Medical Devices 101

An Educational Forum
Introduction

Disclaimers, housekeeping, logistics, laws, regulations, and guidance documents
No Smoking
Cell Phones, Pagers and PDA’s

- Please make sure your cell phones, pagers, and other devices are set on silent mode.
- Please step outside if you must answer or make a call.
Logistics

- Restrooms
- Breaks
- Lunch
- Questions
- Evaluation form
- CEU request form
Disclaimer

- The information provided in this forum does not take the place of the laws and regulations enforced by FDA.
- Any reference to a commercial product, process, service, or company is not an endorsement or recommendation by the U.S. government, HHS, FDA or any of its components.
Disclaimer

- FDA is not responsible for the contents of any outside information referenced in this forum.

- This forum does not convey any waiver of responsibility to the firm, nor impart any immunity to the firm for violations that may occur, even if you implement our recommendations as per 21 CFR 10.85(k).
Safe And Effective

Drugs
Biologics
Medical Devices
Standards And Regulations
What are Regulations?

- Implement the provisions of the law based on the authority provided by the law
- The development of regulations must follow specific procedures that allow public notice and comment
- Legally binding on industry and the agency
Federal Register

- Official daily publication
  - Notices
  - Proposed Rules
  - Final Rules
- Free online through http://www.gpo.gov/
or http://www.fda.gov/
- GPO subscription
Code of Federal Regulations

- Title 21, Food and Drugs
- Published yearly
- Free online through
  - http://www.gpo.gov/
  - http://www.fda.gov/
- Order through GPO at 1-866-512-1800
History of FDA & Medical Device Regulations

- The basic enabling authority enacted by Congress
  - 1906 - Pure Food & Drug Act
    - Prohibited of misbranded & adulterated food, drinks & drugs
  - 1938 - Food, Drug and Cosmetic Act (FD&C)
    - Replaced 1906 Act
    - Legally enforceable food standards
History of FDA & Medical Device Regulations

- 1976 - Medical Device Amendments (MDA)
  - To insure the safety & effectiveness of Medical Devices and IVDs
  - Medical Device Manufacturers required to register with the FDA
  - Established risk classification for devices
  - Good Manufacturing Practice established

- 1990 - Safe Medical Device Act (SMDA)
  - 1st reform since 1976
  - Users required to file MDR’s
  - FDA authority to order Recalls & other actions
History of FDA & Medical Device Regulations

- **1997 - FDA Modernization Act (FDAMA)**
  - Most wide ranging reform since 1938
  - Accelerated review of Medical Devices
  - Regulation of Advertising
  - User Fees

- **2002 - Medical Device User Fee Modernization Act (MDUFMA)**
  - 3rd Party inspection approved
  - User Fees
History of FDA & Medical Device Regulations

- 2012 FDA Safety & Innovation Act (FDASIA)
  - Promoting Innovation - speed up patient access
  - Stakeholder Engagement in decision making process
  - User Fees
Guidance Documents...

...Policy Statements and Advisory Opinions

- Serve to provide the Agency’s interpretation of the law and applicable regulations
- The preamble to a regulation has the status of an advisory opinion
- Are not legally binding on the public or the agency
Device Advice: Device Regulation and Guidance

Information for regulated industry on determining how to comply with the federal laws and regulations governing medical devices.

Additional Information

- DSMICA Staff Directory
- Addresses for Submissions
- Addresses for Electronic Product Radiation Control Reports and Recordkeeping
- CDRH Mailing Addresses and Office Phone Numbers
- CDRH Learn
- CDRH Referral List

Contact Us

CDRH-Division of Small Manufacturers, International and Consumer Assistance (DSMICA)

- 1-800-638-2041
- 301-847-8149 (Fax)
- dsmica@fda.hhs.gov

Office of Communication, Outreach and Education (OCOE)
Is it a medical device?

Claims make the difference
an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, including a component part, or accessory:

- recognized in the National Formulary (NF), or the United States Pharmacopoeia (USP)
an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, including a component part, or accessory:

- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease
an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, including a component part, or accessory:

- intended to affect the structure or any function of the body
Federal Food Drug & Cosmetic Act

- an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, including a component part, or accessory:
  - primary intended purposes **not** achieved through chemical action within or on the body
  - not dependent upon being metabolized to achieve primary intended purposes
Drugs

- Primary intended use is achieved through chemical action or by being metabolized by the body
- Regulated by FDA's Center for Drug Evaluation and Research (CDER)
FFDCA Section 513(g)

- Request for determination via mail to:
  - FDA/CDRH - 513(g) request enclosed
    Document Mail Center (WO66-G609)
    10903 New Hampshire Avenue
    Silver Spring, Maryland 20993

- Describe product, how it works, and indications for use on company letterhead
- User fee: $3,348 or $1,674 for small business
- Turnaround: 60 days
Request For Designation (RFD)

- By the FDA Office of Combination Products
- Determines if product is a device, drug, biologic, or a combination product
- No charge
Device Classification

Based on risk and complexity, determines the path to market
Device Classification System

- Increases with level of risk
  - Class I
  - Class II
  - Class III

- Determines level of regulation applied to the device
Class I Devices

- 45% of all devices
- Low-risk devices
  - Surgical instruments, wound dressings, toothbrush
- General Controls
- Most are exempt from Premarket Notification, 510(k)
CLASS I DEVICES

- Most Class I devices and a few Class II devices are exempt from the premarket notification [510(k)] requirements subject to the limitations on exemptions. However, these devices are not exempt from other general controls.
GENERAL REQUIREMENTS

- All medical devices must be manufactured under a quality assurance program,
- Be suitable for the intended use,
- Be adequately packaged and properly labeled, and
- Have establishment registration and device listing forms on file with the FDA.
CLASS I DEVICES

- A few Class I devices are additionally exempt from the GMP requirements with the exception of complaint files and general record keeping requirements.
CLASS I & II EXEMPT

- Class I/II Devices Exempt from 510(k) and class I Devices Exempt from GMPs
- Devices exempt from 510(k) are:
  - Pre-amendment devices not significantly changed or modified; or
  - Class I/II devices specifically exempted by regulation.
CLASS I NON-EXEMPT

The following class I devices are subject to design controls:

- (i) Devices automated with computer software; and
- (ii) the devices listed in the following slide.
CLASS I NON-EXEMPT

- 868.6810 … Catheter, Tracheobronchial Suction
- 878.4460 …Glove, Surgeon's
- 880.6760…Restraint, Protective
- 892.5740…Source, Radionuclide Teletherapy.
For the purposes of 510(k) decision-making, the term “pre-amendment device” refers to devices legally marketed in the U.S. before May 28, 1976 and have not been:

- Significantly changed or modified since then
- And for which a regulation requiring a PMA Application has not been published by FDA
- Devices meeting this description are “grandfathered” and do not need a 510(k)
Class II Devices

- 49% of all devices
- Moderate-risk devices
  - E.g., blood pressure cuffs, vascular clamps, sutures, aneurysm clips, facial implants, urology catheters, cautery devices
- General and Special Controls
- Most not exempt from Premarket Notification, 510(k)
Special Controls

- Performance standards
- Postmarket surveillance
- Guidance documents
  - Clinical data, special labeling, warnings, precautions, contraindications
- Patient registries for some devices
  - Tracking, Adverse Events
Class III Devices

- Approximately 6% of all devices
- Moderate and high risk devices
  - Pacemakers, heart valves, breast implants, vascular grafts, lithotripters, lasers
- General Controls, Special Controls, and Premarket Approval (PMA)
- Clinical data needed
1746 Categories
- 786 Class I
  - 729 exempt from 510(k)
- 860 Class II
  - 68 exempt from 510(k)
- 100 Class III
How to Determine Classification

- **Product Classification Database**
  - Contains device names and regulations

- Go to the listing for the device panel (medical specialty) to which your device belongs and identify your device and the corresponding regulation

- Pay a fee & request for Classification 513(g)
Classification Regulations

868 Anesthesiology
870 Cardiovascular
862 Clinical Chemistry and Clinical Toxicology
872 Dental
874 Ear, Nose, and Throat
876 Gastroenterology and Urology
878 General and Plastic Surgery
880 General Hospital and Personal Use
864 Hematology and Pathology
866 Immunology and Microbiology
882 Neurology
884 Obstetrical and Gynecological
886 Ophthalmic
888 Orthopedic
890 Physical Medicine
892 Radiology
Establishment Registration

Updated annually, tells FDA where you are and what you do
Requirement

- Establishments producing and distributing devices intended for marketing or leasing in the USA
- Provides location of device manufacturing facilities and importers
- FY-2013 Annual User Fee of $2,575
- 21 CFR 807
Establishment Registration

- Is not an approval of the establishment or its devices
- Does not provide FDA clearance to market
- Unless exempt, premarketing clearance is required before a device can be placed into commercial distribution in the USA
- 21 CFR 807.39
Misbranding

- Any representation that creates an impression of official approval because of registration or possession of a registration number is misleading and constitutes misbranding.

- Labeling and web site cannot reference a registration number or make reference to your establishment being registered or approved by FDA.
Establishment

- Place of business under one management at one physical location at which a device is manufactured, assembled, or processed for commercial distribution
Owner/Operator

- Corporation, subsidiary, affiliated company, partnership, or proprietor directly responsible for the activities of the establishment
- Responsible for registration
Who Must Register

- Manufacturers
  - Manufacture, preparation, propagation, compounding, assembly, or processing of a medical device intended for commercial distribution
  - Manufacturers, contract manufacturers, contract sterilizers, specification developers, repackagers or relabelers, reprocessors of single-use devices, remanufacturers, manufacturers of export-only devices, and manufacturers of components or accessories that are sold or leased directly to the end user
Who Must Register

- Initial Importers
  - Distributor that takes first title to the devices imported into the USA and further distributes the product
  - Not required to list the products imported
Who Must Register

- Foreign establishments
  - Manufacture, prepare, propagate, compound, or process a device that is imported, or offered for import, into the USA
  - Includes contract manufacturers and contract sterilizers
  - Must provide US Agent contact information
US Agent

- Foreign establishments must notify FDA of their US agent name, address, phone, fax, and email
- Only 1 per establishment
- Must reside or maintain a place of business in the USA
- No PO box or answering service
- Must be available during normal business hours
When to Register

- Within 30 days after entering into any activity requiring registration
- 1st time establishment registration must also list devices
How to Register

https://www.access.fda.gov/oaa/
Updating Registration Data

- Annual requirement
- Registration year begins October 1\textsuperscript{st} and ends September 30\textsuperscript{th}
- Submit changes online anytime
Device Listing

Tells FDA what types of devices you make
What Is It?

- Lets FDA know the generic categories of devices an establishment is manufacturing or marketing.
- Most establishments required to register must also list devices in commercial distribution including those for export.
- There is no additional fee for listing your device.
- 21 CFR 807.
Generic Categories

- Represented by a classification regulation found in 21 CFR 862-892
- Each regulation is associated with one or more product codes
- Regulations with more than one product code identify the product in further detail
Device Classification Panels

- 868 Anesthesiology
- 870 Cardiovascular
- 862 Clinical Chemistry and Clinical Toxicology
- 872 Dental
- 874 Ear, Nose, and Throat
- 876 Gastroenterology and Urology
- 878 General and Plastic Surgery
- 880 General Hospital and Personal Use
- 864 Hematology and Pathology
- 866 Immunology and Microbiology
- 882 Neurology
- 884 Obstetrical and Gynecological
- 886 Ophthalmic
- 888 Orthopedic
- 890 Physical Medicine
- 892 Radiology
Product Classification Database

- Contains device names and product codes
- Use 3 letter product code, not the regulation number
Product Codes

- Three letter code
- Example
  - 21 CFR 878.4800, Manual Surgical Instruments for General Use
    - GAB, disposable suturing needle
    - GDX, scalpel
    - HTD, forceps
    - HRQ, hemostat
Not Approval!

- Listing a medical device is **not** approval of the establishment or a device by FDA
- Unless exempt, premarketing clearance is required before a device can be marketed or placed into commercial distribution in the USA
Who Must List

- Owner/operator engaged in the manufacture, preparation, propagation, compounding, assembly, or processing of a medical device intended for commercial distribution
  - manufacturers, repackagers and relabelers, specification developers, reprocessors of single-use devices, remanufacturers, manufacturers of export-only devices, and manufacturers of accessories and components sold directly to the end user
  - Foreign manufacturers must list devices before importing
When to List

- Within 30 days of entering into any activity requiring registration
- 1st time, the registration form must submitted with device listing form
How to List

https://www.access.fda.gov/oaa/
Updating Listing Data

- Required when
  - New device not covered by listed product code
  - Discontinued device
  - Re-marketing discontinued device
  - Changes in type of operations

- Update online listing when change occurs
- Official Correspondent is responsible for keeping listing current
The “route to market” primarily for Class II devices - *Fees required*
“510(k)” refers to the relevant section of the Medical Device Amendments of 1976 - Also known as Premarket Notification

21 CFR 807 - Subpart E

Required for most Class II devices, non-exempt Class I’s, and a special set of Class IIs

Except for certain exceptions, your device must be “substantially equivalent” to another legally marketed Class II device...(the predicate device) ...if not it couldn’t be Class II!
The 510(k) process is under review both within the FDA and previously by the Institute of Medicine (IOM) under commission by the FDA.

8/4/2010 - CDRH releases the results of a Preliminary Internal Evaluation

- Foreword: A Message from the Center Director
- Volume I: 510(k) Working Group Preliminary Report and Recommendations
- Volume II: Task Force Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations
- Basic Questions and Answers on Preliminary Reports
Key points of the Internal Evaluation

- Three major themes:
  - Fostering Medical Device Innovation
  - Enhancing Regulatory Predictability
  - Improving Patient Safety

*All of which is currently still under study!*
Key points of the Internal Evaluation

- Fostering Medical Device Innovation
  - Streamlining for lower-risk novel devices
  - Enhancing CRDH science professional development
  - Outside experts
Key points of the Internal Evaluation

- Enhancing Regulatory Predictability
  - Data requirements (new class IIB?)
  - Improved Notice to Industry tool
  - Terminology clarification
  - Center Science Council
Key points of the Internal Evaluation

- Improving Patient Safety
  - Require more complete safety and effectiveness data
  - Better public database
  - Clarify circumstances under which a 510(k) clearance can be rescinded
The juggle

- innovation
- safety
- patient benefit
- business

Innovation

Safety

Patient benefit

Business
Subpart E--Premarket Notification Procedures

§ 807.81 - When a premarket notification submission is required
§ 807.85 - Exemption from premarket notification
§ 807.87 - Information required in a premarket notification submission
§ 807.90 - Format of a premarket notification submission
§ 807.92 - Content and format of a 510(k) summary
§ 807.93 - Content and format of a 510(k) statement
§ 807.94 - Format of a class III certification
§ 807.95 - Confidentiality of information
§ 807.97 - Misbranding by reference to premarket notification
§ 807.100 - FDA action on a premarket notification
Premarket Notification (510(k))

- Introduction
- What is Substantial Equivalence
- Who is Required to Submit a 510(k)
- When a 510(k) is Required
- When a 510(k) is not Required
- Third Party Review Program

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm
510(k) - Special cases

- Class I’s requiring 510(k)
- Class II’s exempt from 510(k)
- Class III’s still allowing 510(k)*

* see http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances/ucm133989.htm
Non-exempt (Reserved) Class I - Examples

862.1175 – Cholesterol (total) test system
864.9125 – Vacuum-assisted blood collection system
868.5240 – Anesthesia breathing circuit
872.4565 – Dental hand instrument
878.4460 – Surgeon’s glove
880.6960 – Irrigating syringe
886.4070 – Powered corneal burr
890.3850 – Mechanical wheelchair
892.1110 – Positron Camera

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/3151.cfm
## Exempt Class II - Examples

### Part 870 - Cardiovascular

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>870.1875</td>
<td>Stethoscope</td>
</tr>
<tr>
<td>870.2390</td>
<td>Phonocardiograph</td>
</tr>
<tr>
<td>870.2600</td>
<td>Signal Isolation System</td>
</tr>
<tr>
<td>870.2620</td>
<td>Line Isolation Monitor</td>
</tr>
<tr>
<td>870.2640</td>
<td>Portable Leakage Current Alarm</td>
</tr>
<tr>
<td>870.2810</td>
<td>Paper Chart Recorder</td>
</tr>
<tr>
<td>870.3450</td>
<td>Vascular Graft Prosthesis. II</td>
</tr>
<tr>
<td>870.3650</td>
<td>Pacemaker Polymeric Mesh Bag</td>
</tr>
<tr>
<td>870.3670</td>
<td>Pacemaker Charger</td>
</tr>
<tr>
<td>870.3690</td>
<td>Pacemaker Test Magnet</td>
</tr>
<tr>
<td>870.3730</td>
<td>Pacemaker Service Tools</td>
</tr>
<tr>
<td>870.3935</td>
<td>Prosthetic Heart Valve Holder</td>
</tr>
<tr>
<td>870.3945</td>
<td>Prosthetic Heart Valve Sizer</td>
</tr>
<tr>
<td>870.4200</td>
<td>Cardiopulmonary Bypass Accessory Equipment</td>
</tr>
<tr>
<td>870.4500</td>
<td>Cardiovascular Surgical Instruments</td>
</tr>
</tbody>
</table>
Class III’s - “Grandfathered”

25 device categories:

GAO – January 15, 2009
Medical Devices: FDA Should Take Steps to Ensure That High-Risk Device Types Are Approved through the Most Stringent Premarket Review Process

FDA – April 8, 2009
FDA to Review Medical Devices Marketed Prior to 1976

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149560.htm
End of grandfathering?

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances/ucm133989.htm
510(k) - In general

- Required when you:
  - introduce the device for commercial distribution
  - change in the intended use
  - change or modification of your already “cleared” device

- Third Party Review may be an option
510(k)

- Types of 510(k)s
  - Traditional
  - Abbreviated-based on guidance documents, special controls and recognized standards
  - Special - modifications to your own previously cleared device in conformance with Design Controls
  - De novo
Intent to Market a Device for Which a 510(k) is Required

Device represents modification to your own device?
- No
  - FDA guidance or special control/recognized standard for the device?
    - No
      - Conformance Assured
        - "Special 510(k): Device Modification" Submitted
    - Yes
      - Conformance Assured
        - "Abbreviated 510(k)" Submitted
- Yes
  - Modification appropriate for reliance on results from design control process?
    - No
      - Conformance Assured
        - "Abbreviated 510(k)" Submitted
    - Yes
      - Conformance Assured
        - Traditional 510(k) Submitted

INDUSTRY

FDA Assessment

Additional Information
- Cannot determine
  - Is it SE?
    - No
      - NSE
    - Yes
      - SE

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm (Note: scroll down)
510(k) - Traditional

Contents and format - cover materials

- Medical Device User Fee Cover Sheet (Form FDA 3601)
- CDRH Premarket Review Submission Cover Sheet
- Statement of registration of clinical trials
- 510(k) Cover Letter
- Indications for Use Statement
- 510(k) Summary or 510(k) Statement
- Truthful and Accuracy Statement
- Class III Summary and Certification (for Class III devices still regulated under 510(k))
- Financial Certification or Disclosure Statement
- Declarations of Conformity and Summary Reports
- **Contents and format**
  - Executive Summary
  - Device Description
  - Substantial Equivalence Discussion
  - Proposed Labeling
  - Sterilization and Shelf Life
  - Biocompatibility
  - Software
  - Electromagnetic Compatibility and Electrical Safety
  - Performance Testing - Bench, animal, clinical
  - Other

Abbreviated relies on description of compliance with guidance documents, special controls, or recognized standards “to expedite review”.
510(k) - SPECIAL

- Most of the standard material required
- With emphasis on a concise summary of the design changes, verification and validation under design controls
While the basic content requirements of the 510(k) (21 CFR 807.87) remain the same, this type of submission should also reference the cleared 510(k) number and contain a "Declaration of Conformity" with design control requirements.

Manufacturers of Class I devices requiring 510(k) may elect to comply with the design control provision of the QS regulation and submit Special 510(k)s.
510(K) - SPECIAL

- Manufacturers of pre-amendments devices may also submit Special 510(k)s.
- When the legally marketed (unmodified) device is a pre-amendments device, the submitter should clearly state that the device is a pre-amendments device, is legally marketed, and has not been the subject of Premarket Notification 510(k) clearance.
Demonstrating pre-amendments status.

Submitters should maintain this information in their files.
The "Special 510(k): Device Modification" utilizes the design control requirement of the Quality System Regulation (21 CFR 820) and may be submitted for a modification to a device that has been cleared under the 510(k) process.

The Special 510(k) allows the manufacturer to declare conformance to design controls without providing the data.
More on modifications

And see 510(k) Internal Rpt

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134575.htm
A novel type of device may be eligible for the *de novo* process if it has received an NSE determination as a result of a 510(k) submission.

Submit a De Novo petition with detail information why it is low to moderate risk.

FDA will make a decision within 60 days.
510(k) - De Novo

Submit and claim SE

FDA says not SE

Request De Novo classification

If FDA reclassifies, resubmit as a de novo 510(k), i.e. with no predicate device

Similar in effect to a reclassification petition, but different process

Only about 4/year
DE NOVO PROCESS

De novo Suitability and Protocol Review

≤ 60 days

Request Information

Submit PDS

FDA Review

PDS Meeting (if requested)

Missing information?

Appears to be De Novo Suitable?

Yes

Likely class (I or II) and special controls (if any), recommended bench/clinical testing

No

Likely predicate or existing class III type, or not likely to meet requirements for class I or II
# 510(k) Check list

<table>
<thead>
<tr>
<th>Title</th>
<th>Related Information</th>
<th>Present</th>
<th>Inadequate</th>
<th>N/A</th>
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</thead>
<tbody>
<tr>
<td>MDUFMA Cover Sheet</td>
<td>Medical Device User Fee Cover Sheet <a href="http://www.fda.gov/oc/mdufma/coversheet.html">www.fda.gov/oc/mdufma/coversheet.html</a></td>
<td></td>
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<tr>
<td>510(k) Cover Letter</td>
<td>Appendix A of “Guidance for Industry and FDA Staff Format for Traditional and Abbreviated 510(k)s” updated November 17, 2005</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Indications for Use Statement</td>
<td>Device Advice ” Content of a 510(k)” Section D <a href="http://www.fda.gov/cdrh/devadvice/314312.html#link_6">www.fda.gov/cdrh/devadvice/314312.html#link_6</a></td>
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<tr>
<td>510(k) Summary or 510(k) Statement</td>
<td>Device Advice ” Content of a 510(k)” Section E <a href="http://www.fda.gov/cdrh/devadvice/314312.html#link_7">www.fda.gov/cdrh/devadvice/314312.html#link_7</a></td>
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<tr>
<td>Truthful and Accuracy Statement</td>
<td>Device Advice ” Content of a 510(k)” Section G <a href="http://www.fda.gov/cdrh/devadvice/314312.html#link_9">www.fda.gov/cdrh/devadvice/314312.html#link_9</a></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Etc. see:**

[http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm071360.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm071360.htm)
Third Party Review

What is Third Party Review?

- Description
- Expansion Pilot
- Advantages to using this program

Description

The Accredited Persons Program was created by the FDA Modernization Act of 1997 (FDAMA), based on an FDA pilot. The purpose of the program is to improve the efficiency and timeliness of FDA's 510(k) process, the process by which most medical devices receive marketing clearance in the United States. Under the program, FDA has accredited third parties (Accredited Persons) that are authorized to conduct the primary review of 510(k)s for eligible devices. Persons who are required to submit 510(k)s for these devices may elect to contract with an Accredited Person and submit a 510(k) directly to the Accredited Person. The Accredited Person conducts the primary review of the 510(k), then forwards its review, recommendation, and the 510(k) to FDA. By law, FDA must issue a final determination within 30 days after receiving the recommendation of an Accredited Person. 510(k) submitters who do not wish to use an Accredited Person may submit their 510(k)s directly to FDA.

“STED” Program

- Pilot project with respect to the harmonized submission format developed by the Global Harmonization Task Force (GHTF)
- Consistent with “Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices”

Don’t forget everything else

**Determination of SE**

Re: K090782  
Trade/Device Name:  
Regulation Number: 21 CFR 888.3080  
Regulation Name: Intervertebral body fusion device  
Regulatory Class: II  
Product Code: MAX, MQP  
Dated: March 20, 2009  
Received: March 23, 2009

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

Please be advised that FDA’s issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act’s requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Center for Devices and Radiological Health’s (CDRH’s) Office of Compliance at (240) 276-0120. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please contact the CDRH/Office of Surveillance and Biometrics/Division of Postmarket Surveillance at 240-276-3464. For more information regarding the reporting of adverse events, please go to http://www.fda.gov/cdrh/mdr/.

You may obtain other general information on your device through the CDRH/Division of Small Manufacturers, International and Small Business Assistance Center at (800) 638-2041 or (240) 276-3150 or at its Internet site at http://www.fda.gov/cdrh/industry/support/index.htm.

Sincerely yours,

[Signature]

**Misbranding by reference to clearance**

**You may market**
Questions?
The “route to market” for Class III devices - Fees required
PMA

- “515(c)” of the Medical Device Amendments of 1976 (but no one calls it a “515(c)"
- 21 CFR 814 (Humanitarian)
- Required primarily for Class III devices
- All “new” devices, that are not substantially equivalent to a Class I or Class II device are automatically class III - until otherwise acted on
Subpart A--General

§ 814.1 - Scope
§ 814.2 - Purpose
§ 814.3 - Definitions
§ 814.9 - Confidentiality of data and information in a premarket approval application (PMA) file
§ 814.15 - Research conducted outside the United States
§ 814.17 - Service of orders
§ 814.19 - Product development protocol (PDP)

Subpart B--Premarket Approval Application (PMA)

§ 814.20 - Application
§ 814.37 - PMA amendments and resubmitted PMA's
§ 814.39 - PMA supplements
Subpart C--FDA Action on a PMA

§ 814.40 - Time frames for reviewing a PMA
§ 814.42 - Filing a PMA
§ 814.44 - Procedures for review of a PMA
§ 814.45 - Denial of approval of a PMA
§ 814.46 - Withdrawal of approval of a PMA
§ 814.47 - Temporary suspension of approval of a PMA

Subpart D--Administrative Review [Reserved]

Subpart E--Postapproval Requirements

§ 814.80 - General
§ 814.82 - Postapproval requirements
§ 814.84 - Reports
Premarket Approval (PMA)

Please note: As of October 1, 2002, FDA charges a fee for review of Premarket Approvals.

- Overview
- When a PMA is Required
- Devices Used in Blood Establishments
- Data Requirements
- References

Overview

Premarket approval (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. Please note that some Class III preamendment devices may require a Class III 510(k). See "Historical Background" for additional information.

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.

The PMA applicant is usually the person who owns the rights, or otherwise has authorized access, to the data and other information to be submitted in support of FDA approval. This person may be an individual, partnership, corporation, association, scientific or academic establishment, government agency or organizational unit, or other legal entity.
PMA Device Advice Topics

- Definitions
- Review Process
- Fees
- Application Methods
- Application Contents
- Quality System
- Labeling
- Clinical Studies

- Postapproval requirements
- Supplements and Amendments
- Special Considerations
- Import/Export
- FAQ’s
- Regulations
PMA

- The PMA is required to prove safety and efficacy
- It requires substantial information, study, data, time and money.
- It receives the “most stringent” review
- Often requires bench and animal testing, and human clinical trials
PMA

There are (primarily):
- Original PMAs for new submissions
- Modular PMAs
- PMA Supplements for changes
  Real-Time Supplements for “minor” changes
- Streamlined PMAs (clinical lab)

Presubmission meetings are encouraged
Original PMA - Content

- Name and address
- Table of contents
- Summary section (10-15 pages) including
  Indications for use
  Device description
  Alternative practices and procedures
  Marketing history (e.g. non-US)
  Summary of studies
  Conclusions drawn from the studies
Original PMA - Content

- A complete description of the device
- Reference to any performance standard or voluntary standard.
- Technical sections containing data and information in sufficient detail to permit FDA to determine whether to approve or deny the application.
- Results of nonclinical laboratory studies
- Results of clinical investigations involving human
- Justification of a single investigator if applicable
Original PMA - Content

- Bibliography
- One or more samples of the device and its components, if requested by FDA
- Draft copies of labeling
- Environmental assessment if applicable
- Financial certification or disclosure statement or both
- Such other information as FDA may request
And -

- A draft of the FDA releasable Summary of Safety and Effectiveness

  See PMA data base for examples:

  http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/

- Pre-approval inspection generally required
PMA database

Expedited review
3 in 2009
2 in 2010
(through 7/28)
Original PMA

- Six copies each bound in one or more numbered volumes of reasonable size
- Trade secret or confidential commercial or financial information must be included and identified
PMA – Primary Review Steps

- Administrative review by FDA to determine completeness (filing review)
- In-depth scientific, regulatory, and Quality System review by appropriate FDA personnel
- Review and recommendation by the appropriate advisory committee (panel review)
- Final deliberations, documentation, and notification of the FDA decision.
The Approval Letter!

- Approved for marketing
- Post approval requirements may include
  - Restricted sale
  - Continuing evaluation - Post market Surveillance
  - Device tracking
  - Annual reports
  - QSR requirements (e.g. CAPA)
The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has conducted its review of your premarket approval application (PMA) for the LifeStent Vascular Stent System. This device is indicated for improvement of lumenal diameter in the treatment of symptomatic de novo or restenotic lesions up to 160 mm in length in the native superficial femoral artery (SFA) and proximal popliteal artery with reference vessel diameters ranging from 4.0 – 6.5 mm. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions described below and in the "Conditions of Approval" (enclosed).

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition to the periodic report (often referred to as annual report) requirements outlined in the...
Approval letter example

FDA agrees that the study protocol and statistical analysis plan submitted in Amendment 6 are acceptable. When appropriate or as requested by FDA, you should submit PMA supplements requesting approval to update your IFU to include these data. You have agreed to submit progress reports for the post-approval study at 6, 12, 18 and 24 months and annually thereafter until the study is complete following PMA approval.

Expiration dating for this device has been established and approved at 1 year. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(7).

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

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/cdrh/pmapage.html. Written requests for this information can also be made to the Dockets Management Branch, (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

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

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

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

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

If you have any questions concerning this approval order, please contact Allison Kumar at 240-276-4184.

Sincerely yours,

[Signature]

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

Expiration dating

final labeling
Post-Approval Studies

- When ordered, or “agreed to”
- Tracked on line

The CDRH Post-Approval Studies Program encompasses design, tracking, oversight, and review responsibilities for studies mandated as a condition of approval of a premarket approval (PMA) application...

The program helps ensure that well-designed post-approval studies (PAS) are conducted effectively and efficiently and in the least burdensome manner.

Guidance Document: Procedures for Handling Post-Approval Studies Imposed by PMA Order
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm
Generic Conditions of Approval

- Requirements for PMA supplements
- Post approval reports
- Adverse reaction and device defect reporting
- MDR reporting
Also on line

- Summary of Safety and Effectiveness
- Labeling
  - Professional
  - Patient (when applicable)
- Consumer Information
PMA FEES

- Premarket Application - $248K
  - Small Business - $62K
- 180-Day PMA Supplement - $37.2K
  - Small Business - $9.3K
- Real-time PMA Supplement - $17,360
  - Small Business - $4,340
- 30-Day Notice - $3,968
  - Small Business - $1,984
PMA Web Listing

System - P050027

Issued May 28, 2010

- Approval Order
- Summary
- Labeling
- Other Consumer Information

This document is in a Portable Document Format (PDF). Acrobat Reader is required to read this document.

Updated June 14, 2010
Questions?
FDA Medical Device Industry Coalition

IDE

HDE

Investigational Device Exemption

Humanitarian Device Exemption
IDE - Investigational Device Exemption

- Required for *all* clinical trials or testing of devices on humans, whether or not for marketing submission data
- “Exemption” is a bit of a misnomer—you are exempt from certain provisions having to do with legally marketed devices...but you have another set of regulations to deal with instead
Subpart A--General Provisions

§ 812.1 - Scope.
§ 812.2 - Applicability.
§ 812.3 - Definitions.
§ 812.5 - Labeling of investigational devices.
§ 812.7 - Prohibition of promotion and other practices.
§ 812.10 - Waivers.
§ 812.18 - Import and export requirements.
§ 812.19 - Address for IDE correspondence.

Subpart B--Application and Administrative Action

§ 812.20 - Application.
§ 812.25 - Investigational plan.
§ 812.27 - Report of prior investigations.
§ 812.30 - FDA action on applications.
§ 812.35 - Supplemental applications.
§ 812.36 - Treatment use of an investigational device.
§ 812.38 - Confidentiality of data and information.
Subpart C--Responsibilities of Sponsors

§ 812.40 - General responsibilities of sponsors.
§ 812.42 - FDA and IRB approval.
§ 812.43 - Selecting investigators and monitors.
§ 812.45 - Informing investigators.
§ 812.46 - Monitoring investigations.
§ 812.47 - Emergency research under 50.24 of this chapter.

Subpart D--IRB Review and Approval

§ 812.60 - IRB composition, duties, and functions.
§ 812.62 - IRB approval.
§ 812.64 - IRB's continuing review.
§ 812.65 - [Reserved]
§ 812.66 - Significant risk device determinations.
Subpart E--Responsibilities of Investigators

§ 812.100 - General responsibilities of investigators.
§ 812.110 - Specific responsibilities of investigators.
§ 812.119 - Disqualification of a clinical investigator.

Subpart F [Reserved]

Subpart G--Records and Reports

§ 812.140 - Records.
§ 812.145 - Inspections.
§ 812.150 - Reports.
IDE

Also

- 21 CFR 50, *Protection of Human Subjects*
- 21 CFR 54, *Financial Disclosure by Clinical Investigators*
Device Advice: Investigational Device Exemption (IDE)

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. Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices. 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.

An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with other requirements of the Food, Drug, and Cosmetic Act (Act) that would apply to devices in commercial distribution. Sponsors need not submit a PMA or Premarket Notification 510(k), register their establishment, or list the device while the device is under investigation. Sponsors of IDE's are also exempt from the Quality System (QS) Regulation except for the requirements for design control.
IDE

- Pre-IDE discussions are encouraged
- Process depends on degree of risk
  - Significant or Nonsignificant risk
  - **Significant**: IRB ➔ FDA
  - **Nonsignificant**: IRB only

Note: In some Guidance Documents the degree of risk is defined, e.g. *all spinal implants are significant risk*.
IDE - Contents - Significant

- Name and address of sponsor
- Complete report of prior investigations
- Investigational plan
- Design and manufacturing information
- Sample agreement and investigator certification
- Registered clinical trial

and...
IDE - Contents - Significant

- All IRB approvals
- Device charges if any
- Labeling
- Informed consent
- Other
IDE - Contents - Nonsignificant

- IRB approval
- Informed consent
- Appropriate monitoring and records

- There are some investigations that are exempt from the IDE requirements -
  > e.g. non-invasive diagnostics
  consumer preference testing
IDE

Proper conduct of an IDE is subject to monitoring by the FDA, and has been the subject of Warning Letters

WARNING LETTERS

• to a company
Failure to maintain accurate, complete, and current records relating to an investigation [21 CFR 812.140(b)(6)].

• to an investigator

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080202.htm

Numerous other Clinical Trials and IDE Guidance Documents

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm162453.htm
Questions?
HDE - Humanitarian Device Exemption

- Applicable to *Humanitarian Use Devices* (HUDs)
- Small markets (<4000/yr)
- Usually for a device for which a PMA would otherwise be required (Class III)
- If approved by FDA requires IRB approval to be used
Subpart H--Humanitarian Use Devices

§ 814.100 - Purpose and scope.
§ 814.102 - Designation of HUD status.
§ 814.104 - Original applications.
§ 814.106 - HDE amendments and resubmitted HDE's.
§ 814.108 - Supplemental applications.
§ 814.110 - New indications for use.
§ 814.112 - Filing an HDE.
§ 814.114 - Timeframes for reviewing an HDE.
§ 814.116 - Procedures for review of an HDE.
§ 814.118 - Denial of approval or withdrawal of approval of an HDE.
§ 814.120 - Temporary suspension of approval of an HDE.
§ 814.122 - Confidentiality of data and information.
§ 814.124 - Institutional Review Board requirements.
§ 814.126 - Postapproval requirements and reports.
Humanitarian Device Exemption

Overview

An Humanitarian Use Device (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. A device manufacturer's research and development costs could exceed its market returns for diseases or conditions affecting small patient populations. The HUD provision of the regulation provides an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations.

To obtain approval for an HUD, an humanitarian device exemption (HDE) application is submitted to FDA. An HDE is similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Additionally, the applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market.

An approved HDE authorizes marketing of the HUD. However, an HUD may only be used in facilities that have established a local institutional review board (IRB) to supervise clinical testing of devices and after an IRB has approved the use of the device to treat or diagnose the specific disease. The labelling for an HUD must state that the device is an humanitarian use device and that, although the device is authorized by Federal Law, the effectiveness of the device for the specific indication has not been demonstrated.
HDE Application for a HUD

- Must establish that
  - does not pose an unreasonable risk
  - probable benefit to health outweighs risk
  - no comparable devices/treatment available
  - could not market if PMA required
  - price does not exceed cost of research, development, fabrication and distribution
HDE Application for a HUD

- Similar to PMA, but without *proof* of effectiveness from a clinical trial

- Successful application requires:
  > ongoing IRB approval for use
  > registration as an ongoing clinical trial
  > appropriate labeling as to HUD status
HUDs with HDEs

- 2010 - 1 (through 7/28)
- 2009 - 1
- 2008 - 4
- 2007 - 4
- 2006 - 2
- 2005 - 2
- 2004 - 5

PMA – about 50/year
510(k) – about 3700/year

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/ucm161827.htm
Recent HUDs with HDEs

- Heart valve
- Deep brain stimulator
- Lung air leak valve
- Spinal treatment device
- Temporary circulatory support
- Breathing device for spinal cord injured
Questions?
Device Labeling Requirements

Contributes to the safety and effectiveness of the device
Background - Introduction

Labeling regulations

- 21 CFR 801 - General Device Labeling
- 21 CFR 809 - In Vitro Diagnostic Products
- 21 CFR 812 - Investigational Device Exemptions
- 21 CFR 820 - Good Manufacturing Practices
- 21 CFR 1010 - General Electronic Products
Definitions

- Label
  - What is on the ‘immediate container’

- Labeling
  - All written material including:
    - IFU
    - Advertising
    - Sales materials
    - Pamphlets - Professional and Patient
    - Etc
General Device Labeling

- Label content
- Label design
- Label management
Label contents

- Proper identification
  - Manufacturer
  - Intended use
  - Adequate directions for use*

- Nothing false or misleading

* Varies for lay user vs. professional user
Label contents - Lay user

- Statements of all purposes for which, and conditions under which, the device can be used
- Quantity of dose for each use and usual quantities for persons of different ages and physical conditions
- Frequency of administration
- Duration of application
- Time of administration in relation to other factors
- Route or method of application
- Any preparation necessary for use

21CFR801.5
Label contents - Professional

Information for use including

- Indications
- Effects
- Routes
- Methods and frequency and duration of administration
- Relevant hazards, contraindications, side effects, and precautions

Note: Professional devices may also need a patient IFU
Other considerations (\textit{non reg})

- Can the instructions actually be effectively followed?
  
  \textit{“Do not use excessive force”}

- Address residual risks arising from the design process under Design Controls
  
  - those that could not reasonably be designed out
Some devices have specified label contents

- Dentures
- Impact resistant glasses
- Chlorofluorocarbon containing
- Hearing aids
- Tampons
- Condoms
- Latex containing
- And as suggested in Guidance Documents
Additional Labeling Requirements

- Sterile Device Labeling
  - What is sterile if only part
  - Handling
  - Expiration

- Contract Sterilization
  - Control issues

- Unique Device Identification*
  - Coming? (Under active discussion since 2007, Jay Crowley is the expert)

- Investigational Device Labeling

*http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/UniqueDevic...
Label design - *(non reg)*

- Who are the users?
  - Are there multiple users?
    - MDs, nurses, technicians, patients?

- Avoiding product confusion

- Physical design
  - Fonts
  - Layout
  - Colors
HUMAN FACTORS PRINCIPLES FOR MEDICAL DEVICE LABELING

James R. Callan
John W. Gwynne
Pacific Science & Engineering Group
6310 Greenwich Drive, Suite 200
San Diego, California 92122-5918
Phone: (619) 535-1661
Fax: (619) 535-1665
September, 1993
FDA Contract No. 223-89-6022

Dick Sawyer
Margaret T. Tolbert
Food and Drug Administration
Center for Devices and Radiological Health
Office of Training and Assistance (HFZ-210)
1901 Chapman Avenue, Rockville, Maryland 20857

Write It Right

Recommendations for Developing User Instruction Manuals for Medical Devices Used in Home Health Care


Good Manufacturing Practice
Labeling Requirements

- Maintain procedures to control labeling activities

General Device Labeling Requirements

- Design documents
- Label Integrity
- Receipt Inspection
- Storage
- Check and Record
- Changes
- Re-labeling

21CFR 820.129

The right label on the right device
Labeling Problems

- **Misbranding**
  - Including asserting “approval” for a “cleared” device

Any representation that creates an impression of official approval of a device because of complying with the premarket notification regulations is misleading and constitutes misbranding. 21CFR807.97

- And a variety of other deviations
Labeling Problems - Recalls

- Label Content
  - Additional warning in Instructions for Use for guide wire management
  - The firm is updating their instructions for use to require inspection of the IUI connectors for blue or green discoloration (corrosion) before every use of the device.

- Mix-up
  - A label for an indicated use was applied to product sizes that are not approved for that use
  - Mislabeled as to size. An 18 mm x 65 mm tibula implant is enclosed in a package labeled as 12 mm x 80 mm
Off-label Use

- Medical professionals may use a device “off label” at their discretion.

- But manufacturers may not promote off-label uses - including on web sites or by links to web sites.

Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices

http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm
Labeling

Questions?
Overview of Quality System Regulations (QSR) for Medical Devices

Al Alonso
FMDIC Member Representing RAPS
Definitions - Important Differences

- **Regulations** (GMPs, QSRs, F,D & C, etc.)
  - Governmental laws that must be followed
    [www.fda.gov](http://www.fda.gov)

- **Standards** (ISO, ASTM, ANSI, etc.)
  - Typically voluntary, but in some countries may be adopted as requirements (i.e., EU)
  - ISO (International Organization for Standards)
    [www.iso.org](http://www.iso.org)
History of Medical Device Regulations

- Pure Food and Drug Act 1906 FDA start
- Medical Device Amendments of 1976 to the FDCA (for the protection and promotion of health)
- Center for Devices and Radiological Health (CDRH)
- Safe Medical Devices Act of 1990 (SMDA)
History of Medical Device Regulations

- Quality System Regulations (QSR) The FDA Modernization Act (FDAMA) of 1997
- The Medical Device User Fee and Modernization Act (MDUFMA) of 2002
QSR Introduction

- 520 of the Food, Drug and Cosmetic Act (FD&C)
- Good Manufacturing Practices (GMP)
- Preamble
- Quality System Regulation (QSR)
QSR Applicability

- Applies to finished devices
- GMP exemptions
- Certain components are considered by FDA to be finished devices
- “Custom" or “Customized" device
- Contract manufacturers
- Contract test laboratories
- Exempt manufacturers still subject to the FD&C Act
Exemptions

- Exemptions from GMP
- Defined GMP responsibilities
- Exemption Responsibilities
- Exemption Conditions
  - FDA Exemption Order - Citizen's Petition
  - FDA without a petition published in the FR
  - by Classification Regulations
  - Intraocular Lens (IOL)
  - FDA policy statement
Types of Establishments *Exempt* from GMP

- **Component Manufacturers**
  - **Component** - any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device.
  - Component Manufacture exemption
  - Or maybe not?
Types of Establishments *Subject* to the GMP

- **Re-manufacturers**
  - Any person who processes, conditions, renovates, repackages, restores, or does any other act to a finished device that changes the finished device's performance or safety specifications or intended use
  - Re-manufacturers = manufacturers

- **Custom Device Manufacturers**
  - One that manufactures devices that deviate from devices generally available; is not generally used by other physicians or dentists; is not generally available in finished form for purchase; is not offered for commercial distribution; is specific for a patient.
Types of Establishments *Subject* to the GMP

- **Contract Manufacturers**
  - A person(s) that manufactures a finished device under the terms of a contract with another manufacturer.

- **Contract Test Laboratory**
  - Designs or test components or finished devices for a manufacturer according to the manufacturer's specifications.
Types of Establishments *Subject* to the GMP

- Re-packagers, Re-labelers, and Specification Developers
  - Manufacturer includes but is not limited to those who perform the functions of contract sterilization, installation, re-labeling, remanufacturing, repacking, or specification development, and initial distributors of foreign entities performing these functions.
Types of Establishments *Subject* to the GMP

- **Manufacturers of Accessories**
  - When finished device manufacturers produce components specifically for use in medical devices they produce, whether in the same building or another location, such production of components is considered part of the device manufacturing operations, and should comply with the QSR.

- **Initial Distributors**
  - An initial importer (or initial distributor) takes first title to the devices imported into the U.S. and further distributes the product.
Background

- The Quality System Regulation (QSR) became effective on June 1, 1997, replacing the 1978 GMP for medical devices
- Preamble to the QS Reg - VERY Important
- Requirements are not prescriptive
  - Provides framework of basic requirements for manufacturers to follow
Relevant Documents

- Preamble to the final rule published 1996 in the Federal Register
- Title 21, Code of Federal Regulations, Part 820 (21CFR 820)
- “Quality System Information for Certain Premarket Application Reviews: Guidance for Industry and FDA Staff”: 2003
- Quality System Inspection Technique (QSIT Guide)
Bottom line ...
It’s your Quality System!

- A manufacturer must develop a Quality System (QS) commensurate with the
  - Extent of the activities to be carried out
  - Risk presented by the device
  - Complexity of the device and manufacturing processes
  - Size and complexity of manufacturing facility
QSIT ELEMENTS

Quality System’s Sub-systems

Corrective & Preventive Actions

Design Controls

Material Controls

Management

Production & Process Controls

Equipment & Facility Controls

Records, Documents, & Change Controls
Management Control 21CFR820.20

- Provide adequate resources
- Assure proper function of the quality system
- Monitor the quality system
- Make any necessary adjustments
- Appoint a management representative
- Conduct management reviews
- Ultimately responsible for the entire Quality System
Management Controls

Management Representative

- Member of Management
- Responsible for ensuring establishment of quality system and reporting on quality system performance to management with executive responsibility
Quality Audits 820.22

- Establish procedures for quality audits
- Conduct audits to assure compliance by individuals not having direct responsibility for areas audited
- Perform corrective action(s), including re-audit of deficiencies.
- Generate a written report of audit results for management review.
Make personnel aware of device defects that could occur from improper job performance.

Personnel who perform verification and validation activities shall be made aware of defects and errors that could be encountered as part of their job.
Control the design process to assure that devices meet user needs, intended uses, and specified requirements

Devices subject to design control requirements:
- Class III & Class II
- Certain Class I as defined by 21 CFR 820.30(a)(2)

Devices automated with computer software and the following:
- Catheter, Tracheobronchial Suction
- Glove, Surgeon's
- Restraint, Protective.
- System, Applicator, Radionuclide, Manual
- Source, Radionuclide Teletherapy
Design and Development Plan

- Maintain plans that describe the design and development activities and who is responsible
- Describe the interfaces or activities involved in the design process
- Review, update, and approve as the design evolves
Design Input

- **Design Input**
  - The physical and performance requirements of a device that are used as a basis for device design

- Ensure requirements are appropriate and address intended use of a device and the needs of the user

- Document, review, and approve the design inputs
Design Output

- Design Output
  - The results of a design effort at each phase and the end of the total design effort
  - Consists of the device, its packaging and labeling, and the device master record

- Ensure an adequate evaluation of conformance to design input requirements

- Document, review, and approve the design output
Ensure that formal documented reviews of the design results are planned and conducted

- Purpose
- Participants
- Timing
- Documentation
Design Verification

- Design Verification...
  - Are the product specifications being met and can I prove it?
  - Did you make what you said you would make?
- Ensure that design output meets design input requirements.
- Results should be documented in the Design History File (DHF).
Design Validation

- **Design Validation...**
  - Is the product meeting user needs and intended uses for all specifications; can I prove it?
  - Does it do what you said it would do?
- Ensure that devices conform to user needs and intended uses
- Results should be documented in the Design History File (DHF)
Design Validation

- **Process Validation...**
  - Does the process consistently produce a result or product meeting predetermined specifications and can I prove it?

- Ensure the device design is correctly translated into production specifications

- Completion of the design transfer is the final phase of product development and the bridge between product design and product manufacturing
Design Transfer

- Ensure the device design is correctly translated into production specifications.
- Completion of the design transfer is the final phase of product development and the bridge between product design and product manufacturing.
Design Changes

- Design Changes must be:
  - Identified
  - Documented
  - Verified
  - Validated
  - Reviewed
  - Approved
  - All performed before implementation
Design History File (DHF)

- DHF: Records that demonstrate the design was developed in accordance with:
  - The approved design plan and
  - Design control requirements
- DHF must be created for each type device as objective evidence of compliance with Design Control
Establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements.

Evaluate suppliers, contractors and consultants.

Describe or reference specified requirements (including notification of change agreements).
Manufacture devices that meet specified requirements

Environmental control

Personnel

Contamination control

Buildings & Equipment

Manufacturing material

Automated processes
  - Computer software used as part of production or the quality system
Process Validation
21 CFR 820.75

- Validate processes that cannot be fully verified by subsequent inspection and testing
- Monitor and control process parameters for validated processes to ensure that the specified requirements continue to be met
- Document all validation activities
Process Validation

- **Installation Qualification (IQ)**
  - Process equipment installed per Mfrs specs

- **Operational Qualification (OQ)**
  - Establishing by objective evidence process control limits and action levels which result in product that meets all requirements.

- **Performance Qualification (PQ)**
  - Establishing by objective evidence that the process consistently produces a product which meets all predetermined requirements.
Acceptance Activities
21 CFR 820.80

- Receiving acceptance activities
  - Procedures for acceptance of incoming product to ensure the product meets specified requirements

- In-process acceptance activities
  - Procedures for acceptance and control of in-process product to ensure the product meets specified requirements

- Final acceptance activities
  - Procedures for finished device acceptance to ensure that acceptance criteria are met
Establish and maintain procedures, including:
- Identification
- Documentation
- Evaluation
- Segregation
- Disposition

Document the evaluation and any investigation.
Non-Conforming Product 21 CFR 820.90

- Nonconformity review and disposition.
  - Establish and maintain procedures defining the responsibility for review and the authority for the disposition, including the review and disposition process.
  - Document disposition of nonconforming product, including the justification for use and the signature of individual(s) authorizing use.
Non-Conforming Product 21 CFR 820.90

- Nonconformity review and disposition.
  - Establish and maintain procedures for rework, including retesting and reevaluation.
  - Document rework and reevaluation activities in the DHR.
Corrective & Preventative Actions 21 CFR 620.100

- Collect and analyze quality information
- **Identify** and investigate product and quality problems
- Take the appropriate and effective corrective and/or preventive actions to address the problem
Corrective and Preventative Action
21 CFR 820.100

- Verify or validate the effectiveness
- Implement and record changes in methods and procedures
- Communicate information about quality problems to staff
- Forward information for management review

“FDA emphasizes that it is always management’s responsibility to ensure that all nonconformity issues are handled appropriately.” Preamble Comment #165
Corrective and Preventative Action
21 CFR 820.100

- **Definitions:**
  - **Correction:** repair, rework, or adjustment and relates to the disposition of an *existing* nonconformity
  - **Corrective Action:** the action taken to eliminate the causes of an *existing* nonconformity, defect or other undesirable situation in order to prevent recurrence
  - **Preventative Action:** action taken to eliminate the cause of a *potential* nonconformity, defect, or other undesirable situation in order to prevent occurrence
Internal Data Source

- Inspection/Test data
- Acceptance activities
- Equipment data
- Returned product
- Rework data
- Internal audits
- Training records
External Data Sources

- Complaints
- MDRs
- Field service reports
- Legal claims
- Customer feedback
CAPA Program

- Identify data sources
- Document the problem
- Establish a priority system
  - Consider the risks and select items with major impact
  - Proceed to items with less impact
- Analyze the problem
  - Perform a root cause analysis
“Healthy” CAPA subsystem procedures include provisions to ...

- Identify and correct existing nonconforming product or other quality problems (“Correction”);

- Identify and eliminate the causes of existing nonconforming product and other quality problems (“Corrective Action”); and,

- Identify and eliminate the causes of potential nonconforming product and other quality problems (“Preventive Action”).
CAPA Program

- Develop an action plan
  - Consider the impact and need for both short term and long term corrective actions

- Verification and Validation
  - Analysis of data may lead to more than one solution, assure the solution is appropriate

- Implementation
  - Tracking for on-time completion
CAPA Program

- Documentation and follow-up
  - Corrective action effective
  - Adverse effect on product
  - Records

- Communicate changes
  - To those directly responsible
  - Management review
Records maintained at the manufacturing site or must be reasonably accessible and readily available for review.

Legible and stored to minimize deterioration or loss

Retention: 2 years or for the life of the product whichever is longer.

Exception to review by the FDA are: Mgmt. Review, Quality Audits & Supplier Audits
Device Master Record 820.181

DMR shall include or refer to the location of:

- Device specs, drawings, equipment specs, production methods, etc.
- Production process specs, methods, etc.
- QA procedures, acceptance criteria, QA equipment
- Packaging & labeling specs, methods used, etc.
- Installation, method and servicing procedure
- Basically the methods, equipment, materials, specs required to manufacture the device
Device History Record 820.184

- DHF contains the documentation of the history of the fabrication of a medical device. Demonstrates compliance with DMR
  - Date manufactured
  - Quantity manufactured
  - Quantity released
  - Acceptance records
  - Primary label identification for each unit
  - Any device identification
Quality System Record 820.186

- This record shall include or refer to the location of:
  - Procedures and documentation activities that are not specific to a particular device
  - Example includes: Training procedure, Recall procedure, Complaint procedure, etc.
All manufacturers must

- Maintain complaint files.
- Designate a formal complaint handling unit.
- Establish and maintain procedures for receiving, reviewing, and evaluating complaints.
Complaint Files

- Procedures must ensure that
  - All complaints are processed in a uniform and timely manner.
  - Oral complaints are documented upon receipt.
  - Complaints are evaluated to determine whether the complaint represents an Medical Device Report
Complaint Files

- Investigations.

- Review and evaluate all complaints to determine whether an investigation is necessary.

- Records of investigation shall be maintained with certain specified information as required.
Complaint Files

- Investigations.

- When no investigation is made, maintain a record that includes the
  - Reason no investigation was made and name of the individual responsible for the decision.
Servicing 820.200

- Where servicing is a specified requirement, each Mfr. shall establish and maintain instruction and procedure for performing and verifying service requirements were achieved.

- Each Mfr. shall analyze service report using statistical techniques.
Where appropriate, each Mfr. shall establish and maintain procedures for identifying statistical techniques required for establishing, controlling and verifying the acceptability of process capability and product characteristics.

Sampling plans, shall be written and based on a valid statistical rationale. These activities shall be documented.
Close the Loop
Additional Resources

- **General**
  - www.fda.gov/MedicalDevices

- **Quality System Regulation**
  - www.accessdata.fda.gov/scripts/cdrh/cfdocs/cf
    cfr/cfrsearch.cfm?cfrpart=820

- **QSIT Guide**
  - http://www.fda.gov/iceci/inspections/inspection
    guides/ucm074883.htm
Additional Resources

- FDA Compliance Program 7382.845 Inspection of Medical Device Manufacturers implemented October 1, 2000

- Guide to Inspections of Quality Systems, August 1999
  www.fda.gov/iceci/inspections/inspectionguides/ucm074883.htm
Questions?
Risk Management & Postmarket Surveillance (PS)
WHAT IS POSTMARKET SURVEILLANCE?

- PS means the active, systematic, scientifically valid collection, analysis, and interpretation of data or other information about a marketed device.
- PS is the pro-active collection of information on quality, safety or performance of Medical Devices after they have been placed in the market.
Postmarket Surveillance Definition

- PS is essential to detecting and addressing safety issues and ensuring that a balance is maintained between the health benefits and the risk posed by the medical device.

The FDA has a specific and more formal approach for PS.
Postmarket Surveillance Definition

21 CFR Part 822: PS
The FDA has the authority to order PS of any Class II or III medical device that meets the following criteria:

- Failure of the device would be reasonably likely to have serious adverse consequences
Postmarket Surveillance Definition

- The device is intended to be implanted in the human body for more than one year, or

- The device is intended to be used to support or sustain life and to be used outside a user facility
Postmarket Surveillance Definition

- The FDA will inform you in a letter if a PS is required, and the reason it is required.

- Purpose of Part 822 is to implement PS authority to maximize the likelihood that PS plans will result in the collection of useful data.
Postmarket Surveillance Definition

- These data can reveal unforeseen adverse events, the actual rate of anticipated adverse events, or other information necessary to protect the public health.

- Prospective surveillance means that the subjects are identified at the beginning of the surveillance and data or other information will be collected per the clinical protocol from that time forward.
PS Generally

- FDA
  - Inspections
  - Office of Surveillance and Biometrics
  - MDR Medical Device Reporting
  - MedSun data analysis (Medical Product Safety Network)
  - International vigilance
  - Advisories and Safety Alerts
  - Postmarket Transformation Initiative

http://www.fda.gov/AboutFDA/CentersOffices/cdrh/CDRHInitiatives/ucm117698.htm
Postmarket Surveillance Definition

- Vigilance is reactive.
- The purpose of medical device vigilance or MDR is to protect the health and safety of persons using the product;
- Assess the incidents to prevent recurrence;
- Determine the effectiveness of correction and prevention actions; and as a learning experience.
Components of CDRH’s Postmarket Program

- Adverse Event Reporting
- Information Education
- Inspections
- Problem Assessment Groups
- Additional Signals
- Post Approval Studies
- Laboratory Research & Analysis
- External Data Analysis
- Internal Data Analysis
- Postmarket Problem Assessment
- Postmarket Problem Identification Tools
- Premarket Approval Process
- Information Dissemination
- Enforcement
- Postmarket Tools Public Health Response
- Public Health Partners

- Postmarket Problem Identification
- Postmarket Problem Assessment
- Postmarket Public Health Response
Establish A Systematic Process for PS

PS can be a more generic term for collecting Medical Device performance data. Manufacturers should identify the systems in place or that you could establish which will provide product performance feedback for example:

- Complaints and Complaint Trending
- CAPA
Establish A Systematic Process for PS

- Medical Device Reporting/Vigilance
- Recalls/Market Withdrawals
- Customer focus groups
- Customer surveys
- Customer comments for improvement
- Postmarket testing
- Postmarket Clinical Study
Establish A Systematic Process for PS

- Field Sales
- Marketing
- Collecting FDA data on similar devices (MAUDE database)
- Management Review
- Device Tracking
- Servicing
Establish A Systematic Process for PS

The Complaint System may be the most important data source

- Establish a Complaint System that funnels all complaint information to a central point for processing.
- Procedures should define how the information is collected, reviewed, investigated, analyzed and trended.
Establish A Systematic Process for PS

The procedure(s) should specify:

- The frequency of reporting this data
- Who reports the data
- Who reviews the data
Establish A Systematic Process for PS

- Who receives the data
  - Marketing
  - Sales
  - Management
  - Product Development
  - Operations
  - Regulatory Affairs
  - Clinical Affairs
Establish A Systematic Process for PS

Train all personnel on the importance of communicating product performance information to a central point in a timely manner in particular:

- Sales, i.e. representatives, agents, distributors, etc.
- Marketing
- Customer Service
- Management
Establish A Systematic Process for PS

To establish an effective PS system you should identify the hazards of your device(s) with questions such as:

- What is the intended use of the device?
- Is your device provided sterile?
- Is there a shelf life for the product?
- Is it single use?
Establish A Systematic Process for PS

- Is it multi-use requiring cleaning and disinfecting?
- Does the user facility need to sterilize it?
- Is the device susceptible to temperature and humidity?
- Is it susceptible to transportation damage?
Establish A Systematic Process for PS

- Is it susceptible to the environment? Temperature and humidity
- Is maintenance required or calibration?
- Are the instructions for use adequate?

Ensure that these specifics are covered by your PS system
Establish A Systematic Process for PS

When the FDA requires a Postmarket Clinical Study as part of a 510(k) clearance or a PMA approval:

- Plan must be submitted 30 days after clearance/approval letter
- You must follow the plan once it is approved
- Interim and final reports as specified in the plan
- Other reports upon request
Establish A Systematic Process for PS

- Contents of plan
  - Organizational information
  - Objectives
  - Subjects and sample size
  - Methodology
  - Investigator(s) and agreements
  - Source of data (e.g. hospital, physicians)
  - Data forms
Establish A Systematic Process for PS

Contents of plan

> Consent document
> IRB information
> Patient follow-up plan
> Study monitoring
> Duration
> Data analysis and statistics
> Timing of reports
Establish A Systematic Process for PS

- Responsibilities
  > Initiate in a timely manner
  > Due diligence
  > Data collected per plan
  > Reports in a timely manner
  > Responsive to FDA inquiries
Establish A Systematic Process for PS

PROGRAM GOALS

> Help to assure continued device safety effectiveness
> Obtain useful & timely post-market information in the “real world” as the device enters the market
> Better characterize the risk/benefit profile
> Add to our ability to make sound scientific decisions
Establish A Systematic Process for PS

A Company can initiate its own PS Clinical Study

- Follow the plan as a PS FDA Study without the FDA reporting requirements as in a directed study
- For the purposes given on the previous slide
- For a White Paper
- For publication in a medical journal
Establish A Systematic Process for PS

- Determine the areas that you will be following for feedback
- As appropriate document procedurally
- Make appropriate personnel aware of PS activities and that they will be kept informed
Product risks can never be eliminated so:

- Follow established plan
- Companies must continue to monitor feedback and
- Companies must manage risk through the entire life cycle of the product
PS MONITORING & ACTION LIMITS

- As appropriate establish action limits for your various monitoring areas.
- Once the limits are triggered you should have in your procedures what action to take:
  - CAPA
  - Investigation
  - Notification internally
MANAGEMENT AWARENESS OF PS

KEEPING MGMT AWARE OF PS

- Management Reviews
- CAPA
- Recalls
- Complaint Reports
- Trend Reports
- New Product performance
- Email and Orally
DETERMINATION OF ACCEPTABILITY OF RISKS

- Health Hazard Evaluation (HHE)
- Failure Mode Effects Analysis (FMEA)
- Core Risks in your Risk Mgmt File
- Test Reports
- Clinical and Literature Reviews
- Health Professional opinion
BENEFITS OF AN EFFECTIVE PS SYSTEM

- Early warning for removal of suspect product from the market
- Increased user and patient safety
- Fewer product complaints
- Provides R&D with feedback to improve existing products
- Assists R&D with the design of new products
- A more robust QMS
BENEFITS OF AN EFFECTIVE PS SYSTEM

- Increase confidence in Regulatory compliance
- Reduced litigation
- Enhanced quality image of the company
- Increased revenue and profitability
- Better SLEEP
Vision for PS

- Important postmarket questions are addressed
- Studies are realistic & founded on good science
- Studies are timely, accurate, & provide useful results
- Reports are clearly identified & effectively tracked
- Stakeholders are kept apprised
- Collaboration is stressed throughout
- Enforcement options are rarely used
Questions?
Device Recalls

Voluntary action by a company to remove violative product from the market
Device Recall Regulations

- **21 CFR Part 7** - Recall Enforcement Policy
- **21 CFR Part 806** - Medical Device Reports of Corrections & Removals
- **21 CFR Part 810** - Medical Device Recall Authority (also FD&C Act, Sec. 518(e))
21 CFR Part 7

- 21 CFR Part 7, Subpart C: Recalls (Including Product Corrections) - Guidelines on Policy, Procedures, and Industry Responsibility
- “…provides guidelines for manufacturers and distributors to follow with respect to their voluntary removal or correction of a marketed violative products.”
- Governs FDA policy for handling recalls.
Recall means a firm’s removal or correction of a marketed product(s) that the Food and Drug Administration considers to be in violation of the laws it administers and against which the agency would initiate legal action, e.g., seizure.
Market Withdrawal (21 CFR 7.3(j))

- Removal or Correction
- Marketed Product
- Minor or NO Violation
Stock Recovery (21 CFR 7.3(k))

- Removal or Correction
- Violation
- No Marketing: product is located on premises owned by, or under the control of, the firm and no portion of the lot has been released for sale or use
Safety Alert

- Notification by responsible persons to device users that the use of a device may, in certain circumstances, pose a risk of substantial harm
- May result from situations such as misuse, failure to follow labeling directions, and improper connection to other devices
- Does not encompass cessation of distribution or use, removal, or correction of devices that FDA considers to be in violation of the laws it administers
- “Notification alone” takes care of the problem
- Not defined in CFR
- FDA has final decision: Market Withdrawal/Safety Alert or Recall
Types Of Recalls

- Firm Initiated
  On its own volition decides to recall

- FDA requested
  1-Based on risk of illness or injury and/or gross consumer deception
  2-Firm aware of above but not acting on its own initiative
  3-When necessary to protect the public health and welfare

- FDA Ordered- CFR 810.13 and 518(e) The Act
Recall Vs FDA Action

- Generally faster
- Less costly to taxpayer and the firm
- Affords better protection for consumers—seizure at one area
Awareness Of Recall Situations

- FDA inspections
- Consumer complaints
- Adverse event reports
- Medwatch
- MDRs
- 806 Correction and Removal Reports
- The firm, repackager, distributor

- Competition
- Review divisions
- Other Regulatory Agencies-CPSC, CDC, State Health Dept/Medical Boards, FTC, OCI
- MRA and other country agreements
Recall Classification

- FDA will perform a health hazard evaluation (HHE) to determine the level of hazard the recalled product poses (21 CFR 7.41)
- Based on the HHE FDA will assign a recall classification (21 CFR 7.3(m))
- The classification is a numerical designation to indicate the relative degree of health hazard presented by the product being recalled
Recall Classification

- Class I- reasonable probability a violative product will cause serious adverse health consequences or death
- Class II- violative product may cause temporary or medically reversible adverse health consequences or remote probability of serious adverse health consequences
- Class III- violative product is not likely to cause adverse health consequences
Recall Strategy

Assess Hazard and Recall Scope

- What is the problem and when did it begin and end?
- Can additional lots/products be affected other than the lot/product analyzed and found adulterated?
- Ease of identifying the product; is the product coded with a lot number? How many different sizes and different labels?
- Degree to which the product deficiency is obvious to the consumer
- Degree to which the product remains unused in the market-place; what is the shelf-life of the product?
Recall Strategy

Recall Depth

- Class I generally to consumer/user depth via press release
- Class II generally to retail depth; some to consumer/user via press release
- Class III generally to wholesale depth when problem is obvious to consumer
Recall Strategy

Public Warning/ Press Releases

- Used to alert the public that a product presents a serious hazard to health and is usually reserved for urgent situations where other means of preventing use of the recalled product appear inadequate.

- Usually only necessary for Class I recalls but can be useful in some Class II recalls.
Effectiveness Checks

- Verification that all consignees at depth specified have received notification and have taken appropriate action
- Contact may be by telephone, personal visit, letter, or combination
- Accomplished at level specified in recall strategy
Recall Communications
Press Release (21 CFR 7.42)

- Usually only necessary for Class I recalls. However, can be useful in some Class II recalls.
- Follow FDA models as closely as possible - “fill in the blanks”
- Do not change hazard statement - e.g. don’t take out “life threatening”
- Issue press release to Associated Press
- Provide FDA with confirmation that press release was sent to AP
- FDA will issue if firm will not or if firm’s press is inadequate
- Press Releases posted on FDA website
Recall Communications
Recall Letters (21 CFR 7.49)

- Clearly identify the name of the product
- Concisely explain the reason for the recall and the hazard involved
- Explain that further distribution or use of any remaining product should cease immediately
- Include instructions regarding what to do with the product.
- When appropriate, requests that the direct account should conduct a sub-recall
- Provide a means for the recipient to report back to the recalling firm
Technical Bulletins

- Technical Bulletins, Service instructions, etc

ARE NOT REPLACEMENTS FOR

- Recall Letters- (Urgent Device Recall or Urgent Device Correction)

End users need to be made aware of recall and possible risks as well as your instructions or corrections.
Status Reports

- Submit to FDA office after recall classification
- Used to assess recall progress
- Normally contain:
  1- Number consignees notified
  2- Number responses & product
  3- Number non-responders
  4- Amount of product returned
  5- Number/result of effectiveness checks performed
A firm that recalls should immediately notify the appropriate FDA office (21 CFR 7.46)
- Voluntary reporting regardless of perceived classification

Special requirements for medical device reporting
- 21 CFR part 806- Medical Device Reports of Corrections and Removals
21 CFR Part 806

- Requires medical device manufacturers and importers to:
  - report to FDA any correction or removal of a medical device(s) if the correction or removal was initiated to reduce a risk to health posed by the device or to remedy a violation of the act caused by the device which may present a risk to health
  - Keep records of those corrections and removals that are not required to be reported to FDA
Risk to Health defined as:

- A reasonable probability that use of, or exposure to, the product will cause serious adverse health consequences or death; or
- That use of, or exposure to, the product may cause temporary or medically reversible adverse health consequences, or an outcome where the probability of serious adverse health consequences is remote.
- (Same basic definitions as the Class I and Class II definitions found in 21 CFR 7.3(m))
21 CFR Part 806

Following actions are exempt from reporting requirements:

- Market withdrawals
- Routine Servicing (i.e. any regularly scheduled maintenance of a medical device, including the replacement of parts at the end of their normal life expectancy)
- Stock recoveries
How/What do I Report?


- Info needed by FDA includes:
  - Registration #, date report made, sequence # (001, 002, etc.), and either a “C” for correction or “R” for removal;
    - i.e. 1234567-10/21/07-001-C
  - Name/full contact info and contact person of firm conducting recall;
  - Product info (identity, size and type of containers, brand names, lot numbers, 501(k)/PMA number);
  - Model/catalog number, lot codes/serial numbers;
  - Manufacturer’s full contact info (if different than recalling firm);
  - Complete reason for recall;
  - Any illness or injuries reported (include MDR numbers, if applicable);
  - Number of devices subject to the recall;
  - Dates of manufacture or distribution; expiration date or expected life;
  - Number of and types of consignees, area of distribution;
  - Consignee list with full address and telephone number for each consignee;
Expected District Office Requests

- Firm's Recall Letter
- All labeling for products under Recall
- Firm's Health Hazard Evaluation
- Firm's Press Release (if applicable)
- MDR reports or summary of reports
- Copy of 806 submission-Correction and Removal Report
- Any firm investigation (with sample results)
- Firm's complaints- (or summary if too large)
- CAPA Records (Device Correction, Validation/Verification of Device Correction, Root Cause, Corrective and Preventative actions to address Root Cause, verification or validation of CAPA)
- Device Manual
- Root Cause
Where Do I Report?

- District Recall Coordinator see link: http://www.fda.gov/ICECI/Inspections/IOM/ucm124063.htm

Recall Coordinators are a wealth of knowledge. Recalls are their daily business. It’s their job to ensure you do an effective recall. Use them!!
Open Communication with FDA

- Discuss recall strategy with FDA early in the process.
- Let FDA review text of phone notifications, written recall notifications, press releases (follow models provided in FDA guidance)
- Discuss your plan for disposition of recalled product with your recall coordinator
FDA Responsibilities

- Discuss and approve recall strategy - including press releases (district/center - Office of Public Affairs for press)
- Classify the recall (center)
- Monitor the recall by reviewing firm’s status reports and conducting audit checks (district)
- Terminate the recall (district for class II and III; center approval needed for class I)
Top 10 Root Causes

1. Non-Conforming Material-Components
2. Process Control
3. Software Change Control
4. Employee Error
5. Device Design
Top 10 Root Causes

6. Labeling False/Misleading
7. Component Design/Selection
8. Labeling Mix-ups/Errors
9. Component Change Control
10. Process Design
Road to Recall Reduction

- Design controls/change controls
- Specifications
- Validation (Product, Manufacturing, Testing)
- Component Acceptance
- In-process controls (justify reworks-higher QA audit)
- Audits-include vendors/suppliers
- In depth review of Complaints/MDRs (resist user-error as conclusion)
Recall Toolbox

- Industry recall guidance, model recall press releases for industry, and links to recall information.

  
  - [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/RecallsCorrectionsAndRemovals/](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/RecallsCorrectionsAndRemovals/)
Medical Device Recall Database

- Product Name
- Recall Class
- Date Initiated
- Reason For Recall
- Recalling Firm
- Sort By

Device Recall Actions by Fiscal Year

- **Class I**
- **Class II**
- **Class III**
Contact Info

Tamera Hunt
Acting Recall and Emergency Coordinator
FDA Dallas District Office
4040 N. Central Expressway, Ste. 300
Dallas, TX 75204
214-253-5222
fax 214-253-5314
ANY QUESTIONS?
Medical Device Reporting

Keeping FDA on the loop about significant adverse events
Medical Device Reporting

- Requires reporting to FDA
  - Adverse events
  - Certain malfunctions

- Requires written procedures and files for
  - Manufacturers
    - Foreign manufacturers
  - Distributors
  - User facilities
Manufacturer Requirements

- Written MDR procedures (§ 803.17)
- MDR event files (§ 803.18)
- Individual adverse event reports (§ 803.50 and § 803.52)
- Fiveday MDR reports (§ 803.53)
- MDR baseline reports (§ 803.55)
- MDR supplemental reports (§ 803.56)
MDR Trigger

- When you receive or otherwise become aware of information, from any source, that reasonably suggests that a device that you market:
  - 1) May have caused or contributed to a death or serious injury; or
MDR Trigger

(2) Has malfunctioned and this device or a similar device that you market would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur.

*Serious injury* means an injury or illness that:

(1) Is life-threatening,
MDR Trigger

- (2) Results in permanent impairment of a body function or permanent damage to a body structure, or

- (3) Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

*Permanent* means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.
<table>
<thead>
<tr>
<th>REPORTER</th>
<th>WHAT TO REPORT</th>
<th>REPORT FORM #</th>
<th>TO WHOM</th>
<th>WHEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>30 day reports of deaths, serious injuries and malfunctions</td>
<td>Form FDA 3500A</td>
<td>FDA</td>
<td>Within 30 calendar days from becoming aware of an event</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>5-day reports on events that require remedial action to prevent an unreasonable risk of substantial harm to the public health and other types of events designated by FDA</td>
<td>Form FDA 3500A</td>
<td>FDA</td>
<td>Within 5 work days from becoming aware of an event</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Baseline reports to identify and provide basic data on each device that is subject of an MDR report. At this time, FDA has stayed the requirement for denominator data requested in Part II, Items 15 and 16 on Form 3417.</td>
<td>Form FDA 3417</td>
<td>FDA</td>
<td>With 30 calendar, and 5 work day reports when device or device family is reported for the first time. Interim and annual updates are also required if any baseline information changes after initial submission.</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Annual Certification</td>
<td>Form FDA 3381</td>
<td>FDA</td>
<td>Coincide with firm's annual registration dates.</td>
</tr>
<tr>
<td>REPORTER</td>
<td>WHAT TO REPORT</td>
<td>REPORT FORM #</td>
<td>TO WHOM</td>
<td>WHEN</td>
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<tr>
<td>--------------</td>
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<td>---------------------------</td>
</tr>
<tr>
<td>User Facility</td>
<td>Death</td>
<td>Form FDA 3500A</td>
<td>FDA &amp; Manufacturer</td>
<td>Within 10 work days</td>
</tr>
<tr>
<td>User Facility</td>
<td>Serious injury</td>
<td>Form FDA 3500A</td>
<td>Manufacturer. FDA only if manufacturer unknown</td>
<td>Within 10 work days</td>
</tr>
<tr>
<td>User Facility</td>
<td>Annual reports of death &amp; serious injury</td>
<td>Form FDA 3419</td>
<td>FDA</td>
<td>January 1</td>
</tr>
</tbody>
</table>
Implants, life-sustaining and life-supporting devices, or those likely to cause serious adverse health consequences
Implants Subject to Tracking

- Temporomandibular Joint (TMJ) prosthesis
- Glenoid fossa prosthesis
- Mandibular condyle prosthesis
- Implantable pacemaker pulse generator
- Cardiovascular permanent implantable pacemaker electrode
- Replacement heart valve (mechanical only)
- Automatic implantable cardioverter/defibrillator
- Implantable cerebellar stimulator
- Implantable diaphragmatic/phrenic nerve stimulator
- Implantable infusion pumps
- Abdominal Aortic Aneurysm (AAA) stent grafts
- Silicone gel-filled breast implants
- Cultured epidermal autografts
- Thoracic Aortic Aneurysm (TAA) stent grafts
When Used Outside A User Facility

- Breathing frequency monitors
- Continuous ventilators
- Ventricular bypass (assist) device
- DC-defibrillators and paddles
Tracking Requirements

- Establish written SOP for tracking devices
- Establish Quality Assurance Program
  - Audit Procedures
- Final Distributors must provide manufacturers with patient information
- Required for the useful life of the device
- Patients may refuse
Guidance For Industry

- Medical Device Tracking; Guidance for Industry and FDA Staff
- [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071756.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071756.htm)
Special Cases

Where to get additional information
Combination Products

- Device/drug and device/biologic combinations
  - e.g., interactive wound and burn dressings, infusion pumps, antibiotic bone cement
- Primary mode of action determines the lead center
  - CDRH, CDER, CBER
Office of Combination Products

- Assign FDA center to have primary jurisdiction for review
- Oversee reviews involving multiple centers to ensure timely and effective reviews
- Ensure consistency and appropriateness of postmarket regulation
- Resolve disputes regarding the timeliness of premarket reviews
Office of Combination Products

- Update agreements, guidance documents or practices specific to the assignment of combination products
- Working with FDA Centers to develop guidance or regulations to clarify the agency regulation of combination products
- Serving as a focal point for combination products issues for internal and external stakeholders
Office of Combination Products

- 15800 Crabbs Branch Way (HFG-3) Suite 200 Rockville, MD 20855
- Phone 301-427-1934
- Fax 301-427-1935
- Email combination@fda.gov
- http://www.fda.gov/CombinationProducts/
Office of In-Vitro Diagnostics

- Integrated regulatory oversight for IVD’s
  - Regulates all aspects of in-home and laboratory diagnostic tests
  - Categorizes the complexity of IVD’s according to CLIA defining the type of regulatory oversight applied to the product
OIVD Contact Information

- 10903 New Hampshire Avenue WO66-5521
  Silver Spring, MD 20993
- Phone 301-796-5450
- [http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/](http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/)
Radiological Health Program

- Office of Communication, Education, and Radiation Programs
  10903 New Hampshire Avenue WO66-4613
  Silver Spring, MD 20993
- Phone 800-638-2041
Device Advice: Device Regulation and Guidance

Search Device Advice

Information for regulated industry on determining how to comply with the federal laws and regulations governing medical devices.

Additional Information
- DSMICA Staff Directory
DSMICA

- Division of Small Manufacturers, International, and Consumer Assistance
- 10903 New Hampshire Avenue WO66-5429
  Silver Spring, MD 20993
- Toll-free in the USA 1-800-638-2041
- Outside the USA 301-796-7100
- dsmica@cdrh.fda.gov
DSMICA’s Function

- Handle industry inquiries and training opportunities relating to medical devices and radiation emitting products
- Regulatory policies, guidance documents, forms and other publications
- Staff directory by area of expertise: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ucm142656.htm
FDA Mailing Lists

- Sign up for any of more than 20 specialized lists
- Free!
- [http://www.fda.gov/AboutFDA/ContactFDA/StayInformed/GetEmailUpdates/](http://www.fda.gov/AboutFDA/ContactFDA/StayInformed/GetEmailUpdates/)
My Contact Information

- David Arvelo
- FDA/ORA/SWRO (HFR-SW2)
  4040 N. Central Expwy Ste 900
  Dallas, TX 75204
- Telephone 214-253-4952
- Fax 214-253-4970
- Email david.arvelo@fda.hhs.gov
Device Workshop 101
July 19, 2013
Austin, Texas

Iris C. MacInnes
Consumer Safety Officer
U.S. Food and Drug Administration
Dallas District Office
Austin Resident Post
FDA Medical Device Industry Coalition

FDA Inspections

Using the Quality System Inspection Technique (QSIT)
The FDA’s Office of Regulatory Affairs is the lead office for all FDA Field activities as well as providing FDA leadership on imports, inspections, and enforcement policy.

ORA supports the six FDA Product Centers by inspecting regulated products and manufacturers, conducting sample analysis on regulated products, and reviewing imported products offered for entry into the United States.

ORA also develops FDA-wide policy on compliance and enforcement and executes FDA’s Import Strategy and Food Protection Plans.
ORA Staff

- ORA staff are dispersed throughout the United States. Over 85 percent of ORA’s staff works in 5 Regional Offices, 20 District Offices, 13 Laboratories, and more than 150 Resident Posts and Border Stations.

- ORA Headquarters is comprised of the Office of Resource Management; Office of Regional Operations; and, the Office of Enforcement located in Rockville, Maryland and the Office of Criminal Investigations located throughout the United States.

- FDA maintains offices and staff in Washington, D.C., the U.S. Virgin Islands, Puerto Rico, and in all States except Wyoming.
Investigators

- Also known as a Consumer Safety Officer.
- Have a science background.
- Work in Food, Devices, Drugs, BIMO, Blood & Biologics, and Imports.
- Receive training according to discipline.
- May be part of international inspection Cadre
How does FDA decide who to inspect?

- Registration database identifies who manufacturers devices for distribution in the U.S.
- Listing database identifies what devices they distribute
- FDA prioritizes inspections by risk and gives higher risk devices/situations a higher priority
How often does FDA inspect firms?

- Mandated by law, every 2 years for Class II and Class III device manufacturers
- Risk of the device
- Follow up inspections to regulatory action
- Complaints (public & industry)
Investigator Tools

- Federal Food, Drug, and Cosmetic Act
- 21 Code of Federal Regulations (800-1299)
- Quality System Inspection Techniques (QSIT)
- CP 7382.845 Inspection of Medical Device Manufacturers available on-line
Investigator Tools

- Previous Establishment Inspections Reports
- DSMICA
- Guidance Documents (can be accessed from www.FDA.gov website under Medical devices CDRH Device Advice
- Internet
- Other Federal, State and Local agencies
What is high priority for an inspection?

- Make Class II or Class III devices
- Make implantable devices and life supporting and life sustaining devices
- Recently introduced a new device to the market
- Have had significant violations and complaints in the past
Does FDA notify the manufacturer of an upcoming inspection?

- FDA calls domestic manufacturers up to 5 calendar days before the inspection.
- FDA contacts foreign manufacturers 2 - 3 months in advance to schedule inspection.
- Manufacturer may be requested to send Quality System Manual or equivalent for pre-inspection review.
Preannouncements

To be eligible for pre-announcements the firm should meet the following requirements.

- Non-violative QS/GMP inspection histories NAI or VAI where no regulatory action occurred.

- To remain eligible the firm must have a history of having individuals and/or documents identified in previous pre-announced inspection reasonably available at the time of inspection.
The following inspections may qualify for pre-announcement.

- Premarket Approval
- Foreign Inspections
- Biennial Routine Inspections
- Initial Inspections.
What happens when the FDA Investigator arrives at the site?

- Ask to see the top management (“most responsible person” at the firm).
- Present credentials (identification as an authorized FDA investigator)
- Issue FDA-482 “Notice of Inspection” (explains FDA’s legal authority to inspect)
This is an example of Form FDA 482, Notice of Inspection.
Can you refuse an inspection?

- Under section 704 of the FD&C Act, FDA is authorized to enter establishments.
- They are further authorized to inspect “at reasonable times and within reasonable limits and in a reasonable manner”.
- FDA can also seek an Administrative Inspection Warrant from a United States District Court.
What happens next?

- Gather information about size and structure of company, who are the responsible officials, what products are manufactured there.

- Evaluate the manufacturer’s Quality System using the Quality System Inspection Technique (QSIT)
What happens during the inspection?

- Investigator may tour the facility to get an idea of layout, workflow, and areas that may need closer inspection.
- The Investigator will review written procedures and records related to the manufacturing of the device.
- They may request to interview employees, and will make copies of documents.
- The Investigator may also request to take pictures during the inspection.
What is QSIT?

- Identifies 4 major subsystems to evaluate and states the purpose and importance of each subsystem
- Provides flowcharts and inspectional objectives to cover during inspection
- Offers advice on inspection
- Provides tables for statistical sampling of records for review
Subsystems of the Quality System

- Design Controls
- Corrective & Preventive Actions
- Production & Process Controls
- Material Controls
- Management
- Records, Documents, & Change Controls
- Equipment & Facility Controls
Does FDA conduct different types of inspections?

Investigators may conduct 1 of 4 types of inspections for medical devices:

- Level 1 – Abbreviated QSIT
- Level 2 – Baseline QSIT (Comprehensive)
- Compliance follow-up
- “For Cause”
What is a Level 2 baseline (comprehensive) inspection?

- Covers all 4 main subsystems
- Is conducted when the firm has never had Level 2 inspection and every 6 years thereafter, resources permitting
- Provides an overall evaluation of the firm’s quality system
What is a Level 1 abbreviated inspection?

- Is conducted after firm has had a Level 2 inspection, and quality system was in compliance with requirements
- Covers CAPA plus one other major subsystem
- Covers a different subsystem each time
What is a “For Cause” Inspection?

- Initiated at the request of CDRH, ORA Headquarters, Regional or District Directive
- Dictated by the source of information and may differ from typical QSIT approach
- These inspections are generally more in depth in particular areas than typical QSIT inspections
- Conducted as the need arises
  - Important note in CP, if the Investigator encounters a serious public health risk during the QSIT inspection the investigator may switch to a for cause inspection
What is a compliance follow-up inspection?

- Is conducted to verify adequate correction of previous violations or document continuing violations to support possible regulatory action
- Is conducted to follow up on information indicating serious problems at firm
- May include elements of QSIT
What happens at the end of the inspection?

- Meet with management to discuss the inspection
- Present the FDA 483 “List of Observations” of any significant observations
- Discuss the observations
Inspectional Observations

- This is an example of the FDA Form 483, Inspectional Observations.

- The header identifies the FDA district office that performed the inspection, the date(s) of inspection, name and address of the facility that was inspected, the name and title of the individual to whom the 483 is issued to (usually the most responsible individual physically present in the facility), a brief description of the type of facility, and the facility's FEI (FDA Establishment Identification) number.
FDA-483 “Inspectional Observations”

- The content of a 483 may be handwritten, typed, completed in a PDF file and printed, or completed via the FDA's computer system called Turbo EIR.

- The observations listed on this form do not represent a final agency determination regarding your compliance. An additional statement only included for medical devices is that the observations are not an exhaustive listing of objectionable conditions. Under law your firm is responsible for conducting internal self-audits to identify and correct any and all violations of the quality system requirements.”

- If the firm has promised and/or completed a corrective action to an FDA 483 prior to the completion of the inspection, the FDA 483 should be annotated.
Turbo EIR

TurboEIR is a software program designed to standardize FDA-483s and Establishment Inspection Reports (EIR).

- Links citations to underlying regulations and statutes
- Provides uniform FDA-483s and EIRs
- Improves data analysis
What are annotations to the 483?

As of 1997, the FDA established an annotation policy for medical device inspections. The investigator(s) should offer to annotate the 483 with one or more of the following:

- Reported corrected, not verified
- Corrected and verified
- Promised to correct
- Under consideration

The actual annotation of the 483 occurs during the final discussion with the firm's management; if the firm prefers no annotation, then annotation will not be performed. The annotations may be after each observation, at the end of each page, or at the bottom of the last page prior to the investigator's signature(s).
Promised to Correct?

- If the firm has promised correction and furnishes a date or timeframe for completion, this may be added to the annotation.

- If the investigator and firm have “agreed to disagree” about the validity of an observation, the observation may be annotated with “under consideration” or no annotation is used, based on the firm’s decision.
## Top 10 Devices Observations Used in Turbo EIR

<table>
<thead>
<tr>
<th>Cite ID</th>
<th>Count</th>
<th>Reference No.</th>
<th>Citation Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>3130</td>
<td>1686</td>
<td>21 CFR 820.100(a)</td>
<td>Procedures for corrective and preventive action have not been [adequately] established. Specifically, ***</td>
</tr>
<tr>
<td>630</td>
<td>1179</td>
<td>21 CFR 803.17</td>
<td>Written MDR procedures have not been [developed] [maintained] [implemented]. Specifically, ***</td>
</tr>
<tr>
<td>4189</td>
<td>1093</td>
<td>21 CFR 820.198(a)</td>
<td>Complaint handling procedures for [receiving] [reviewing] [evaluating] complaints have not been [established] [defined] [documented] [completed] [implemented]. Specifically, ***</td>
</tr>
<tr>
<td>3696</td>
<td>1074</td>
<td>21 CFR 820.100(b)</td>
<td>Corrective and preventive action activities and/or results have not been [adequately] documented. Specifically, ***</td>
</tr>
<tr>
<td>546</td>
<td>975</td>
<td>21 CFR 820.75(a)</td>
<td>A process whose results cannot be fully verified by subsequent inspection and test has not been [adequately] validated according to established procedures. Specifically, ***</td>
</tr>
<tr>
<td>3415</td>
<td>833</td>
<td>21 CFR 820.22</td>
<td>Quality [audits][re audits] have not been performed. Specifically, ***</td>
</tr>
<tr>
<td>2327</td>
<td>786</td>
<td>21 CFR 820.22</td>
<td>Procedures for quality audits have not been [adequately] established. Specifically, ***</td>
</tr>
<tr>
<td>2371</td>
<td>704</td>
<td>21 CFR 820.30(a)</td>
<td>Procedures for design control have not been established. Specifically,***</td>
</tr>
<tr>
<td>3103</td>
<td>692</td>
<td>21 CFR 820.30(i)</td>
<td>Procedures for design change have not been [adequately] established. Specifically,***</td>
</tr>
<tr>
<td>479</td>
<td>858</td>
<td>21 CFR 820.50</td>
<td>Procedures to ensure that all purchased or otherwise received product and services conform to specified requirements have not been [adequately] established. Specifically, ***</td>
</tr>
</tbody>
</table>

---

The table above lists the top 10 Devices Observations Used in Turbo EIR, along with their respective counts and details regarding the specific issues observed.
What should the manufacturer do after the inspection?

- Send a letter to FDA identifying how they have corrected observations or will correct them.
- Provide documentation of any corrections that have been completed.
- Provide a timetable or estimated completion date for future corrections.
What happens next?

- Investigator returns to office to write an “Establishment Inspection Report” or EIR
- Inspection is classified based on inspectional findings
- Compliance officer decides whether to recommend regulatory action
How does FDA classify inspection reports?

- NAI – No action indicated
- VAI – Voluntary action indicated – some deficiencies identified but not serious
- OAI – Official action indicated – serious deficiencies identified, and FDA must take action to assure correction
What actions can FDA take to address OAI inspections?

- Warning Letter
- Seizure
- Injunction
- Civil penalties
- Criminal
Warning Letter

- FDA sends “Warning Letter” describing manufacturer’s violations of FDA regulations and requesting a reply within 15 days
- FDA inspects the manufacturer 6 - 12 months after sending the Warning Letter to confirm correction of deficiencies
Providing Industry Education and Assistance - CDRH Resources

- **CDRH Learn – Online Regulatory Training Tool**
  - Over 50 Medical device and Radiological Health modules
  - Video and PowerPoint presentations available 24/7
  - Certificate of completion upon passing post-tests
  - Many modules are translated into Chinese and Spanish
  - [http://www.fda.gov/Training/CDRHLearn/](http://www.fda.gov/Training/CDRHLearn/)

- **Device Advice – Online Regulatory Information**
  - Searchable by topic
  - [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance)
  - dsmica@fda.hhs.gov
Providing Industry Education and Assistance - CDRH Resources

- CDRH Learn – Regulatory Topics
  - Overview of Regulatory Requirements: Medical Devices
  - Guidance Documents and Standard Operating Procedures (SOPs)
  - Premarket Notification Process - 510(k)
  - Investigational Device Exemption Process – IDE
  - Bioresearch Monitoring (BIMO)
  - Device Establishment Registration and Listing
  - CDRH Regulated Software: An Introduction
  - Quality System Regulation 21 CFR Part 820
  - Medical Device Recalls
  - Medical Device Reporting (MDR)
  - Export Certificates for Medical Devices
  - Regulation of Radiation-Emitting Products
  - Global Initiatives
  - Medical Devices In the Home
  - Unique Device Identification (UDI) System