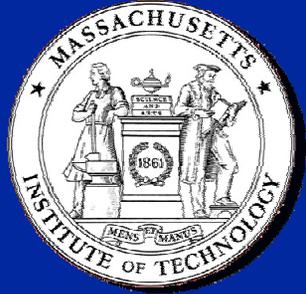
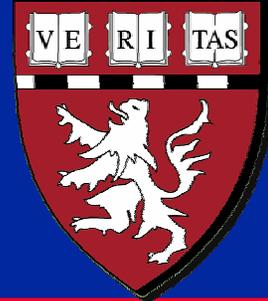


Harvard-MIT Division of Health Sciences and Technology  
HST.535: Principles and Practice of Tissue Engineering  
Instructors: Myron Spector



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



**HST535**

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

**M. Spector, Ph.D.**

# **FEDERAL AGENCIES THAT REGULATE MEDICAL DEVICES AND TISSUE ENGINEERED PRODUCTS**

<b>US</b>	<b>Food and Drug Administration</b>
<b>China</b>	<b>Chinese FDA</b>
<b>Europe</b>	<b>Various agencies; “CE mark”</b>
<b>India</b>	<b>None yet</b>

# 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

Center for Devices and  
Radiological Health  
<http://www.fda.gov/cdrh/index.html>

The screenshot shows the FDA website homepage with the following elements:

- Header:** U.S. Department of Health and Human Services, Food and Drug Administration logo.
- Search:** A search bar powered by Google with a "GO" button and links for "Advanced Search", "A-Z Index", and "Site Map".
- Products FDA Regulates:** A vertical menu listing categories such as Medical Devices, Biologics, Animal Feed and Drugs, Cosmetics, Radiation-Emitting Products, and more.
- FDA NEWS:** A central section with a headline: "Supplement Company Agrees to Stop Selling Ephedrine-Related Products." Below it, a brief summary of the news item.
- Hot Topics:** A list of trending items including Antibiotics, Bioterrorism, BSE (Mad Cow Disease), Buying, LASIK, PPA, and More Hot Topics.
- FDA Activities:** A list of activities including Advisory Committees, Clinical Trials/Human Subject Protection, FDA Modernization, Field Operations, Freedom of Information, Imports, International, MedWatch: Safety Information/ Adverse Event Reporting, Science @ FDA, and User Fees.
- Information For:** A list of target audiences including Consumers, Patients, Health Professionals, State/Local Officials, Industry, Press, Women, Seniors, and Kids.
- Footer:** A red banner with the URL "www.fda.gov" and a small FDA logo in the bottom right corner.

# 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

# FDA APPROVAL PROCESS

Classification of Product as I, II, or III

I. General Controls

II. Special Controls

III. Premarket Approval (PMA)

TE products

No approval of FDA prior to selling the product.

Good Manuf. Practice

GMP

# FDA APPROVAL PROCESS

Classification of Product as I, II, or III

**I. General Controls**

No approval of FDA prior to selling the product.

Good Manuf. Practice

GMP

**II. Special Controls**

Equivalent to Marketed Device?;  
Premarket Notification

510 (k)

**III. Premarket Approval (PMA)**

TE products

# FDA APPROVAL PROCESS

Classification of Product as I, II, or III



No approval of FDA prior to selling the product.

Equivalent to Marketed Device?;  
Premarket Notification

510 (k)

Good Manuf. Practice

GMP

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

Good Lab Pract.

GLP

# FDA APPROVAL PROCESS

Classification of Product as I, II, or III

TE products

I. General Controls

II. Special Controls

III. Premarket Approval (PMA)

No approval of FDA prior to selling the product.

Equivalent to Marketed Device?;  
Premarket Notification

Human Trial Investigational Device Exemption

510 (k)

IDE

Good Manuf. Practice

GMP

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

PMA

Good Lab Pract.

GLP

# 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 the next year 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.
- Congress has continued to give FDA new responsibilities over the years, including the requirement that drugs and medical devices be proven effective as well as safe before they can be sold (Medical Devices Amendment of 1976).

# 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

## Overview of Regulations

- The CDRH is responsible for regulating firms who manufacture, repack, 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 I or 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, and also some joint replacement prostheses and bone graft substitute materials.**

# 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>).

# **FEDERAL REGULATORY ISSUES**

## **Recommended Biocompatibility Testing and Clinical Trials**

# **Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices**

<http://www.fda.gov/cdrh/g951.html>

- **FDA-modified matrix that designates the type of testing needed for various medical devices.**
- **It also includes a flow chart entitled "Biocompatibility Flow Chart for the Selection of Toxicity Tests for 510(k)s."**
- **The guidance will be effective for all submissions that will be received on or after July 1, 1995. The former guidance, #G87- 1 entitled "Tripartite Biocompatibility Guidance," may continue to be applied until a final decision is reached on each submission received prior to July 1, 1995.**

# **Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices**

- **Biological evaluation of medical devices is performed to determine the potential toxicity resulting from contact of the component materials of the device with the body.**
- **The device materials should not, either directly or through the release of their material constituents:**
  - (i) produce adverse local or systemic effects;
  - (ii) be carcinogenic; or
  - (iii) produce adverse reproductive and developmental effects.
- **Therefore, evaluation of any new device intended for human use requires data from systematic testing to ensure that the benefits provided by the final product will exceed any potential risks produced by device materials.**

# **Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices**

- **When selecting the appropriate tests for biological evaluation of a medical device, one must consider the chemical characteristics of device materials and the nature, degree, frequency and duration of its exposure to the body.**
- **In general, the tests include:**
  - acute, sub- chronic and chronic toxicity;
  - irritation to skin, eyes and mucosal surfaces;
  - sensitization;
  - hemocompatibility;
  - genotoxicity;
  - carcinogenicity; and
  - effects on reproduction including developmental effects.
- **Additional tests for specific target organ toxicity, such as neurotoxicity and immunotoxicity may be necessary for some devices.**
  - For example, a neurological device with direct contact with brain parenchyma and cerebrospinal fluid (CSF) may require an animal implant test to evaluate its effects on the brain parenchyma, susceptibility to seizure, and effects on the functional mechanism of choroid plexus and arachnoid villi to secrete and absorb (CSF).
- **The specific clinical application and the materials used in the manufacture of the new device determines which tests are appropriate.**

# **International Organization for Standards, ISO**

[http://www.iso.ch/iso/en/CatalogueListPage.CatalogueList?ICS1=11&ICS2=100  
&ICS3=](http://www.iso.ch/iso/en/CatalogueListPage.CatalogueList?ICS1=11&ICS2=100&ICS3=)

ISO 10993-1:1997 Biological evaluation of medical devices --  
Part 1: Evaluation and testing

ISO 10993-2:1992 Biological evaluation of medical devices --  
Part 2: Animal welfare requirements

ISO 10993-3:1992 Biological evaluation of medical devices --  
Part 3: Tests for genotoxicity, carcinogenicity and  
reproductive toxicity

ISO 10993-4:2002 Biological evaluation of medical devices --  
Part 4: Selection of tests for interactions with blood

ISO 10993-5:1999 Biological evaluation of medical devices --  
Part 5: Tests for in vitro cytotoxicity

ISO 10993-6:1994 Biological evaluation of medical devices --  
Part 6: Tests for local effects after implantation

# **International Organization for Standards, ISO**

[http://www.iso.ch/iso/en/CatalogueListPage.CatalogueList?ICS1=11&ICS2=100  
&ICS3=](http://www.iso.ch/iso/en/CatalogueListPage.CatalogueList?ICS1=11&ICS2=100&ICS3=)

**ISO 10993-7:1995 Biological evaluation of medical devices --  
Part 7: Ethylene oxide sterilization residuals**

**ISO 10993-8:2000 Biological evaluation of medical devices --  
Part 8: Selection and qualification of reference materials for  
biological tests**

**ISO 10993-9:1999 Biological evaluation of medical devices --  
Part 9: Framework for identification and quantification of  
potential degradation products**

**ISO 10993-10:2002 Biological evaluation of medical devices --  
Part 10: Tests for irritation and delayed-type hypersensitivity**

**ISO 10993-11:1993 Biological evaluation of medical devices --  
Part 11: Tests for systemic toxicity**

**ISO 10993-12:2002 Biological evaluation of medical devices --  
Part 12: Sample preparation and reference materials**

# International Organization for Standards, ISO

[http://www.iso.ch/iso/en/CatalogueListPage.CatalogueList?ICS1=11&ICS2=100  
&ICS3=](http://www.iso.ch/iso/en/CatalogueListPage.CatalogueList?ICS1=11&ICS2=100&ICS3=)

ISO 10993-13:1998 Biological evaluation of medical devices --  
Part 13: Identification and quantification of degradation  
products from polymeric medical devices

ISO 10993-14:2001 Biological evaluation of medical devices --  
Part 14: Identification and quantification of degradation  
products from ceramics

ISO 10993-15:2000 Biological evaluation of medical devices --  
Part 15: Identification and quantification of degradation  
products from metals and alloys

ISO 10993-16:1997 Biological evaluation of medical devices --  
Part 16: Toxicokinetic study design for degradation products  
and leachables

ISO 10993-17:2002 Biological evaluation of medical devices --  
Part 17: Establishment of allowable limits for leachable  
substances

# **American Society for Testing and Materials**

<http://www.astm.org>

**Search “Biocompatibility”**

# **FDA**

## **TISSUE ENGINEERING PRODUCTS**

**FDA's Tissue Reference Group Workshop**

**August 29, 2001 - Slide Presentation**

**Human Cells, Tissues, and Cellular and Tissue-  
Based Products (HCT/Ps) Regulated as Devices**

**Mark N. Melkerson**

**CDRH / FDA**

**Tissue Reference Group (TRG)**

**“FDA’s TRG Process”**

**<http://www.fda.gov/cber/summaries/melkersontrg.htm>**

# **Premarket Review of Biological Products & Medical Devices**

- **Biological Products**
- **Medical Devices**
- **Combination Products**

# Definition of a Medical Device

- “...apparatus,...., implant, *in vitro* reagent, including any component...or accessory...
- intended for the diagnosis, mitigation, treatment, or prevention of disease...
- or intended to affect the structure or function of the body...
- **and does not achieve its primary intended purposes through chemical action within or on the body...and which is not dependent upon being metabolized...**”

# Examples of Medical Devices & Combination Products

- **Medical Devices - collagen, hyaluronic acid and synthetic implants**
  - FocalSeal-L - aqueous PEG solutions modified to photo-polymerize *in situ*
  - Emdogain - porcine enamel matrix proteins
- **Combination Products -**
  - Apligraf - cells on bovine collagen

# Marketing Applications

- **Premarket Notification (Class II Devices)**  
**Section 510(k) of the FD&C Act (21 CFR 807)**
- **Premarket Approval Application (Class III Devices)**  
**Section 515 of the FD&C Act (21 CFR 814)**
- **Humanitarian Device Exemption (requires HUD Designation)**  
**Section 520(m) of the FD&C Act (21 CFR 814.100)**

# Premarket Notification Review

- Case-by-case approach, except if can demonstrate “equivalent” to predicate device
- Basic elements:
  - Same Intended Use(s)
  - Preclinical equivalence of Product Manufacture, *In vitro* and/or *in vivo* testing
  - May need to demonstrate equivalence of Clinical Performance, if seeking specific indication(s) for use under general intended use(s) or differences in technological characteristics

# **Food and Drug Administration Modernization Act of 1997**

- **Gave CDRH authority to recognize national and international standards in product reviews**
  - **Allows for “Declaration of Conformity”**
  - **Somewhat mirrors device marketing authorities used in Europe**

# CDRH Standards Program

[www.fda.gov/cdrh/stdsprog.html](http://www.fda.gov/cdrh/stdsprog.html)

- **Standards Participation**

- **ASTM F04**

- **Division IV - Tissue Engineered Medical Products (TEMPS)**

- **ISO TC 150**

- **Working Group 11 - Tissue Engineered Implants (Reviewing Other Standards Development Activities)**

# Premarket Approval Review

- **Case-by-case approach**
- **Both safety and effectiveness evaluations**
- **Basic elements:**
  - **Product Manufacture**
  - *In vitro* and *in vivo* testing
  - **Clinical Performance**
  - **Product Labeling**
- **Product Manufacture**
  - **Cell, tissue & biomaterial sourcing**
  - **Product Processing**
  - **In-process and final product tests**
  - **Adventitious agents & co-purifying impurities**
  - **Lot - to - lot consistency**
  - **Quality control procedures**

# Premarket Approval Review

- *In vitro* and *in vivo* testing
  - Toxicity / Genotoxicity
  - Biomaterials biocompatibility
  - Immunogenicity /inflammatory responses
  - Models of product effectiveness
  - Product resorption/decomposition
- Investigating product safety and clinical benefit:
  - Patient population
  - Investigational and control treatments
  - Study endpoints
  - Study conduct
  - Data analysis
  - Labeling claims

# Investigational Human Studies

- **An exemption from marketing approval is required when unapproved products are studied in humans.**
  - **Investigational Device Exemption (IDE) 21 CFR 812**
- **For significant risk medical devices:**
  - **FDA approval of IDE**
  - **IRB approval**

# Humanitarian Device Exemption

- Requires HUD (maximum of 4000 cases/per year) and requires no alternatives be marketed
- Case-by-case approach
- Both safety and probable benefit evaluations
  - Product Manufacture
  - *In vitro* and *in vivo* testing
  - Clinical Perform
  - Product Labeling

# Internet Access to FDA Documents

- **Proposed Approach to Regulation of Cellular and Tissue-Based Products - 2/28/97 -**  
**<http://www.fda.gov/cber/gdlns/CELLTISSUE.txt>**
- **Tissue Action Plan -**  
**<http://www.fda.gov/cber/tissue/tissue.htm>**
- **Intercenter Agreement Between The Center for Biologics Evaluation and Research and The Center for Devices and Radiological Health -**  
**<http://www.fda.gov/oc/ombudsman/bio-dev.htm>**
- **Guidance on Applications for Products Comprised of Living Autologous Cells Manipulated Ex Vivo and Intended for Structural Repair or Reconstruction (5/96)**  
**- <http://www.fda.gov/cber/gdlns/GDEXV.TXT>**

# Internet Access to FDA Documents

- **Guidance For the Submission of Chemistry, Manufacturing and Controls Information and Establishment Description for Autologous Somatic Cell Therapy Products - 1/10/97 -**  
**<http://www.fda.gov/cber/gdlns/xvcmc.txt>**
- **Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices 5/1/95 (G95-1)**  
**- <http://www.fda.gov/cdrh/g951.html>**
- **Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation**  
**<http://www.fda.gov/cber/gdlns/xenophs0101.htm>**
- **FDA PMA Database Search Engine**  
**<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm>**

# Tissue Related Documents

<http://www.fda.gov/cber/tissue/docs.htm>

- **Guidance for Industry: Availability of Licensed Donor Screening Tests Labeled for Use with Cadaveric Blood Specimens - 6/23/2000**
- **Suitability Determination for Donors of Human Cellular and Tissue-Based Products; Proposed Rule; reopening of comment period - 4/18/2000**
- **Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products - 5/14/98**
- **Guidance for Industry - Screening and Testing of Donors of Human Tissue Intended for Transplantation - 7/29/97**
- **Guidance for the Preparation of a Premarket Notification Application for Processed Human Dura Mater - <http://www.fda.gov/cdrh/ode/054.html>**

# Specific Product Information

- **FocalSeal-L Sealant- Focal - SSE**
  - <http://www.fda.gov/cdrh/pdf/p990028b.pdf>
- **Apligraf - Organogenesis - SSE**
  - <http://www.fda.gov/cdrh/pdf/p950032.pdf>
- **CCS - Ortec, Inc. - SSPB (H990013)**
  - <http://www.fda.gov/cdrh/pdf/h990013b.pdf>

# **Multi-Agency Tissue Engineering Science (MATES) Working Group**

**The Multi-Agency Tissue Engineering Science (MATES) Working Group is proposed as a means for the various federal agencies involved in Tissue Engineering to stay informed of each other's activities and better coordinate their efforts.**

# **Multi-Agency Tissue Engineering Science (MATES) Working Group**

## **Five Year Plan; Subcommittee on Biotechnology**

The term “Tissue Engineering” was coined at an NSF-sponsored meeting in 1987(1). At a subsequent NSF sponsored workshop, Tissue Engineering was defined as “the application of principles and methods of engineering and life sciences toward fundamental understanding of structure-function relationships in normal and pathological function” (2). This multidisciplinary technology involves the development of biological substitutes for the repair or regeneration of tissue or organ function and has led to a broad range of products.

1. Heineken FG and Skalak R. Tissue Engineering: A Brief Overview, *Journal of Biomechanical Engineering* 113, 111 (1991).
2. Skalak R and Fox CF, eds. Tissue Engineering, Proceedings for a Workshop held at Granlibakken, Lake Tahoe, California, February 26-29, 1988, Alan Liss, New York.

# Multi-Agency Tissue Engineering Science (MATES) Working Group

To date, some of these products have been approved by the U.S. Food and Drug Administration while many are under either preclinical investigation or regulatory evaluation (3, 4). Since 1990, the Tissue Engineering industry has grown to become more than a \$3.5 billion worldwide R&D effort by over seventy biotechnology start-ups and business units (5, 6). Less than ten percent of this effort is funded by the U.S. government, but this contribution is rapidly increasing.

3. Hellman KB, Knight E, and Durfor CN. Tissue Engineering: Product Applications and Regulatory Issues, pp. 341-366, Frontiers in Tissue Engineering, Charles W. Patrick, Antonio G. Mikos, and Larry V. McIntire (eds.), Amsterdam, Elsevier Science (1998).
4. Hellman KB., Solomon RR, Gaffey C, Durfor C and Bishop JG, III. Tissue Engineering: Regulatory Considerations, Principles of Tissue Engineering, 2nd Edition, Robert Lanza, Robert Langer, and Joseph P. Vacanti (eds.), Academic Press, San Diego, California (in press).
5. Lysaght MJ, Nguy AS, and Sullivan K. An Economic Survey of the Emerging Tissue Engineering Industry, Tissue Engineering: 4, 231 (1998).
6. Lysaght MJ, and Reyes J. The Growth of Tissue Engineering, Tissue Engr.

# FDA APPROVAL PROCESS

Classification of Product as I, II, or III

TE products

I. General Controls

II. Special Controls

III. Premarket Approval (PMA)

No approval of FDA prior to selling the product.

Equivalent to Marketed Device?;  
Premarket Notification

Human Trial Investigational Device Exemption

510 (k)

IDE

Good Manuf. Practice

GMP

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

PMA

Good Lab Pract.

GLP