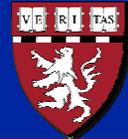




**Massachusetts Institute of Technology
Harvard Medical School
Brigham and Women's Hospital
VA Boston Healthcare System**



2.782J/3.961J/BEH.451J/HST524J

**FEDERAL REGULATORY ISSUES:
US Food and Drug Administration
Medical Device Amendments**

M. Spector, Ph.D.

2.782 FDA REPORT

- **10% of grade**
- **Total length: 8 pages**
 - Includes text, all images and all references
- **Line spacing: 1.5**
- **Minimum font: 12**

GOVERNMENT REGULATION OF MEDICAL DEVICES

US	FDA
Canada	Health Canada
Mexico	Health Ministry (uses US FDA)
Europe	European Union “CE Mark”
China	Chinese FDA
India	None

INDIA

- **India does not regulate the sale of medical devices.**
- **India accepts non-U.S. Food & Drug Administration-approved as well as non-CE-marked medical devices**
 - **however, in accordance with U.S. FDA requirements, U.S. manufacturers may only export to India and to other countries medical devices that have been approved either by the US FDA**

www.ita.doc.gov/td/mdequip/indiaregs.html

US FDA ORGANIZATION

Center for **Biologics** Evaluation and Research (CBER)

Center for **Devices** and Radiological Health (CDRH)

Center for **Drug** Evaluation and Research (CDER)

Center for Food Safety and Applied Nutrition
(CFSAN)

Center for Veterinary Medicine (CVM)

National Center for Toxicological Research (NCTR)

Office of the Commissioner (OC)

Office of Regulatory Affairs (ORA)

Which center to review your application?

FDA



for Devices and
ological Health
[www.fda.gov/cdr
index.html](http://www.fda.gov/cdr/index.html)

FDA APPROVAL PROCESS

Classification of Product as I, II, or III

I. General Controls

II. Special Controls

III. Premarket Approval (PMA)

TE products

Good Manuf. Practice

GMP

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Equivalent to Marketed Device?;
Premarket Notification

510 (k)

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510 (k)

Analysis of composition and properties, and *in vitro* and *in vivo* studies

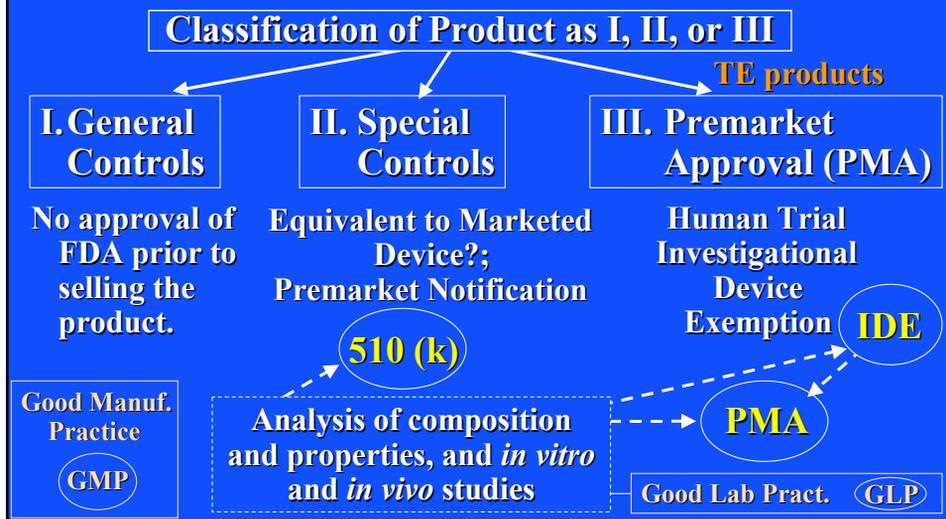
III. Premarket Approval (PMA)

TE products

Good Lab Pract.

GLP

FDA APPROVAL PROCESS



FDA History

<http://www.fda.gov/oc/opacom/fda101/sld017.html>

- In **1906**, President Theodore Roosevelt signed into law the **Food and Drugs Act**. The 1906 law's relevant background in America starts with colonial food statutes concerned with bread and meat. The first national law came in 1848 during the Mexican War. It banned the importation of adulterated drugs, a chronic public health problem.
- In 1937, a public health disaster demonstrated the need for a stronger federal law. Sulfanilamide, the first "wonder drug" and a popular and effective treatment for diseases like strep throat and gonorrhea, was formulated into an Elixir of Sulfanilamide and marketed for use in children. But the liquid formulation contained a poison, the same chemical used in antifreeze, and it killed 107 people, most of them children. The earlier law did not require the drug's manufacturer to test the formulation for safety before it was sold.
- Congress corrected this weakness in the law in **1938** when it passed the **Federal Food, Drug, and Cosmetic Act**. This law, for the first time, required companies to prove the safety of new drugs before putting them on the market. The new act also added the regulation of cosmetics and therapeutic devices, and generally updated the law to improve consumer protection.
- **1976 Medical Devices Amendment**
- Congress continues to give FDA new responsibilities.

FDA STAFFING

- To carry out its mission, FDA employs some 9,000 staff who work in locations around the country.
- The network of 167 field offices is generally the first point of contact for the public and regulated manufacturers. The employees in these offices focus on inspection and surveillance, laboratory work, and public and industry education.
- The FDA staff who work in the greater Washington, D.C., area focus on product review and regulatory policy.

CDRH Advisory Committees

- The Center for Devices and Radiological Health has established **advisory committees** to provide independent, professional expertise and technical assistance on the development, safety and effectiveness, and regulation of medical devices and electronic products that produce radiation. Each committee consists of experts with recognized expertise and judgment in a specific field. The committees are advisory -- they provide their expertise and recommendations -- but final decisions are made by FDA.
- The Center has four advisory committees, including a Medical Devices Advisory Committee which consists of **18 panels** that cover the medical specialty areas. These advisory committee meetings are open to the public, and time is provided for public comment on the topic under consideration.

CDRH Advisory Committees

- **Medical Devices Advisory Committee**
 - Consists of 18 Panels
- **Devices Good Manufacturing Practice (GMP) Advisory Committee**
- **National Mammography Quality Assurance Advisory Committee**
- **Technical Electronic Product Radiation Safety Standards Committee**

FDA ADVISORY PANELS

- **Anesthesiology and Respiratory Therapy Devices**
- **Circulatory System Devices**
- **Clinical Chemistry and Clinical Toxicology Devices**
- **Dental Products**
- **Ear, Nose, and Throat Devices**
- **Gastroenterology and Urology Devices**
- **General and Plastic Surgery Devices**
- **General Hospital and Personal Use Devices**
- **Hematology and Pathology Devices**

FDA ADVISORY PANELS

- **Immunology Devices**
- **Medical Devices Dispute Resolution**
- **Microbiology Devices**
- **Molecular and Clinical Genetics**
- **Neurological Devices**
- **Obstetrics and Gynecology Devices**
- **Ophthalmic Devices**
- **Orthopaedic and Rehabilitation Devices**
- **Radiological Devices**

FDA ADVISORY PANELS **Current Role in the Regulatory Process**

- **Each Panel is made up of experts in the field including physicians, surgeons, scientists and engineers, a consumer representative, and an industry representative (non-voting member)**
- **FDA staff requests that the Panel review certain submissions to FDA and make a recommendation to FDA regarding the acceptance or rejection of the documentation with respect to sufficient evidence to support safety and efficacy; the Panel takes a vote to determine the recommendation**
- **At the Panel meeting, the company makes a presentation to the Panel to support its documentation**
- **FDA may choose to accept or reject the Panel recommendation**

FDA ADVISORY PANELS

Initial Role in the Regulatory Process

- Each Panel reviewed every medical device in its specialty to determine of the classification of the device should be I, II, or III.
- The Panels currently make recommendations about the “down-classification” of devices; *e.g.*, hip replacement prostheses were down-classified from III to II.

CDRH

Overview of Regulations

- The CDRH is responsible for regulating firms who manufacture, repackage, relabel, and/or import medical devices sold in the United States.
- Medical devices are classified into **Class I, II, and III**. A description of device classification and a link to the Product Classification Database can be found at: <http://www.fda.gov/cdrh/devadvice/313.html>. Regulatory control increases from Class I to Class III. The device classification regulation defines the regulatory requirements for a general device type.
 - Most Class I devices are exempt from **Premarket Notification 510(k)**
 - Most Class II devices require **Premarket Notification 510(k)**;
 - Most Class III devices require **Premarket Approval**.

CDRH Overview of Regulations

- The basic regulatory requirements that manufacturers of medical devices distributed in the U.S. must comply with are:
 - Premarket Notification 510(k), unless exempt, or Premarket Approval (PMA),
 - Establishment registration on form FDA-2891,
 - Medical Device Listing on form FDA-2892,
 - Quality System (QS) regulation,
 - Labeling requirements, and
 - Medical Device Reporting (MDR)

Is My Product Regulated by FDA's Center for Devices and Radiological Health?

The FDA regulates medical devices to assure their safety and effectiveness. The CDRH is the component within the FDA that is responsible for this program. To fulfill the provisions of the FD&C Act that apply to medical devices and radiation emitting products, the FDA develops, publishes and implements regulations. These regulations are initially published in the Federal Register (FR) for public comment. The FR is a compilation of the daily government activities including proposed and final regulations. Final regulations are subsequently placed or codified into the Code of Federal Regulations (CFR) on an annual basis.

One of the most important aspects of getting a medical device to market is to know where to begin. The starting point is determining whether the product you plan to market is a medical device, as defined in section 201(h) of the FD&C Act. If your product meets the definitions, it will be subject to the provisions of the FD&C Act, that is, there are FDA regulatory requirements that must be met before a product can be marketed in the U.S. The purpose of Device Advice is to help you decide whether your product is subject to FDA regulations, and if so, to identify what these regulatory requirements are and help you comply with them.

Medical Device Definition

- Medical devices range from simple tongue depressors and bedpans to complex programmable pacemakers with micro-chip technology and laser surgical devices. If a product is labeled, promoted or used in a manner that meets the following definition in section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act it will be regulated by the FDA as a medical device and is subject to premarketing and postmarketing regulatory controls.
- 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 Pharmacopoeia, 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."

Medical Device Definition

- The definition provides a clear distinction between a medical device and other FDA regulated products such as drugs. If the primary intended use of the product is achieved through chemical action or by being metabolized by the body, the product is usually a drug. Human drugs are regulated by FDA's Center for Drug Evaluation and Research (CDER). Biological products which include blood and blood products, and blood banking equipment are regulated by FDA's Center for Biologics Evaluation and Research (CBER).
- FDA's Center for Veterinary Medicine (CVM) regulates products used with animals.
- If your product is not a medical device but regulated by another Center in the FDA, each component of the FDA has an office to assist with questions about the products they regulate.
- In cases where it is not clear whether a product is a medical device there are procedures in place to use DSMICA Staff Directory to assist you in making a determination.

FDA DEVICE CLASSIFICATION

- The **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:
 - Class I General Controls
 - Class II General Controls and Special Controls
 - Class III General Controls and Premarket Approval
- The class to which your device is assigned determines, among other things, the type of premarketing submission/application required for FDA clearance to market.
 - If your device is classified as Class II a 510k will be required for marketing.
 - For Class III devices, a premarket approval application (PMA) will be required.

FDA DEVICE CLASSIFICATION

- Device classification depends on the ***intended use*** of the device and also upon ***indications for use***. For example, a scalpel's intended use is to cut tissue. A subset of intended use arises when a more specialized indication is added in the device's labeling such as, "for making incisions in the cornea." Indications for use can be found in the device's labeling, but may also be conveyed orally during sale of the product.
- In addition, classification is risk based, that is, the risk the device poses to the patient and/or the user is a major factor in the class it is assigned. Class I includes devices with the lowest risk and Class III includes those with the greatest risk.
- As indicated above all classes of devices are subject to General Controls. General Controls are the baseline requirements of the Food, Drug and Cosmetic (FD&C) Act that apply to all medical devices, Class I, II, and III.

How to Determine Classification

To find the classification of your device you need to find the regulation number that is the classification regulation for your device. There are two methods for accomplishing this: go directly to the [classification database](#) and search for a part of the device name, or, if you know the [device panel](#) (medical specialty) to which your device belongs, go directly to the listing for that panel and identify your device and the corresponding regulation.

If you already know the appropriate panel you can go directly to the CFR and find the classification for your device by reading through the list of classified devices, or if you're not sure, you can use the keyword directory in the [PRODUCT CODE CLASSIFICATION DATABASE](#). In most cases this database will identify the classification regulation in the CFR. You can also check the [classification regulations](#) below and the [Precedent Correspondence](#) for information on various products and how they are regulated by CDRH.

Once you have identified the correct classification regulation go to [What are the Classification Panels](#) below and click on the correct classification regulation or go to the [CFR Search](#) page. Some Class I devices are exempt from the premarket notification and/or parts of the good manufacturing practices regulations. Approximately 572 or 74% of the Class I devices are exempt from the premarket notification process. These exemptions are listed in the classification regulations of 21 CFR and also has been collected together in the [Medical Device Exemptions](#) document.

DEVICE CLASSES

[Class I](#) - General Controls

[Class II](#) - Special Controls

[Class III](#) - Premarket Approval

DEVICE CLASSES

Class I - General Controls

- Class I devices are subject to the least regulatory control. They present minimal potential for harm to the user and are often simpler in design than Class II or Class III devices. Class I devices are subject to "General Controls" as are Class II and Class III devices.
- General controls include:
 - Establishment Registration of companies which are required to register under 21 CFR Part 807.20, such as manufacturers, distributors, repackages and relabelers.
 - Medical Device Listing (use FDA Form 2892) with FDA of devices to be marketed.
 - Manufacturing devices in accordance with Good Manufacturing Practices (GMP).
 - Labeling devices in accordance with labeling regulations.
 - Submission of a *premarket notification [510(k)]* before marketing a device.
- Examples of Class I devices include elastic bandages, examination gloves, and hand-held surgical instruments.

DEVICE CLASSES

Class II - Special Controls

- Class II devices are those for which general controls alone are insufficient to assure safety and effectiveness, and existing methods are available to provide such assurances. In addition to complying with general controls, Class II devices are also subject to special controls.
- Special controls may include special labeling requirements, mandatory performance standards and postmarket surveillance.
- Examples of Class II devices include powered wheelchairs, infusion pumps, and surgical drapes.

DEVICE CLASSES

Class III - Premarket Approval

- Class III is the most stringent regulatory category for devices. Class III devices are those for which insufficient information exists to assure safety and effectiveness solely through general or special controls.
- 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.
- Premarket approval is the required process of scientific review to ensure the safety and effectiveness of Class III devices. Not all Class III devices require an approved premarket approval application to be marketed. Class III devices which are equivalent to devices legally marketed before May 28, 1976 may be marketed through the premarket notification [510(k)] process until FDA has published a requirement for manufacturers of that generic type of device to submit PMA data.
- Class III devices which require an approved premarket approval application to be marketed are those:
 - regulated as new drugs prior to May 28, 1976, also called transitional devices.
 - devices found not substantially equivalent to devices marketed prior to May 28, 1976.
 - Class III preamendment devices which, by regulation in 21 CFR, require a premarket approval application.

DEVICE CLASSES

Class III - Premarket Approval

- Examples of Class III devices which require a premarket approval include replacement heart valves, silicone gel-filled breast implants, and implanted cerebella stimulators.
- Class III devices which can be marketed with a premarket notification 510(k) are those:
 - postamendment (i.e., introduced to the U.S. market *after* May 28, 1976) Class III devices which are substantially equivalent to preamendment (i.e., introduced to the U.S. market *before* May 28, 1976) Class III devices and for which the regulation calling for the premarket approval application has not been published in 21 CFR.
- Examples of Class III devices which currently require a premarket notification include implantable pacemaker pulse generators and endosseous implants.

What is Premarket Notification [510(k)]

- Each person who wants to market Class I, II and some III devices intended for human use in the U.S. must submit a 510(k) to FDA at least 90 days before marketing unless the device is exempt from 510(k) requirements.
- A 510(k) is a premarketing submission made to FDA to demonstrate that the device to be marketed is as safe and effective, that is, **substantially equivalent** (SE), to a legally marketed device that is not subject to premarket approval (PMA). Applicants must compare their 510(k) device to one or more similar devices currently on the U.S. market and make and support their substantial equivalency claims.

What is Premarket Notification [510(k)]

- A legally marketed device is
 - a device that was legally marketed prior to May 28, 1976 (preamendments device), or
 - a device which has been reclassified from Class III to Class II or I,
 - a device which has been found to be substantially equivalent to such a device through the 510(k) process.
- The legally marketed device(s) to which equivalence is drawn is known as the "predicate" device(s).

What is Premarket Notification [510(k)]

- **Applicants must submit descriptive data and, when necessary, performance data to establish that their device is SE to a predicate device. Again, the data in a 510(k) is to show comparability, that is, substantial equivalency (SE) of a new device to a predicate device.**

What is Substantial Equivalence

- **Unlike PMA, which requires demonstration of reasonable safety and effectiveness, 510(k) requires demonstration of substantial equivalence. SE means that the new device is as safe and effective as the predicate device(s).**
- **A device is SE if, in comparison to a predicate device it:**
 - has the same intended use as the predicate device; and
 - has the same technological characteristics as the predicate device; or
 - has different technological characteristics, that do not raise new questions of safety and effectiveness, and the sponsor demonstrates that the device is as safe and effective as the legally marketed device.

IDE Overview

- An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification [510(k)] submission to FDA.
- Clinical studies are most often conducted to support a PMA.
- Only a small percentage of 510(k)'s require clinical data to support the application.
- All clinical evaluations of investigational devices, unless exempt, must have an approved IDE before the study is initiated.
- Clinical evaluation of devices that have not been cleared for marketing requires:
 - an IDE approved by an institutional review board (IRB). If the study involves a significant risk device, the IDE must also be approved by FDA;
 - informed consent from all patients;
 - labeling for investigational use only
 - monitoring of the study and;
 - required records and reports.

Premarket Approval (PMA)

- PMA is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices.
 - Class III devices are 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.
- PMA is the most stringent type of device marketing application required by FDA. The applicant must receive FDA approval of its PMA application prior to marketing the device. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). An approved PMA is, in effect, a private license granting the applicant (or owner) permission to market the device. The PMA owner, however, can authorize use of its data by another.

PMA Data Requirements

- A PMA application is a scientific, regulatory documentation to FDA to demonstrate the safety and effectiveness of the class III device. Good science and scientific writing is a key to the approval of PMA application. If a PMA application lacks valid clinical information and scientific analysis on sound scientific reasoning, it will delay FDA's review and approval. PMA applications that are incomplete, inaccurate, inconsistent, omit critical information, and poorly organized have resulted in delays in approval or denial of PMA applications. Manufacturers should perform a quality control audit of a PMA application before sending it to FDA to assure that it is scientifically sound and presented in a well organized format.
- **Technical Sections:** The technical sections containing data and information should allow FDA to determine whether to approve or disapprove the application. These sections are usually divided into non-clinical laboratory studies and clinical investigations.
- **Non-clinical Laboratory Studies' Section:** Non-clinical laboratory studies' section includes information on microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests. Non-clinical studies for safety evaluation must be conducted in compliance with 21CFR Part 58 (Good Laboratory Practice for Nonclinical Laboratory Studies).

PMA Data Requirements

- **Clinical Investigations' Section:** Clinical investigations' section includes study protocols, safety and effectiveness data, adverse reactions and complications, device failures and replacements, patient information, patient complaints, tabulations of data from all individual subjects, results of statistical analyses, and any other information from the clinical investigations. Any investigation conducted under an Investigational Device Exemption (IDE) must be identified as such.
- Like other scientific reports, FDA has observed problems with study designs, study conduct, data analyses, presentations, and conclusions. Investigators should always consult all applicable FDA guidance documents (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfGGP/Search.cfm>).