

Special Controls

SPECIAL CONTROLS MATRIX

Risks/Hazards	SPECIAL CONTROLS						
	Common				Additional		
	Guidance	Data	Standards	Labeling	Certification	Device Model	Tracking
Adverse Biological Response (Implant)	X	X	ISO 10993		X		registry
Wrong Therapeutic Dose (Device Malfunction)		Perfor- mance	X		X		
Wrong Therapeutic Dose (Use Error)		Human Factors		labeling	X	X	
Electrical Hazard		X	IEC 601		X		
EMC	X	X	X	labeling			
Sterility Issues	X	X	X	instructions	X		X
Device Reliability	X	X	X	maintenance instructions			X
New Implant Material	X	animal clinical postmarket	ISO 10993				registry

DRAFT

Center for Devices and Radiological Health

Parent Page	Device Advice Home	Device Advice Assistance & Help	DSMA Home	CDRH Home	FDA Home	FDA Search	CDRH Comments
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Postmarket Surveillance Studies

(This page last updated: June 8, 1998)

Page 3.5.2 describes postmarket surveillance study requirements.

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This page is currently being revised to include provisions of the FDA Modernization Act of 1997 (*the Modernization Act*) and resultant CDRH re-engineering efforts. In the interim, supplementary information and guidance on this topic area can be found in the "Overview of FDA Modernization Act of 1997, Medical Device Provisions."

- [Introduction](#)
- [Devices Subject to Postmarket Surveillance Studies](#)
- [Postmarketing Surveillance Guidance Documents](#)

Do you know the purpose of Postmarket Surveillance Studies?

YES	NO
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Introduction

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Manufacturers must conduct postmarket surveillance studies to gather safety and efficacy data for certain devices introduced into interstate commerce after January 1, 1991. This requirement applies to devices that:

- are permanent implants, the failure of which may cause serious adverse health consequences or death;
- are intended for use in supporting or sustaining human life; or
- present a potential serious risk to human health.
- Under a discretionary provision FDA may require postmarket surveillance for other devices if deemed necessary to protect the public health.

The primary objective of postmarket surveillance is to study 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. The major interest lies in device failure and its attendant impact on the patient.

Postmarket surveillance is considered a warning system for the early detection of potential problems within a reasonable time of their first marketing. The intent of the regulation is to:

- Identify problems
- Provide safety warnings
- Provide information not available from the medical device reporting regulation
- Provide actual use of safety and effectiveness information.

Manufacturers will receive notification that their device is subject to postmarket surveillance upon acceptance of a 510(k) or PMA and again when a decision of substantial equivalence or approval has been made. Within 30 days of introducing their device into interstate commerce, manufacturers must submit a postmarket surveillance protocol to FDA for approval.

Failure to comply with the postmarket surveillance regulation is a prohibited act and will render a device misbranded under the FD&C Act.

Important Note: Effective, February 19, 1998, manufacturers will no longer be automatically required to conduct postmarket surveillance studies for particular devices. Rather, FDA may order such studies to be conducted for certain Class II and Class III devices. The FDA can now order postmarket surveillance for any Class II and Class III device:

- the failure of which would be reasonably likely to have serious adverse health consequences; or
- which is intended to be implanted in the human body for more than one year; or
- which is intended to be a life sustaining or life supporting device used outside a device user facility.

Manufacturers must, within 30 days of receiving an order to conduct a postmarket surveillance study from FDA, submit, for approval, a plan for the required surveillance. The FDA may order a study for up to 36 months. Any longer period has to be mutually agreed upon by the manufacturer and FDA. If no agreement on a longer time period can be reached, then a dispute resolution process is to be followed.

After receiving the manufacturer's proposed plan, FDA has 60 days to determine if the person designated to conduct the surveillance is qualified and experienced, and if the plan will collect useful data that can reveal unforeseen adverse events or other information necessary to protect the public health.

All postmarket surveillance studies ordered under Section 522 of the FFD&C Act should continue at this time. The FDA plans to individually contact the manufacturers currently conducting postmarket surveillance studies to confirm whether the ongoing studies should be completed.

Do you know the devices subject to Post Market Surveillance?



Devices Subject to Postmarket Surveillance Studies

[Page Contents](#)

The effective date requiring these studies for the permanent implant devices listed below was November 8, 1991.

- Annuloplasty Ring
- Automatic Implantable Cardioverter Defibrillator
- Cardiovascular Permanent Pacemaker Electrode (Lead)
- Coronary Vascular Stent
- Implantable Pacemaker Pulse Generator
- Implanted Diaphragmatic/Phrenic Nerve Stimulator
- Replacement Heart Valve
- Total Artificial Heart
- Tracheal Prosthesis
- Vascular Graft Prosthesis (any diameter)
- Ventricular Assist Device - Implant

Added to the list effective August 29, 1993 were:

- Glenoid Fossa Prosthesis
- Implantable Infusion Pumps
- Implanted Cerebellar Stimulators
- Interarticular Disc Prosthesis (Interpositional Implant)
- Mandibular Condyle Prosthesis
- Total Temporomandibular Joint Prosthesis

Postmarketing Surveillance Guidance Documents

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General guidance on the development of post market surveillance protocols can be found on the [CDRH Facts-On-Demand \(F-O-D\)](#), document number 497. There are also two product specific guidance documents, implantable cardiac pacemaker electrodes (number 206), and orthopedic implants with metallic plasma sprayed porous coatings (number 946).

Medical Device Reporting	Medical Device Tracking	Choose Another Topic	Exit Device Advice
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[Top of Postmarket Surveillance Studies](#)

2 OVERVIEW OF THE PMA REGULATION

GENERAL

PREMARKET APPROVAL APPLICATION

FDA ACTION ON A PMA

POSTAPPROVAL REQUIREMENTS

PRODUCT DEVELOPMENT PROTOCOLS

THE SAFE MEDICAL DEVICES ACT OF 1990

This chapter summarizes the Premarket Approval (PMA) regulations as codified in Title 21, Part 814 of the Code of Federal Regulations (CFR). All references are to 21 CFR unless otherwise noted. Section numbers of Part 814 are identified in parentheses for reference to the regulation, which is reprinted in Appendix A of this manual.

PART 814 - PREMARKET APPROVAL OF MEDICAL DEVICES

Subpart A - General

Scope (814.1)

The PMA regulation implements section 515 of the Food, Drug and Cosmetic (FD&C) Act by providing procedures for premarket approval of medical devices intended for human use. A device requiring PMA approval is one which:

- was not on the market before May 28, 1976, and is not substantially equivalent to a device on the market before May 28, 1976, or to a device first marketed on or after that date, which has been classified into class I (general controls) or class II (special controls); or
- is required by a regulation issued under 515(b) of the FD&C Act to have an approved premarket approval application (PMA) or a declared completed product development protocol (PDP); or
- was regulated by the Food and Drug Administration (FDA) as a new drug or an antibiotic drug before May 28, 1976, and therefore is governed by 520(l) of the FD&C Act (transitional devices).

The regulation also amends the conditions of approval for any PMA previously approved. Any condition of approval for an approved PMA that is inconsistent with the regulation is revoked, while those conditions of approval that are consistent with this regulation remain in effect.

Premarket Approval

Center for Devices and Radiological Health

Information on Premarket Approval Applications

Topics Covered

- General Information
- Searching The Releasable PMA Database
- PMA Files for Downloading
- Monthly PMA/ PDP Decisions and Summary Statistics
- "Real-Time" Program for PMA Supplements
- Fax Form for Real-Time PMA Supplement Applications PDF
- Modifications To Devices Subject to Premarket Approval - The PMA Supplement Decision Making Process PDF

General Information

The Medical Device Amendments of 1976 to the Federal Food, Drug, and Cosmetic Act (the act) established three regulatory classes for medical devices. The three classes are based on the degree of control necessary to assure that the various types of devices are safe and effective. The most regulated devices are in Class III. The amendments define a Class III device as one that supports or sustains human life or is of substantial importance in preventing impairment of human health or presents a potential, unreasonable risk of illness or injury. Insufficient information exists on a Class III device so that performance standards (Class II) or general controls (Class I) cannot provide reasonable assurance that the device is safe and effective for its intended use. Under Section 515 of the act, all devices placed into Class III are subject to premarket approval requirements. Premarket approval by FDA is the required process of scientific review to ensure the safety and effectiveness of Class III devices.

An approved Premarket Approval Application (PMA) -- like an approved New Drug Application (NDA) -- is, in effect, a private license granted to the applicant for marketing a particular medical device. A Class III device that fails to meet PMA requirements is considered to be adulterated under Section 501(f) of the act and cannot be marketed. Premarket approval requirements apply differently to preamendments devices, postamendments devices, and transitional Class III devices.

A preamendments device is one that was in commercial distribution before May 28, 1976, the enactment date of the Medical Device Amendments. Manufacturers of Class III preamendments devices are not required to submit a PMA until 30 months after the promulgation of a final classification regulation or until 90 days after the publication of a final regulation requiring the submission of a PMA, whichever period is later. FDA may allow more than 90 days after promulgation of a final rule for submission of a PMA.

A postamendments device is one that was first distributed commercially on or after May 28, 1976. Postamendments devices that FDA determines are substantially equivalent to preamendments Class III devices are subject to the same requirements as the preamendments devices. FDA determines substantial equivalence after reviewing an applicant's premarket notification submitted in accordance with Section 510(k) of the act. Postamendments devices determined by FDA to be not substantially

equivalent to either preamendments devices or postamendments devices classified into Class I or II are "new" devices and fall automatically into Class III. Before such devices can be marketed, they must have an approved premarket approval application or be reclassified into Class I (general controls) or Class II (standards).

Class III transitional devices and "new" devices (described in the paragraph above) are automatically classified into Class III by statute and require premarket approval by FDA before they may be commercially distributed. Applicants may either submit a PMA or Product Development Protocol (PDP), or they may petition FDA to reclassify the devices into Class I or Class II. Clinical studies in support of a PMA, PDP, or a reclassification petition are subject to the investigational device exemption (IDE) regulations. (For further details on these regulations, refer to 21 CFR 812 for general devices or 21 CFR 813 for intraocular lenses.)

New section 515 (d)(6) of the act added by the FDA Modernization Act of 1997, provides that PMA supplements are required for all changes that affect safety and effectiveness unless such change involves modifications to manufacturing procedures or method of manufacture. These types of manufacturing changes require a 30-day Notice or, where FDA finds such notice inadequate, a 135-day PMA supplement.

Requesting Administrative Review of CDRH's Decision to Approve a Premarket Approval (PMA) Application or a Notice of Completion for a Product Development Protocol *

As of January 30, 1998, FDA discontinued publication of individual PMA approvals in the Federal Register (Final Rule in Federal Register Vol 63 No. 20, Friday January 30, 1998, pg 4571). Instead, FDA will notify the public of its decision to approve a PMA by making available, via FDA's CDRH Internet HomePage (see <http://www.fda.gov/cdrh/pmapage.html#monthly>), a summary of the safety and effectiveness data upon which the approval is based. Written requests for this information can also be made to the Dockets Management Branch at the addressed identified below.

The 30-day period to submit petitions for administrative review will begin on the day the summary information is placed on the Internet. Section 10.33(b) provides that FDA may, for good cause, extend this 30-day period. Petitioners may, at any time on or before the 30th day, file with the Dockets Management Branch two copies of each petition and supporting data and information, identified with the name of the device and appropriate docket number. Petitions for administrative review must be submitted to:

The Dockets Management Branch
Division of Management Systems and Policy
Office of Human Resources and Management Services
5630 Fishers Lane, Room 1061, HFZ-305
Rockville, Maryland 20852
Telephone (301) 827-6860
Fax (301) 827-6870

Received petitions may be seen in the office above between 9 a.m. and 4p.m., Monday through Friday.

Section 515(d)(3) of the act authorizes any interested person to petition, under section 515(g) of the act, for administrative review of CDRH's decision to approve a PMA application. A petitioner may request either a formal hearing under 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 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.

* Under 21 CFR 814.19 a class III device for which a PDP has been declared completed by FDA is considered to have an approved PMA.

Searching The Releasable PMA Database

The PMA database may be searched by a variety of fields. A search query will produce information from the database in the following format:

- Classification Name
- Generic Name
- Applicant
- PMA Number
- Supplement Number
- Trade Name
- Date Received
- Decision Date
- Product Code
- Advisory Committee
- Supplement Type
- Supplement Reason
- Expedited Review Granted (Y/N)

PMA/PDP Files for Downloading

You can download the following zipped file, [pma1ist.zip](#), which contains information about the releasable PMA's. Information about how to [unzip](#) this file is available. These files are replaced monthly (usually on the 5th of each month) with a more recent version (files last updated on 7/6/99). In addition there is a [file description](#) and an explanation of some of the codes used in the file. You can also download or search the [Product Code Classification Database](#) which contains medical device names and associated information.

Monthly PMA Listings (in standard text format)

The monthly listing contains information regarding decisions for PMAs, PDPs, Supplements, and Notices. The date of the decision and application information such as address, device trade name, indication (in the case of an original or panel track supplement approval) or the nature of the change are provided. In addition, a table of summary statistics are provided for the numbers of submissions and review times.

1999 Monthly PMA Listings		
June	May	April
March	February	January

1998 Monthly PMA Listings		
<u>December</u>	<u>November</u>	<u>October</u>
<u>September</u>	<u>August</u>	<u>July</u>
<u>June</u>	<u>May</u>	<u>April</u>
<u>March</u>	<u>February</u>	<u>January</u>

1997 Monthly PMA Listings		
<u>December</u>	<u>November</u>	<u>October</u>
<u>September</u>	<u>August</u>	<u>July</u>
<u>June</u>	<u>May</u>	<u>April</u>
<u>March</u>	<u>February</u>	<u>January</u>

1996 Monthly PMA Listings		
<u>December</u>	<u>November</u>	<u>October</u>
<u>September</u>	<u>August</u>	<u>July</u>
<u>June</u>	<u>May</u>	<u>April</u>
<u>March</u>	<u>February</u>	<u>January</u>

1995 Monthly PMA Listings		
<u>December</u>	<u>November</u>	<u>October</u>
<u>September</u>	<u>August</u>	<u>July</u>
<u>June</u>	<u>May</u>	<u>April</u>
<u>March</u>	<u>February</u>	<u>January</u>

1994 Monthly PMA Listing		

CDRH Home Page	FDA HOME PAGE	SEARCH	COMMENTS
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(Updated July 14, 1999)

HHS Publication FDA 97-4214

Premarket Approval Manual

1ST CHAPTER

**CENTER FOR
DEVICES AND
RADIOLOGICAL HEALTH**

CDRH

January 1998

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Rockville, Maryland 20850**

FOREWORD

The Center for Devices and Radiological Health (CDRH) develops and implements national programs to protect the public health in the fields of medical devices and radiological health. These programs are intended to assure the safety, effectiveness, and proper labeling of medical devices; to promote quality in mammographic services; and to control unnecessary human exposure to potentially hazardous radiation, and to ensure the safe, efficacious use of such radiation.

The Center publishes the results of its work in scientific journals and in its own technical reports. These reports disseminate results of CDRH and contractor projects. They are sold by the Government Printing Office and/or the National Technical Information Service.

We welcome your comments and requests for further information.

Bruce Burlington, M.D.
Director
Center for Devices and
Radiological Health

PREFACE

The Medical Device Amendments of 1976 mandated the establishment of “an identifiable office to provide technical and other nonfinancial assistance to small manufacturers of medical devices to assist them in complying with the requirements of the Federal Food, Drug, and Cosmetic Act” The Division of Small Manufacturers Assistance (DSMA) in the Center for Devices and Radiological Health (CDRH) was established to meet these requirements. DSMA sponsors workshops and conferences to provide small medical device firms with firsthand working knowledge of device requirements and compliance policies. Many persons in CDRH provided invaluable assistance to DSMA in preparing these materials and in formulating regulatory interpretations.

This manual, which describes the required arrangement and content of a premarket approval application (PMA), is intended to aid applicants in the preparation of a PMA as required by the Medical Device Amendments of 1976 and the PMA procedural regulation (21 CFR Part 814). This manual also addresses the changes in the PMA process required by the Safe Medical Devices Act of 1990 and the Medical Device Amendments of 1992. The manual details the type of information needed in a PMA so that the Food and Drug Administration (FDA) can evaluate the safety and effectiveness of a medical device. Sufficient flexibility is allowed for the applicant to submit all relevant information in a format suitable for review by FDA. Whenever possible, an applicant should follow the guidance presented in this manual. The submission of a PMA that contains all of the necessary information and follows the guidance in this manual will facilitate the review.

If you have questions regarding a premarket approval application, or its requirements, please contact the Premarket Approval Staff on 301-594-2186 or DSMA on 301-443-6597, 800-638-2041, or FAX to 301-443-8818. Comments on improving this manual and other DSMA activities are always welcome.

John Stigi
Director
Division of Small Manufacturers
Assistance

ABSTRACT

Park, J., Poneleit, K., Parr, R., Project Officers, Premarket Approval (PMA) Manual. HHS Publication FDA 97-4214 (July 1997) (227pp.).

This manual details the type of information needed in a PMA so that the Food and Drug Administration (FDA) can evaluate the safety and effectiveness of a medical device. Information in this manual is intended to aid applicants in the preparation of a PMA application as required by the Medical Device Amendments of 1976 and the PMA procedural regulation, 21 Code of Federal Regulations, Part 814.

This manual contains information on the premarket approval process such as compliance policy and guidance, procedural guidance, and guidance on developing an adequate investigational plan. This manual also addresses the changes in the PMA process required by the Safe Medical Devices Act of 1990 and the Medical Device Amendments of 1992.

The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services.

Although this guidance document does not create or confer any rights for or on any person and does not operate to bind FDA or the public, it does represent the agency's current thinking on premarket approval.

Where this document reiterates a requirement imposed by statute or regulation, the force and effect as law of the requirement is not changed in any way by virtue of its inclusion in this document.

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- C. Master Files
- D. CPG 7124.18, Class III Devices Subject to 515(b) Requirements
- E. Color Additives for Medical Devices
- F. CDRH Document Retrieval Systems
- G. Obtaining Quality System/Current Good Manufacturing Practice Documents

* The preamble to the PMA regulation is available in hard copy from DSMA by faxing a request to 301/443-8818. Request the document as ~~The PMA Regulation and Its Preamble.~~ This document clarifies FDA position on the various provisions of the regulation.

1 INTRODUCTION

WHAT IS A MEDICAL DEVICE
GENERAL CONTROLS
SPECIAL CONTROLS
PREMARKET NOTIFICATION
INVESTIGATIONAL DEVICE EXEMPTIONS
PREMARKET APPROVAL
NEW REGULATIONS

Chapter 1, "Introduction," is an overview of the medical device regulations with general information pertaining to premarket approval.

Products meeting the definition of a medical device under section 201(h) of the Federal Food, Drug and Cosmetic Act (FD&C Act) are regulated by the Food and Drug Administration (FDA). Medical devices are subject to general controls and other controls in the FD&C Act. General controls of the FD&C Act are the baseline requirements that apply to all medical device manufacturers. Unless specifically exempted, medical devices must be properly labeled and packaged, be cleared for marketing by the FDA, meet their labeling claims, and be manufactured in accordance with FDA's Quality Systems (QS) Regulation.

FDA regulates devices to assure their safety and effectiveness. To fulfill provisions of the FD&C Act, FDA develops and promulgates rules to regulate devices intended for human use. These regulations are published in the *Federal Register*. Final regulations are codified annually in the Code of Federal Regulations (CFR). Most medical device regulations are described in Title 21 CFR Parts 800 to 1299.

WHAT IS A MEDICAL DEVICE

The definition of a medical device appears in section 201(h) of the FD&C Act. A device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component, part, or accessory, which is recognized in the official National Formulary, or the United States Pharmacopeia (USP), or any supplement to them, intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

FDA has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device. The three classes and the requirements which apply to them are:

CLASS	REGULATORY CONTROLS
Class I	General Controls
Class II	General Controls and Special Controls
Class III	General Controls and Premarket Approval

GENERAL CONTROLS

As noted above, general controls are the baseline requirements of the FD&C Act that apply to all medical devices. Unless specifically exempted by regulation, general controls contain **requirements** for device manufacturers or other designated persons to:

- comply with the registration and listing regulations in 21 CFR Part 807;
- comply with the labeling regulation in 21 CFR Part 801, 809 or 812;
- comply with the reporting regulations in 21 CFR Part 803 and 804;
- submit a premarket notification [510(k)] (21 CFR Part 807) to FDA; and
- design and produce devices under the Quality Systems Regulation (21 CFR Part 820).

The controls in the above list other than reporting regulations are briefly described in this chapter.

Registration and Listing

Section 510 of the FD&C Act requires that U.S. device manufacturers and distributors register their establishments with FDA on Form FDA-2891. All manufacturers are required to list the generic type of devices they have in U.S. commerce with FDA on Form FDA-2892. Establishment registration and medical device listing should be submitted prior to commercial distribution.

Labeling

All medical devices in U.S. commerce must be properly labeled. Device labeling requirements of the FD&C Act are found in the following parts of Title 21:

General Device Labeling	21 CFR Part 801
In Vitro Diagnostic Products	21 CFR Part 809

Investigational Device Exemptions	21 CFR Part 812
Quality Systems Regulation	21 CFR Part 820
General Electronic Products	21 CFR Part 1010

Basic labeling requirements and recommended labeling for medical devices can be found in the ODE Blue Book Memorandum, "Device Labeling Guidance," #G91-1 (see Chapter 4), and in the booklet, *Labeling; Regulatory Requirements for Medical Devices*, available from the Division of Small Manufacturers Assistance (DSMA). Details concerning Blue Book memoranda are found in Chapter 4.

Good Manufacturing Practices

As required by section 520(f) of the FD&C Act, the Quality System (QS) regulation covers the methods used for, and the facilities and controls used for, the design, manufacture, labeling, packaging, storage, and installation of devices. The QS regulation is codified in 21 CFR Part 820. Some class I devices, such as an manual surgical instruments for general use, 21 CFR Section 878.4800, are exempt by regulation from most of the QS requirements.

The QS regulation contains general quality assurance (QA) or quality system requirements in areas of concern to all manufacturers of finished devices. Among other requirements, it covers organization and personnel; design practices and procedures; buildings and environmental control; design of labeling and packaging; controls for components, processes, packaging and labeling; finished device evaluation; distribution and installation; device and manufacturing records; complaint processing; and QA system audits.

SPECIAL CONTROLS

In addition to general controls, class II and III devices are subject to further requirements such as special controls and premarket approval, respectively.

Class II devices are defined in section 513(a)(1)(B) of the FD&C Act to include any device for which reasonable assurance of safety and effectiveness can be obtained by applying "special controls". Only general controls will apply to class II devices until special controls are established by regulation(s). Special controls may include special labeling requirements, mandatory performance standards, patient registries and postmarket surveillance.

PREMARKET NOTIFICATION

A premarket notification [510(k)] is a marketing application submitted to FDA to demonstrate that a medical device is as safe and as effective or substantially equivalent to a legally marketed device that was or is currently on the U.S. market and that does not require premarket approval. The premarket notification requirements are found in 21 CFR Part 807, Subpart E.

Most devices are cleared for commercial distribution in the U.S. by the premarket notification [510(k)] process. Most class I devices are exempt from the 510(k) requirement by regulation. However, they are not exempt from other general controls, such as establishment registration and device listing. Before marketing a medical device which is not exempt from the marketing clearance process, the manufacturer must submit a premarket notification [510(k)] or a premarket approval (PMA) application to FDA. The manufacturer cannot market the device in these cases, unless the firm receives a marketing clearance letter from FDA as stated in section 513(i)(1)(A) or section 515(d)(1)(A)(I) of the FD&C Act. Detailed guidance on the 510(k) requirements can be found in the manual, *Premarket Notification 510(k): Regulatory Requirements for Medical Devices*.

INVESTIGATIONAL DEVICE EXEMPTIONS

To allow manufacturers of devices intended solely for investigational use to ship devices for use on human subjects (clinical evaluation), the FD&C Act authorizes FDA to exempt these devices from certain requirements of the Act that would apply to devices in commercial distribution. Clinical evaluation of devices not cleared for marketing, unless exempt, requires an approved investigational device exemption (IDE) either by an institutional review board (IRB) or an IRB and FDA, informed consent for all patients, adequate monitoring and necessary records and reports. These requirements can be found in 21 CFR Parts 50, 56, and 812. Detailed guidance on the IDE requirements can be found in the *Investigational Device Exemption Manual*.

PREMARKET APPROVAL

Premarket approval (PMA) is the FDA process to evaluate the safety and effectiveness of class III devices. Class III is the most stringent regulatory category for medical devices. Class III devices are usually those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. Due to the level of risk associated with class III devices, FDA has determined that general and special controls alone are insufficient to assure the safety and effectiveness of class III devices. Therefore, these devices require a premarket approval (PMA) application under section 515 of the FD&C Act, in order to obtain marketing clearance.

Devices Subject to Premarket Approval

Under section 515 of the FD&C Act, all devices placed into class III by FDA are subject to premarket approval requirements. Premarket approval is the process of scientific and regulatory review to ensure the safety and effectiveness of class III devices. An approved PMA is, in effect, a private license granted to the applicant for marketing a particular medical device. A class III device that fails to meet PMA requirements is considered to be adulterated under section 501(f) of the FD&C Act and cannot be marketed. Premarket approval requirements apply differently to preamendments devices, postamendments devices, and transitional class III devices.

Manufacturers of class III preamendments devices, devices that were in commercial distribution before May 28, 1976, are not required to submit a PMA until 30 months after the promulgation of a final classification regulation or until 90 days after the publication of a final regulation requiring the submission of a PMA, whichever period is later. FDA may allow more than 90 days after promulgation of a final rule for submission of a PMA.

A postamendments device is one that was first distributed commercially on or after May 28, 1976. Postamendments devices that FDA determines are substantially equivalent to preamendments class III devices are subject to the same requirements as the preamendments devices. FDA determines substantial equivalence after reviewing an applicant's premarket notification submitted in accordance with section 510(k) of the FD&C Act. Postamendments devices determined by FDA to be not substantially equivalent to either preamendments devices or postamendments devices classified into class I or II are "new" devices and fall automatically into class III. Before such devices can be marketed, they must have an approved premarket approval application or be reclassified into class I or class II.

Class III transitional devices and "new" devices are automatically classified into class III by statute and require premarket approval by FDA before they may be commercially distributed. Applicants may either submit a PMA or a Product Development Protocol (PDP), or they may petition FDA to reclassify the devices into class I or class II. Clinical studies in support of a PMA, a PDP, or a reclassification petition are subject to the Investigational Device Exemption (IDE) regulation.

The PMA requirements are found in 21 CFR Part 814. Not all class III devices require an approved PMA to be marketed at this time. Class III devices that are substantially equivalent to devices legally marketed before May 28, 1976, and do not currently require premarket approval may be marketed through the premarket notification [510(k)] process until FDA publishes a regulation requiring the submission of a premarket approval (PMA) application for those Class III devices.

The PMA Review Process

The review of a premarket approval application is a four-step review process consisting of:

- administrative and limited scientific review by FDA staff to determine completeness (filing review);
- in-depth scientific and regulatory review by appropriate FDA scientific and compliance personnel (in-depth review);
- review and recommendation by the appropriate advisory committee (panel review); and
- an FDA good manufacturing practices (GMP) inspection.

During the administrative and limited scientific review, FDA determines whether a PMA includes the type of information required by the FD&C Act and the PMA procedural regulations (21 CFR, Part 814) and is suitable for filing. The filing of a PMA application means that FDA has made a threshold determination that the application is sufficiently complete to permit a substantive review. If the information or data are presented unclearly or incompletely or are not capable of withstanding rigorous scientific review, FDA may consider the PMA incomplete and not file it. The 180-day review period provided by the FD&C Act begins when the PMA is filed.

Any PMA accepted for filing may undergo an in-depth scientific review by FDA personnel and may be presented to an advisory committee representing the appropriate medical field. FDA notifies the PMA applicant of any deficiencies. Within the 180-day review period, FDA will send the applicant an approval order under 814.44(d), an approvable letter under 814.44(e), a not approvable letter under 814.44(f), or an order denying approval under 814.45.

An FDA GMP inspection is conducted for all original PMAs and for PMA supplements requesting approval of alternate or additional manufacturing and sterilization facilities. The Compliance Program #7383.001, Medical Device Premarket Approval and Postmarket Inspections, directs FDA field offices to consider the extent to which the applicant has established a formal quality assurance program and has assured that the approved design is properly transferred into specifications.

FDA will notify the applicant by letter of its decision to approve or deny, and in a *Federal Register* notice will announce the decision and the availability of a summary of the safety and effectiveness data on which the decision is based. The notice also provides the applicant and other interested persons an opportunity for administrative review of the FDA approval or denial action.

Obtaining approval for a PMA application is not a simple process. FDA realizes that filing a PMA application may be the applicant's first contact with the agency. This manual has been designed to assist those applicants. Chapter 2 is an overview of the PMA regulation and subsequent chapters present information on specific topics in the PMA program.

In addition to using this manual, applicants are encouraged to contact FDA to obtain further guidance prior to the submission of a PMA application. This will be especially beneficial to new applicants who have not previously had contact with FDA and for applicants proposing to study new technologies or new uses for existing technologies. Early interaction with FDA should help to increase the applicant's understanding of FDA requirements, regulations, and guidance documents, and will allow FDA personnel to familiarize themselves with the new technologies. Increased interaction between FDA and applicants should help to speed the regulatory process and minimize delays in the development of useful devices intended for human use.

Chapter 4 provides a list of most PMA guidance documents that have been prepared by the Office of Device Evaluation which are available from the CDRH Facts-on-Demand (FOD) (301) 827-0111 or (800) 899-0381 and the CDRH Homepage on the world wide web (WWW). Information accessing both the FOD and the WWW are included in Appendix F (CDRH Document Retrieval Systems). Applicants are especially encouraged to contact the review divisions within the Office of Device Evaluation to discuss device-specific requirements. The PMA staff may be contacted for general questions relating to the PMA laws, regulations, policies, and administrative issues on (301) 594-2186.

PMA submission, normally 6 copies of an original PMA and 3 copies of amendments and supplements, must be clearly identified as such and should be addressed to:

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

As mentioned before, copies of the Premarket Approval Manual, ODE guidance documents and the Standard Conditions of Approval applicable to all approved original and supplemental PMAs are available on the CDRH WWW (see Appendix F). In addition, copies of this manual can be obtained on disc on Microsoft Word from:

Food and Drug Administration
Division of Small Manufacturers Assistance (HFZ-220)
1350 Piccard Drive
Rockville, Maryland 20850
Telephone: 800-638-2041 or 301-443-6597
FAX: 301-443-8818

NEW REGULATIONS

Quality System Regulation

On October 7, 1996, FDA issued a new good manufacturing practice regulation now called Quality System (QS) regulation which became effective June 1, 1997. This rule revised the 1978 Good Manufacturing Practices (GMP) regulation. The QS regulation includes requirements related to the methods used in and the facilities and controls used for: designing, purchasing, manufacturing, packaging, labeling, storing, installing, and servicing of medical devices.

To assist manufacturers in complying with this final rule, CDRH released guidance

documents which includes: 1) DSMA's *Medical Device Quality Systems Manual: A Small Entity Compliance Guide*, which addresses the entire regulation and includes examples of forms and procedures which can be adopted or modified by manufacturers; 2) *Design Control Guidance for Medical Device Manufacturers*, which is intended to assist manufacturers in understanding the intent of the design control requirements; and 3) *Do It By Design: An Introduction to Human Factors in Medical Devices*, which contains background information about human factors as a discipline, as well as descriptions and illustrations of the device control system. FDA also issued guidance on validation, and a draft of the "Design Control Inspectional Strategy," which focuses on the types of questions FDA investigators will be asking to assure compliance with the design control requirements.

The length of the QS regulation (over 180 pages) makes it impractical to include in this manual, but a copy can be accessed through the World Wide Web at the address below:

<http://www.fda.gov/cdrh/dsma/gmp-man.html>

Availability of the aforementioned and other QS regulation documents are included in appendix G (Obtaining Quality System/Current Good Manufacturing Practice Documents).

Reporting Under the Medical Device Reporting Regulation

The new Medical Device Reporting (MDR) regulation (21CFR Part 803) became effective on July 31, 1996, and requires that all manufacturers of medical devices, including in vitro diagnostic devices, report to FDA within 30 days whenever they receive or otherwise become aware of information that reasonably suggests that one of their 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 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 identified with the PMA reference number. The envelope should be marked "Manufacturer Report" and sent to the following address:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting

P.O. Box 3002
Rockville, MD 20847-3002
Telephone: (301) 594-2731

The new regulation specifies that the MedWatch Form FDA 3500A must be used by manufacturers for individual adverse event reporting and that they must also submit a baseline report using form FDA 3417 for a device when the device model is first reported on an individual report.

Copies of the MDR regulation, MDR manual, and related documents and forms are available from the CDRH Home Page, <http://www.fda.gov/CDRH> or from DSMA Facts-on-Demand (FOD) system, 800-899-0381, 301- 827-0111 (request document #799).

Humanitarian Use Devices Regulation

The FDA issued a final rule effective October 24, 1996, to implement the provisions of the Safe Medical Devices Act of 1990 (SMDA) regarding humanitarian use devices (HUD's). An HUD is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. This final rule prescribes the procedures for submitting humanitarian device exemption (HDE) applications, amendments, and supplements; procedures for obtaining an extension of the exemption; and the criteria for FDA review and approval of HDE's. The purpose of the HDE is, to the extent consistent with the protection of the public health and safety and with ethical standards, to encourage the discovery and use of devices intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States.

For further information or if you have questions, please contact Ms. Joanne Less, Office of Device Evaluation (301) 594-1190.

Perrin, Luc and Amalio Telenti, "HIV Treatment Failure: Testing for HIV Resistance in Clinical Practice," *Science*, Vol. 280, June 19, 1998, 1871-1873

Van Gijn, Jan, "Preoperative parathyroid scanning in secondary hyperparathyroidism," *The Lancet*, Vol. 353, June 26, 1999, 2174-2175

Hirsch et al, "Drug Resistance Testing in HIV-Infected Adults," *JAMA*, June 24, 1998, Vol. 279, No. 24, 1984-1991

Durant, J, et al "Drug-resistance genotyping in HIV-1 therapy: The VIRADAPT randomised controlled trial," *The Lancet*, Vol. 353, June 26, 1999, 2195-2199

Wainerg, M and G. Friedland, "Public Health Implications of Antiretroviral Therapy and HIV Drug Resistance," *JAMA*, June 24, 1998, Vol. 279, No. 24, 1977-1983

Cockerill, F, "Minireview, genetic Methods for Assessing Antimicrobial Resistance," *Antimicrobial Agents and Chemotherapy*, Feb. 1999, p 199-212

These documents contain copyrighted material. The documents may be viewed at:

**Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852**

Center for Devices and Radiological Health

Guidance for Industry and FDA Staff

Guidance on

Amended Procedures for

Advisory Panel Meetings

Document issued on: January 26, 1999

This document supersedes the document entitled
Guidance on Amended Procedures for Advisory Panel Meetings
that was issued on March 20, 1998



**U.S. Department Of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health**

**Office of Device Evaluation
Office of the Director**

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to:

Nancy J. Pluhowski

Office of Device Evaluation, HFZ-400
9200 Corporate Boulevard
Rockville, MD 20850

William Freas
Center for Biologics Evaluation and Research (HFM-21)
1401 Rockville Pike
Rockville, MD 20852

Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact Nancy J. Pluhowski (CDRH) at 301-594-2022, or William Freas (CBER) at 301-827-1295.

Additional Copies

World Wide Web – CDRH home page at <http://www.fda.gov/cdrh/modact/amendpan.pdf> or connect to CBER at <http://www.fda.gov/cber/guidelines.htm>.

To receive this document at your fax machine, call CDRH Facts on Demand at 1-800-899-0381 or 301-827-0111, specify number 413 when prompted for the document shelf number.

Guidance on Amended Procedures for Advisory Panel Meetings

Purpose

The purpose of this guidance is to establish standard operating procedures to be followed by the Center for Devices and Radiological Health (CDRH), the Center for Biologics Evaluation and Research (CBER), Food and Drug Administration (FDA) personnel and interested persons outside FDA, in carrying out Section 513 (b)(6) of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by Section 208 of the FDA Modernization Act of 1997 (FDAMA). The standard operating procedures outlined below apply to advisory panel meetings where a specific submission is being considered by the panel.

Background on the New Provision

As stipulated in the new Section 513 (b)(6)(A)(i) of the Act, FDA is required to provide, to any person whose device is specifically the subject of a classification panel review, the same access to data and information about the device as that submitted to a classification panel, except for data and information that are not available for public disclosure under {5 U.S.C. 552}.

In accordance with Section 513 (b)(6)(A)(ii), FDA is required to provide to such persons the opportunity to submit information, based on the data or information provided in the application under review, to the panel for its review.

Section 513 (b)(6)(A)(iii) amended the Act to also allow such persons the same opportunity as FDA to participate in meetings of the panel.

Section 513 (b)(6)(B) of the Act requires of device classification panel meetings that: (1) adequate time be provided for initial presentations; (2) adequate time be provided for response to any differing views by persons whose devices are the subject of a classification panel; and (3) free and open participation by all interested persons be encouraged.

¹ This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Standard Operating Procedures

I. Premeeting Mailouts

- A. At least 3 weeks before a device classification panel meeting to consider an action on a specific sponsor's device, FDA will provide to the panel members and the sponsor a prepared panel package (all pre-meeting materials that are sent to the entire panel, except for the industry representative who may receive a package that has been redacted at the sponsor's request) which contains:
1. appropriate sections of the product submission (i.e. preclinical and clinical data, summary of safety and effectiveness, labeling),
 2. related information submitted by the sponsor,
 3. FDA review memos (preclinical, clinical, statistical), or a summary of the FDA review memos,
 4. FDA questions for panel consideration, and
 5. outline or slides prepared for an FDA presentation (if available).
- B. The following timeline and preparation of the panel package is recommended:
1. When available, but generally by six weeks before an advisory panel meeting, FDA will send to the sponsor an index of materials the Agency intends to include in the panel package. FDA will ask the sponsor to determine whether there is any additional information, directly related to the submission, that the sponsor wants to include in the panel package.
 2. The sponsor will therefore have approximately two weeks to submit additional

information to be distributed to the panel. Such information should include a complete table of contents and an index. To be included in the initial panel package, the information should arrive at the Agency at least four weeks before the advisory panel meeting. The sponsor is asked to provide twenty copies of this information.

3. Upon receipt of the sponsor's materials for the panel package, FDA will assess the proposed panel package for completeness and relevance. FDA will determine if the added information is based on data or information in the PMA. Any question about the relatedness of the additional information will be discussed by telephone with the sponsor. This discussion will occur prior to the Agency's redacting material not based on data or information provided in the application.
4. FDA will send the complete panel package to the panel members and the sponsor simultaneously. Additional pertinent information, available to FDA after the initial panel package has been distributed, will be provided to the panel and sponsor as a panel package addendum. FDA will make every effort to mail the addendum package, if there is one, one week before the advisory panel meeting.
5. In general, new data or information will not be provided to the panel on the day of the meeting or later than one week before the meeting.

II. FDA will provide the sponsor an equal amount of time to address the advisory panel as described below:

A. In order to provide adequate time for panel deliberations and at the discretion of the Chair:

1. The sponsor will generally be provided 60 minutes (up to 90 minutes if the sponsor requests and the Chair agrees they need additional time due to special circumstances) to present a submission to the advisory panel.
2. FDA's presentation will usually be limited to 60 minutes (similarly up to 90 minutes due to special circumstances) and will include specific issues identified during the review process, unresolved issues, and deficiencies in the submission.
3. Following initial presentations, the sponsor and FDA, respectively, will each be provided equal opportunities (up to 15 minutes) to clarify issues or information presented during the panel meeting.
4. The panel may require clarification during the panel's deliberations and before a vote is taken on the submission. In such cases, both FDA and the sponsor will be provided an equal opportunity to respond.

B. Encourage free and open participation by all interested persons:

1. The open public session of the advisory committee meeting provides a time for free and open participation by all interested persons.
2. Generally, the open public session lasts one hour and will be conducted in two segments: approximately 30 minutes at the beginning of the panel meeting for general or specific issues and 30 minutes near the end of the panel deliberations, prior to the vote, for interested persons to address issues specific to the submission before the panel.

These standard operating procedures also will be applied to device classification panel meetings on issues involving more than one sponsor. In such cases, however, the time available per sponsor may be more limited than indicated above. Further discussion of these procedures will be in the revised Policy and Guidance Handbook for FDA's Advisory Committees.

[CDRH Home Page](#) [FDA HOME PAGE](#) [SEARCH](#) [COMMENTS](#)

(Page last updated: January 26, 1999)

Description of Innogenetics Products for HIV Resistance Genotyping

Intended use: detection of genetic variants of HIV-1 genotype B, present in human plasma, and conferring resistance to HIV reverse transcriptase inhibitors and protease inhibitors. The kits, in conjunction with clinical history and other relevant laboratory tests (i.e. viral load, CD4) can help the physician in gaining insight into the possible clinical effectiveness of an antiviral drug for a specific patient.

Description of the product: viral RNA is isolated from plasma. Complementary DNA from the RNA and the first round PCR amplicon are obtained with specific outer primers. The second PCR round is performed with specific biotinylated nested primers. Biotinylated amplification product is hybridized with specific oligonucleotide probes immobilized as parallel lines on membrane-based strips. This method is based on the principle of reverse hybridization. After hybridization, streptavidin labelled with alkaline phosphatase is added and bound to any biotinylated hybrid previously formed. Incubation with BCIP/NBT chromogen results in a purple/brown precipitate.






















K/P-1062 LiPA HIV-1 RT Detects wild type and/or resistance mutations at reverse transcriptase codons 41 (M41L), 69/70 (T69D/N, K70R), 74 (L74V), 184 (M184/V), and 214/215 (F/L214, T215Y/F).

K/P-1093 LiPA HIV-1 PI (90) Detects wild type and/or resistance mutations at protease gene codon 90 (L90M).

K/P-1092 LiPA HIV PI (30-84) Detects wild type and/or resistance mutations at protease gene codons 30 (D30N), 46/48 (M46I,G48V), 50 (I50V), 54 (I54V/A), and 82/84 (V82F/A/T, I84V).

DRIVEN to Care

INNO-LiPA HIV RT

	<u>CODON</u>	<u>ASSOCIATED RESISTANCE</u>
 Marker line	
 Conjugate control	
 HIV-1 amplification control	
 M41.....	Wild Type
 L41 (TTG).....	AZT Mutant
 L41 (CTG).....	AZT Mutant
 T69K70.....	Wild Type
 T69R70.....	ddC Wild Type AZT Mutant
 D69K70.....	ddC Mutant AZT Wild Type
 D69R70.....	ddC Mutant AZT Mutant
 N69R70.....	AZT Mutant
 L74.....	Wild Type
 V74.....	Ddl-ddC Mutant
 M184.....	Wild Type
 V184.....	3TC Mutant
 F214T215.....	Wild Type
 L214T215.....	Wild Type
 214 /T215.....	Wild Type
 F214Y215.....	AZT Mutant
 L214Y215.....	AZT Mutant
 F214F215.....	AZT Mutant

FOR INVESTIGATIONAL USE ONLY

INNOGENETICS

5335 Triangle Parkway, Ste. 300
Norcross, GA 30092
678-393-1672 phone
678-393-1673 fax

K10620899

DRIVEN to Care

INNO-LiPA

HIV PI 1

<u>CODON</u>	<u>ASSOCIATED RESISTANCE</u>
..Marker line	
..Conjugate control	
..HIV-1 amplification control	
..D30.....	Wild Type
..N30.....	Nelfinavir
..M46-G48.....	Wild Type
..I46-G48.....	Indinavir
..M46-V48.....	Saquinavir
..I50.....	Wild Type
..V50.....	Amprenavir
..I54.....	Wild Type
..V54.....	Ritonavir; Saquinavir; Indinavir
..A54.....	Polymorphism
..V/I82-I84.....	Wild Type
..V82-V84.....	Indinavir; Amprenavir
..I82-I84.....	Saquinavir; Indinavir; Ritonavir; Ampremavir
..F82-I84.....	Saquinavir; Indinavir; Ritonavir; Ampremavir
..F82-V84.....	Saquinavir; Indinavir; Ritonavir; Ampremavir
..A82-I84.....	Saquinavir; Indinavir; Ritonavir; Ampremavir
..T82-I84.....	Saquinavir; Indinavir; Ritonavir; Ampremavir
..T82-V84.....	Saquinavir; Indinavir; Ritonavir; Ampremavir
..QSPR14.....	Internal Control

INNO-LiPA

HIV PI 2

<u>CODON</u>	<u>ASSOCIATED RESISTANCE</u>
..Marker line	
..Conjugate control	
..HIV-1 amplification control	
..L90.....	Wild Type
..M90.....	Mutant; Saquinavir; Indinavir; Nelfinavir
..QSPR14.....	Internal Control

FOR INVESTIGATIONAL USE ONLY

INNOGENETICS

5335 Triangle Parkway, Ste. 300
Norcross, GA 30092
678-393-1672
678-393-1673 fax

Inno0899a

CPCRA 046 demonstrated that patients whose antiretroviral drug management was not based upon plasma genotypic antiretroviral resistance testing (GART) received fewer drugs that were active against the strain of HIV that they were infected with. As a corollary to this observation, they were exposed to the toxicities of a higher number of drugs which were inactive against their virus strains and thus had little or no clinical benefit to add to their management. The fact that these patients were treated often with only 2 active antiretroviral drugs, and in 10% of the patients, 1 or less active antiviral drugs, makes these patients even more likely to rapidly develop resistance to the few remaining active drugs in their regimen.

Baxter, et al., 3rd International Workshop on HIV Drug Resistance and Treatment Strategies, San Diego, June 1999

Initial pharmacoeconomic analysis of drug resistance genotyping for adaption of treatment in the VIRADAPT study showed no significant difference in total costs over 12 months of followup but a trend towards a significant reduction ($p=0.06$) for antiretroviral drugs in the genotyping arm.

Antiretroviral drug costs accounted for approximately 55% of total costs.

The cost of genotyping (by sequencing in this study) was offset by the savings in antiretroviral drug costs.

C. Chaix et al., 3rd International Workshop on HIV Drug Resistance and Treatment Strategies, San Diego, June 1999

Apheresis Red Cell Technology

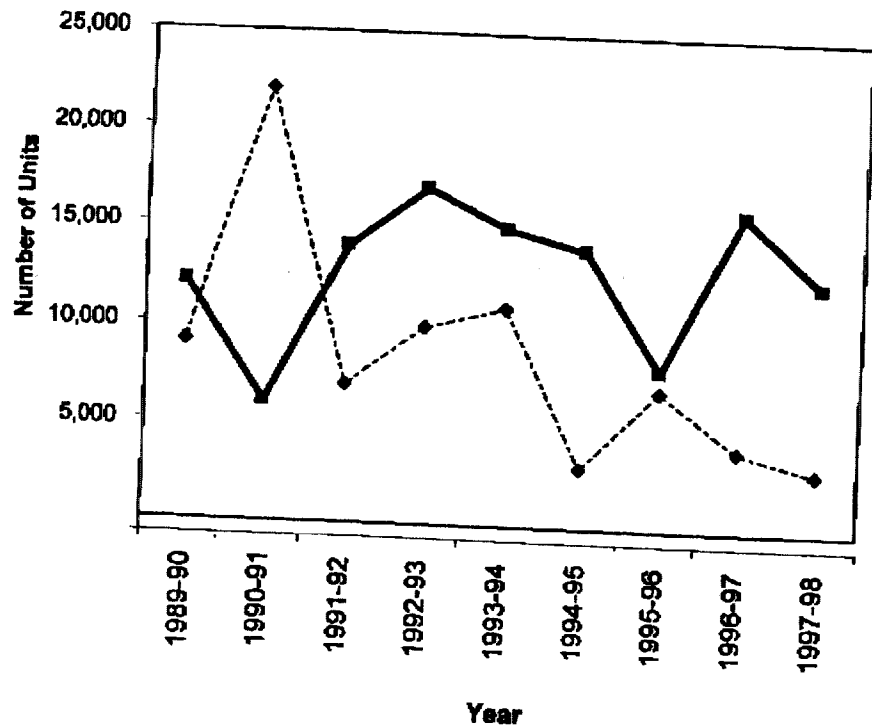
*Strategy for Increasing the Blood
Supply*

National Blood Exchange - Supply and Demand

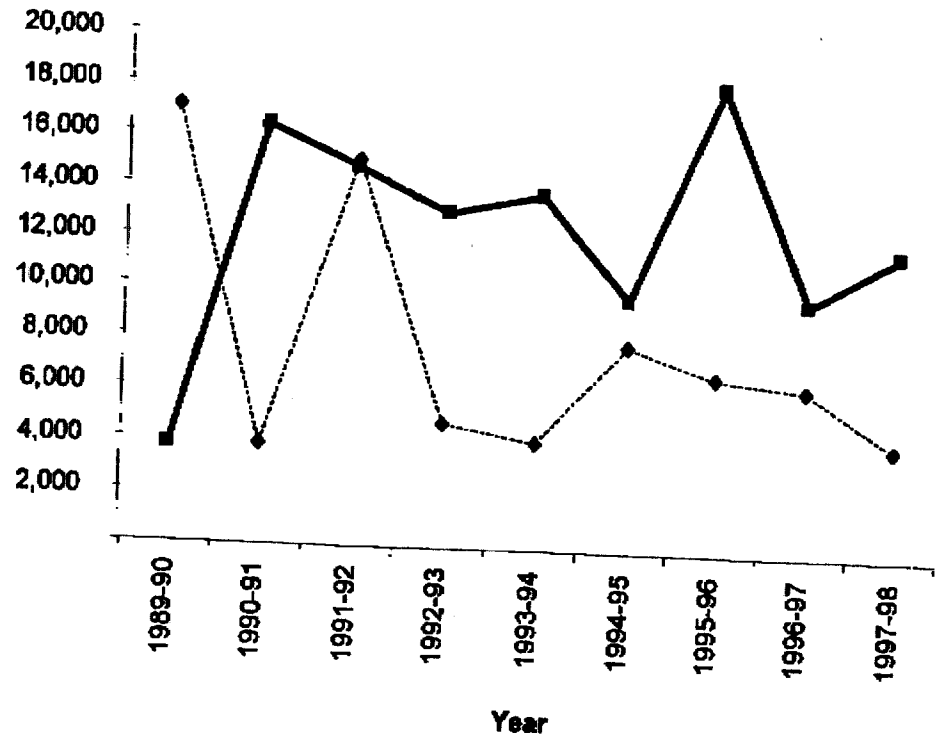
— Units requested
 - - - Units listed

• Units of Group O positive blood listed as available versus requested by Blood Centers

Winter



Fall



Source: AABB News, March 1999

U.S. Blood Donation Decline

National Blood Data Resource Center

Blood Supply ↓, Transfusions ↑

By year 2000 the blood supply will ↓ by 600,000 units.

This is 249,000 units < expected need

Blood supply trend:

Units Transfused

1992 - 11.3 million transfusion

1997 - 11.5 million transfusions

Units Collected

1992 - 13.2 million donations

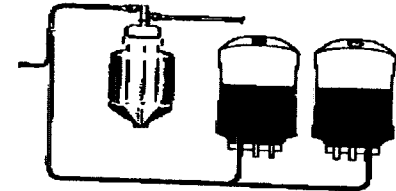
1994 - 12.9 million donations

1997 - 12.3 million donations

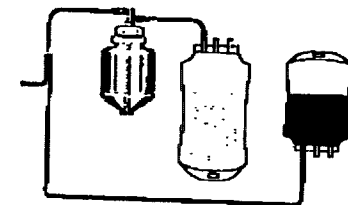
Red Cell Apheresis Protocols



- Two-Units of Red Cells



- Red Blood Cells and Plasma



- From 1 donation

Apheresis Red Cell FDA Clearance History

April 1998

First 2-RBC Autologous Bank License

1997

510(k) clearance for Allogeneic 2-RBC

1996

510(k) clearance for Autologous 2-RBC

1995

510(k) clearance for Allogeneic /
Autologous RBC & Plasma

2RBC Allogeneic Nomogram

- **Males**

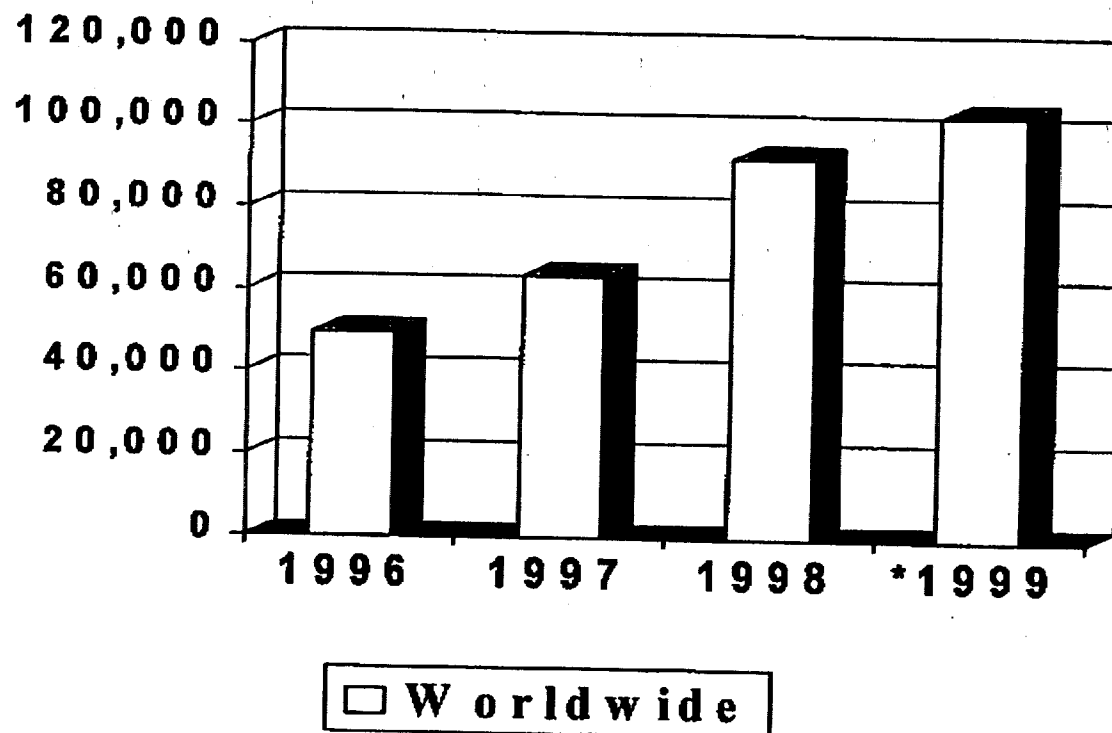
- 130 pounds
- 5'1" height
- 40% hematocrit
- 112 day deferral

- **Females**

- 150 pounds
- 5'5" height
- 40% hematocrit
- 112 day deferral

RBCP nomogram is the same as whole blood.

Worldwide Apheresis Red Cell Growth



** Actual data annualized.*

2RBC Conversion Strategy: Group O & B Donors

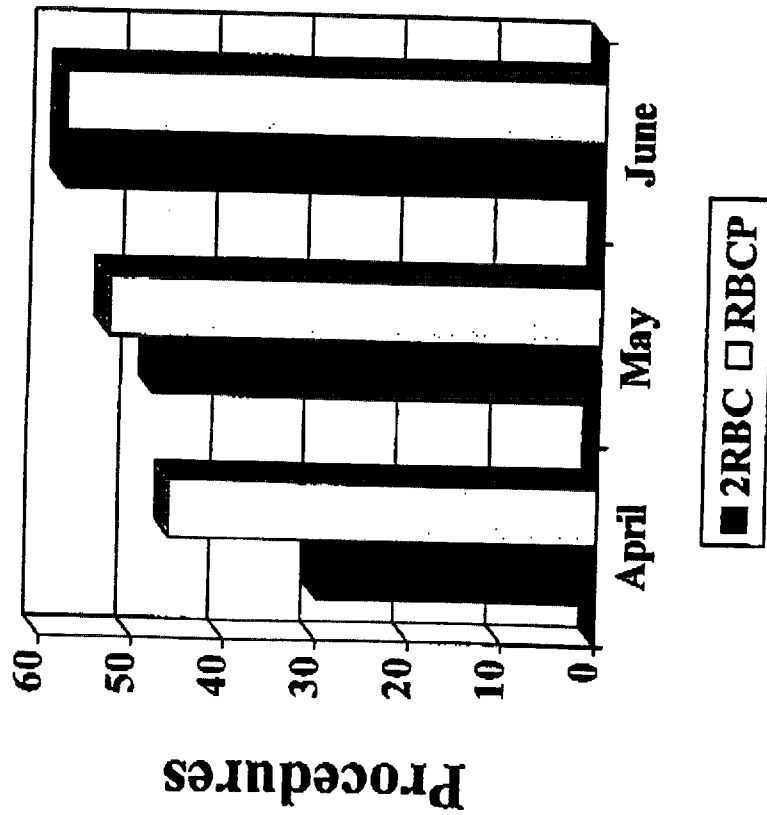
962,000 more RBC Products (Early) (8%)

1,620,000 more RBC Products (Mature) (14%)

Assumption: 12 Million WB Donations. 70% Mobile.

	Mobile	Fixed
12 Million Donations	8.4 Million	3.6 Million
Conversion Rate	15.5%	15.5%
Additional Donations	1.3 Million	0.5 Million
Additional Products	2.0 Million	0.8 Million
Additional Revenue	\$1.0 Million	\$0.4 Million
Additional Profit	\$0.7 Million	\$0.3 Million
Additional EBITDA	\$0.7 Million	\$0.3 Million
Additional Cash Flow	\$0.7 Million	\$0.3 Million

Face-to-Face Conversion Success



**Whole Blood to Apheresis
Collection through *face-to-face* conversion.**

- No telerecruitment used
- Approximately 50% increase in 2RBC procedures from April to June
- Approximately 21% increase in RBCP procedures from April to June

Apheresis Red Cell Leukoreduction

- Europe in-line leukoreduction since 1996.
- Domestic 2RBC in-line leukoreduction in clinical trials.

Economics

- Recently Haemonetics and an economics consulting firm collected data from 15 blood centers across the United States pertaining to whole blood collections.
- Study conclusion of 15 Blood Centers:
clear cut advantage in replacing certain whole blood collections.

Conclusion

Apheresis Red Cell Technology