen Ruiz explained the justification in reference to the similarities between the 4195 model and other leads. They also showed the evidence in reference to the worst case lead processed at the Villalba facility and how the 4195 falls into the same procedure. They indicated that all CDRM leads are sterilized under the same procedure and parameters.

I also reviewed procedure no (b) (4), titled (b) (4) of product for (b) (4) Mrs. Ruiz explained the activities to include loading patterns for the 4195. I also reviewed the Sterilization Certification Report (b) (4) Doc. No. (b) (4) which show all the loading configurations and aeration times for all CDRM lead products. No significant objectionable conditions were observed.

POSTMARKET EVALUATION

The product subject to this Post-PMA inspection was the P970004/S33 InterStim® Sacral Nerve Stimulator (a system comprised of various finished devices working together). Medtronic Villalba is

engaged in the manufacture of the leads (finished device) used in this system. Other finished devices used together as part of this system are manufactured at the Juncos, PR plant.

As part of the evaluation of the subject product, I requested and reviewed the following documents:

- List of consumer complaints since PMA approval.
- Manufacturing and sales volumes since approval.
- List of changes since approval.
- List of qualifications/validations since approval.
- Copies of all protocols and reports for qualifications/validations for models 3093 and 3889 since approval.
- For manufacturing process no. (b) (4) copy of versions (b) (4) and (b) (4) For no. (b) (4) (b) (4) copy of versions (b) (4) and (b) (4)

I reviewed the documentation for the process/document changes implemented since approval. I also reviewed the Qualifications/Validations No. (b) (4) and (b) (4) for laser equipment (b) (4) and (b) (4) for laser equipment (b) (4) and Master Validation Plan/Report no. (b) (4) and (b) (4) for equipments relocation.

I selected a total of 15 PCR's (Product Comment Report - complaints for Neuromodulation business) from the list of consumer complaints since the PMA approval. The PCR numbers are: (b) (4) (b) (4) (b) (4) and (b) (4)

I also requested one set of labeling for both models being evaluated for Post-PMA, P97004/S33 (**Exhibit #39**). Mr. Beltran provided all the documentation I requested. No objectionable conditions were observed upon evaluation of post market activities and data for the InterStim® Sacral Nerve Stimulator model.

RECALL PROCEDURES

During this inspection I covered Class I recall Z-0067-2008 for Sprint Fidelis Leads. The firm found lead breaks (fractures) resulting in inappropriate shocks and hence loss of adequate therapy. This product was subject to a voluntary recall initiated by the firm on 10/7/07. At the time of the closing of this inspection, an FDA investigation was still in progress at Medtronic headquarters in Minneapolis, MN.

This product has four different models: 6930, 6931, 6948, and 6949. The manufacturing of these lead began about 3-4 years ago. The 6949 is the lead with the highest sales volume and it is also the model with the highest number of reported complaints. The chronic conductor fracture was

identified by Medtronic headquarters to be the cause of the failures which triggered the product recall.

I requested the following:

- Process flow chart (for the 6949 model, **Exhibit #40**).
- List of PRR's related to fractures/test failures.
- Trend report for defect related to fracture in Fidelis models since two years ago.
- Description of all four conductors for the 6949 and 6948 models (for the 6930 and 6931 models, three conductors only)
- List of SCAR's (Supplier Corrective Action Request) for conductors used in Fidelis models

(b) (6) explained the manufacturing process and the fracture defect. She indicated that the Fidelis models are smaller in diameter than other leads manufactured at the Villalba plant. She also indicated that the (b) (4) and (b) (4) cables are unique to the Fidelis family. Mr. Murillo indicated that all leads are 100% tested for resistance and intermittency. He added that these tests will capture any defects on the leads that might be caused by fractures.

Complaints are handled at a corporate level in Minneapolis, MN. MPROC, Villalba receives for investigation only those deemed to be related to manufacturing issues but have access to all within the (b) (4) database. Upon receipt, an (b) (4) (b) (4) is generated. There has been no (b) (4) generated related to fractures in Fidelis. Mr. Murillo and Mr. Ganion indicated that manufacturing process has been ruled as one possible cause of the fracture failures.

The raw material, supplier audits, and supplier corrective actions and investigations are handled by a group/department called SQA (Supplier Quality Assurance). This group is mainly located at the MPROC Juncos facility but their work extends to all three MPROC facilities in Puerto Rico (Juncos, Villalba, and Humacao). The group is composed by a SQA Director, Sr. QA's and inspectors (Juncos facility only).

(b) (6) provided a list of components used in the manufacture of Fidelis models. All part numbers are unique to the Fidelis family except for part no. (b) (4) which is the sense cable (b) (4). This cable is also used by the (b) (4) models. The Fidelis models are a new generation of the (b) (4)

Only (b) (4) have been generated. Both are not manufacturing related but instead for mix-up problems. I requested and reviewed (b) (4) and (b) (4) No deficiencies were noted.

MPROC Villalba discontinued the manufacturing and distribution of the Sprint Fidelis leads when Medtronic headquarters decided to voluntarily recall the leads. LPHO (Local Product Hold Order) no. (b) (4) (**Exhibit #41**) was generated and (b) (4) finished units were placed in SPNFG (Stop Processing Notice Finished Good). In addition, several components at the assembly level were also placed on hold (**Exhibit #42**). The final disposition for these products will be scrap.

I requested and reviewed the following six PRR's related to resistance and intermittency failures involving Fidelis models: V012059, V005766, V008084, V008114, V008223, and V008642. Mr. Murillo explained the documents. No objectionable conditions were observed.

I also requested for review non-conformance report no. (b) (4) Mr. Murillo explained the PRR's, defect trend reports and (b) (4) He mentioned that the defect was related to the crimping of the cross groove and the tooling in use. He added that the problem was causing high resistance. He also mentioned that it is not related to fracture problems leading to recall Fidelis, which ruled out as being manufacturing related. I reviewed the trend reports showing resistance and intermittency defects as major contributors for high DPM's. All of them were addressed on (b) (4) (b) (4)

Mr. Murillo explained that fractures are caused mostly by mishandling of the leads by the physicians during implant. He indicated that during the process they inspect 100% for resistance and intermittency, 100% verification of crimp indentations, and pull strength sample test.

I visited the room where all the Fidelis (both finished and unfinished) models are stored awaiting disposition. All products are already in scrap status in the system. Mrs. Rosario and Mr. Ganion indicated that the "how" and "when" of the final disposition is not yet determined and that the decision will come from headquarters and firm lawyers when all FDA inspections are finished.

I also reviewed CAPA 000778 which is related to contamination of raw material. I also reviewed (b) (4) which is related to damage inner coil and was deemed as an isolated event due to operator technique. Finally, I reviewed (b) (4) which is related to training and qualification activities. No objectionable conditions were observed.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

The following verbal observations were discussed with firm's management during the inspection:

1- **Not all the equipments involved in an out-of-specifications sterilization non-conformance were included within the scope of the corrective and preventive actions implemented.**

During the evaluation of nonconformance report number (b) (4) (**Exhibit #43**) and all pertinent documentation, I noticed that corrective and preventive actions were not implemented to all sterilizers involved in the incidents.

On 12/6/07, I requested and reviewed nonconformance report (b) (4) The "final report" version was dated (b) (4). The report was originally opened for the investigation of an incident dated 9/20/06 and described as "ETO gas concentration was lower than specifications at the end of the exposure phase". Since then, four more incidents involving seven more lots have happened and are summarized in the following table. A Product Review Request or PRR was generated as per written procedures for each of the five incidents as showed in the table below. Please refer to **Exhibits #44, # 45, # 46, # 47, # 48, #49, and #50,** for copies of the PRR's mentioned below.

Incident Date	PRR No.	Lot No.	Model	Quantity Affected	Sterilizer /Sterilizer Lot No.	Actual Value EtO Conc. (mg/l)	Specification Eto Conc.(mg/l)
1) 9/20/06	V000230	V012545	3387S-40	47	45 / V6263453	(b) (4)	
2) 11/28/06	0634468V	J0664512V	5076-52	73	22 / V6326224		
3) 12/28/06	V000580	V017927	3998-28	39	44 / V6362442		
4) 1/24/07	V001295 V001296 V001297	V019424 V019449 V019739	3888-33 3887-33 3387-28	44	39 / V7024392		
5) 4/25/07	V004791	V032588	3387-40	27	39 / 7115393		

During my review of related documentation, I noticed that lot no. V032588 from incident #5 was initially found out-of-specifications for EtO concentration (**Exhibit #51,** "Process Inspection Checklist For (b) (4) but upon further reevaluation of the sterilization chart (which is the official record of choice) the lot was found within parameters. However, (b) (4) includes a second lot no. V032336. This lot was found to be OOS with an actual value of (b) (4) (b) (4) This lot is not mentioned within the investigation documentation (b) (4)

I requested for review all the evidence related to the OOS and the disposition for all eight lots involved. PRR's for each indicates that lots from incidents (b) (4) were (b) (4) and lots from incident # were disposed as (b) (4)

(b) (6) clarified that sterilization lot number V7115391 corresponds to lot V03233 only. She mentioned that lot no. V032637 documented on the sterilization process record is a "monitor" number assigned by the system (b) (4) which is part of the routing process of the device. (b) (6) indicated that a monitor number is automatically assigned to a lot when other activities, such as reviews, testing, etc., are pending and the manufacturing process shall continue. Please refer to **Exhibit #52**, for copy of the "Sterilization and Aeration Process Record" for lot no. V7115391, which indicates that lot no. V032637 was rejected due to "ETO gas concentration out of specifications".

(b) (6) indicated that for incident #5 the lots identified on the PRR were disposed as (b) (4) after investigation showed that all parameters were met and that the problem was identified as to be the sensor which was found out of tolerance (OOT). I requested and reviewed the documentation in reference to the OOT (**Exhibit #53**) and the rationale used in the calculations that indicates that the lots involved were indeed within specification (**Exhibit #54**). The sensor (b) (4) was found out of specifications and it was calibrated on 4/27/07 (**Exhibit #55**).

The (b) (4) was logged on (b) (4) The initial report dated '(b) (4) assesses the incident occurred on (b) (4) The ETO sensor was calibrated as corrective action. The product was re-sterilized. An update to the NCR was documented on (b) (4) (**Exhibit #56**). This update added the incidents (b) (4) and (b) (4) to the investigation.

During the evaluation of nonconformance report number (b) (4) (**Exhibit #43**) and all pertinent documentation, I noticed that corrective and preventive actions were not implemented to all sterilizers involved in the incidents as follows:

1- Another update was documented on '(b) (4) (**Exhibit #57**). This update identified new corrective actions since previous ones were not effective. One of the corrective actions was "ETO sensors calibration files for sterilizer (b) (4) will be checked to investigate calibration results". This action only identified sterilizer (b) (4) Other sterilizers involved (b) (4) were not included in the corrective action. In addition, preventive actions were not identified for sterilizers not showing the problem but performing the same process. Mr. Murillo and Mr. Ganion indicated that sterilizer (b) (4) was tagged because it was involved in incident (b) (4) and the sensor was "suspected" to be out of tolerance. They added that the sensor of sterilizer (b) (4) was indeed found OOT and that was the reason for the corrective action to be specific for that sensor only. I verified the dates and found that sensor from sterilizer (b) (4) was found OOT on 4/26/07 (**Exhibit #53, and #55**), which is seven days after the corrective action was identified (4/19/07).

2- Following update was dated (b) (4) and documented as "Final Report" (**Exhibit #58**). Additional corrective actions were recommended. Actions taken to identify root cause include "evaluate ETO sensors historical data to evaluate if calibration time frame can be challenge". This action was completed on (b) (4) (**Exhibit #59**) in which an evaluation was conducted at technical services files for sterilizers: (b) (4) (b) (4) and (b) (4) Mr. Berly provided a table showing all sterilizers at MPROC with its corresponding MPR number (**Exhibit #60**). The sterilizers included in the evaluation were (b) (4) and (b) (4) These sterilizers belong to the (b) (4) business. The sterilizers from CDRM were not included within the scope of this action taken.

Another update dated (b) (4) was also documented as "Final Report" (**Exhibit #61**). ETO sensors calibration timeframe and ETO cartridges were identified as possible root causes of this discrepancy. However, Mr. Beltran indicated that the real root cause have not been identified yet. For that reason a characterization study is being performed in order to test if the EtO cartridges that weight less than 152 grams comply with the net weight requirements range of (b) (4) (**Exhibit #62**).

(b) (6) Mr. Berly, and Mr. Ganion acknowledge the observation. Mr. Berly indicated that the Non-Conformance procedure has been updated and improved some time ago. He added that the current version will be updated to be clearer and to reflect changes based on the inspectional observations. Mr. Ganion agreed and added that any detail or concern expressed during the inspection will be considered for further improvements in any pertinent area or procedure.

On 12/14/07, during the inspection closeout, Mr. Berly provided a copy of a draft version for the updated Non-Conformance Analysis and Report written procedure (**Exhibit #63**) and added that more changes will be added. I indicated that any corrections will be verified during the next inspection.

2- **Written procedure for non-conformance analysis and report is not clear as for the timeframe to log, open and/or initiate an investigation for sterilization failures after any given defect is noticed and reported as a non-conformance.**

On 12/7/07, during the evaluation of the documentation pertinent to the five sterilization incidents referenced on non-conformance report (b) (4) (please refer to previous observation), I noticed a deviation from written procedures and procedures unclear. The incident #2 reported on 11/22/06 (**Exhibit #45**) and rejected on 11/28/06 was not "logged" until 1/10/07 as non-conformance report (b) (4) (**Exhibit #64**).

Written procedure no. (b) (4) titled Non-Conformance Analysis and Report (**Exhibit #65**), indicates on section (b) (4) that "for all sterilization failures that require PRB activity, an investigation and report will be issued". This investigation and report is a non-conformance report or NCR. A PRB is a "designed area to evaluate PRR", and a PRR is a "product review request", which is an initial assessment of a non-conformance by a designated person or group. An NCR is a higher level tool for investigations of non-conformances.

An NCR follows a PRR if the incident needs to be escalated for a more complete and detailed investigation. Written procedure no. (b) (4) titled "Handling of Nonconforming Product" (**Exhibit #66**), indicates on section 1.1 that a PRR form will be filled out and logged (section (b) (4) after segregation of nonconforming product. In addition, section (b) (4) indicates that the "form shall be filled out no later than three working days after the unit(s) is/are rejected".

For sterilization failures specifically, written procedure no. (b) (4), titled "Corrective and Preventive Action System" (**Exhibit #67**), designates on section (b) (4), table (b) (4) magnitude for (b) (4). The same table indicates that for these instances to (b) (4) which is the Non-Conformance Analysis and Report procedure. Mr. Berly indicated that for sterilization failures the procedure requires to initiate a nonconformance (NCR) investigation, thus escalating the investigation directly to a level higher than a PRR.

Given this, for the job rejected on 11/28/06, an NCR was logged on 1/10/07, approximately (b) (4). Written procedure no. (b) (4) titled Non-Conformance Analysis and Report (**Exhibit #65**), does not provide for timeframes to log, open and/or initiate an investigation (NCR) for sterilization failures after any given defect is noticed and reported as a non-conformance or PRR.

Mr. Berly and Mr. Murillo indicated that for this specific incident, (b) (4) was generated (**Exhibit #45**) and a NCR was indeed logged into the "Non-conformance Report Index" on (b) (4) with number (b) (4) (**Exhibit #64**). Mr. Murillo indicated that the NCR was voided on (b) (4) (**Exhibit #68**) as the issue would be covered, investigated, and documented as part of NCR number (b) (4), which was logged on 9/26/06 and initially reported on 10/16/06 (**Exhibit #43**).

I indicated to them that as per procedures, any sterilization failure will require a higher level investigation or NCR. I also indicated that at the moment of the incident there was no assurance that the issue was similar to the one covered by (b) (4) I added that approximately (b) (4) after the incident an NCR was logged and initiated, and that this is a very long period of time compared to the three day timeframe for PRR's which are, besides an initial containment action, a less stringent investigational tool. I also reiterated that written procedure no. (b) (4) titled Non-Conformance Analysis and Report

(**Exhibit #65**), does not provide for timeframes to log, open and/or initiate an investigation (NCR) for sterilization failures after any given defect is noticed and reported as a non-conformance or PRR.

(b) (6) Mr. Berly, and Mr. Ganion acknowledge the observation. Mr. Berly indicated that the Non-Conformance procedure has been updated and improved since some time ago. He added that the current version will be updated to be clearer and to reflect changes based on the inspectional observations. Mr. Ganion agreed and added that any detail or concern expressed during the inspection will be considered for further improvements in any pertinent area or procedure.

On 12/14/07, during the inspection closeout, Mr. Berly provided a copy of a draft version for the updated Non-Conformance Analysis and Report written procedure (**Exhibit #63**) and added that more changes will be added. I indicated that the corrections taken will be verified during the next inspection.

REFUSALS

No refusals were encountered during this inspection.

GENERAL DISCUSSION WITH MANAGEMENT

On 12/14/07, I held a closing meeting with Medtronic Puerto Rico Operations, Co. officials in which I explained all the activities performed during my inspection. Present during the meeting were Mr. Gerardo Mari-Roca, Plant Manager, Mrs. Betsy Rosario, Sr. QA/QS Manager, Mr. Rafael Berly-Torres, Regulatory Compliance Manager, Mr. Miguel O. Beltrán-Delgado, Sr. QA/QS Manager for MPROC Juncos, Mr. Norman Ganion, Sr. Principal Auditor (Minneapolis, MN) plus several other managers and section heads. Please refer to **Exhibit #69,** for the attendance sheet of the closing meeting. Two verbal observations were indicated and discussed. Mr. Mari-Roca and Mr. Ganion expressed their commitment to voluntary correct the observations immediately. Mr. Berly provided a draft copy of the new version of the NCR written procedure which will address part of the observations. I took this opportunity to address on the importance of good communication and documentation practices between businesses units in the work place, for example, CDRM and Neuromodulation. I also stressed on the importance of implementing corrective actions which may apply to other similar situations. Please refer to the "Objectionable Conditions and Management Response" section of this report for details.

I reminded Mr. Mari-Roca that even though the current inspection disclosed only two verbal observations, his firm is still responsible to comply with all the regulations pertinent to their

operations as the current inspection was not an all-inclusive inspection and it only covered part of the whole quality system. I also indicated that legal sanctions including seizure, injunction, civil money penalties and prosecution are available to FDA if establishments do not voluntarily correct serious conditions. No other issues were discussed and I closed the inspection.

SAMPLES COLLECTED

No samples were collected during this inspection.

LTJG Hector J Colon Torres, Investigator
SJN-DO, Ponce RP