Prof. Steven S. Saliterman

FDA Regulation of Medical Devices
Premarket Requirements

Landscape

FDA Authority
- Medical Device Act of 1976
- FDA Modernization Act of 1997
- Federal Food, Drug and Cosmetic Act (FFDCA)
- Medical Device User Fee Act (MDUFA)

Premarket Requirements
- A Premarket Approval (PMA) application or 510(k) must be submitted. Approval or clearance depends on risk!

Products Regulated by the FDA...

Table S2: Products regulated by the FDA

- Blood-related Biologics, Blood derivatives, etc.
- Devices (orthopedic, ophthalmic, etc.)
- Drugs (non-biologic drugs, etc.)
- Foods (cooking and processed foods, etc.)
- Medical devices (implants, surgical devices, etc.)
- Radiation emitting electronic products
- Veterinary products

Device Classification

<table>
<thead>
<tr>
<th>Device Classification</th>
<th>Example</th>
<th>Safety/Effectiveness Controls</th>
<th>Required Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Elastic bandages&lt;br&gt;Examination Gloves&lt;br&gt;Hand-held surgical tools</td>
<td>General Controls</td>
<td>Registration only unless 510(k) specifically required</td>
</tr>
<tr>
<td>Class II</td>
<td>Powered wheelchairs&lt;br&gt;Infusion pump&lt;br&gt;Surgical drapes</td>
<td>General &amp; Special Controls</td>
<td>510(k) unless exempt – IDE possible</td>
</tr>
<tr>
<td>Class III</td>
<td>Heart valve&lt;br&gt;Silicon implants&lt;br&gt;Implanted cerebral stimulators</td>
<td>General Controls &amp; Premarket Approval</td>
<td>PMA application – IDE probable</td>
</tr>
<tr>
<td>Class I</td>
<td>Metal-on-metal joint&lt;br&gt;Dental implants</td>
<td>General Controls</td>
<td>510(k) notification</td>
</tr>
</tbody>
</table>

Device Classification...

- **Class I**
  - General controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device.
  - Low risk of illness or injury to patients.
  - Many are exempt from the premarket notification and/or the Quality System (QS) regulation requirements.
- **Class II**
  - General controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness of the device.
  - Special Controls are available to reduce or mitigate risk.
  - Most require 510(k) notification – some are exempt (FDA determined).
- **Class III**
  - Insufficient information to exists to determine that Special Controls would provide reasonable assurance of their safety and effectiveness.
  - Most require premarket approval (PMA).
**Premarket Review Path**

To Market

- 510(k) Notification
  - Substantially equivalent to a device already in the market (predicate device).
  - Must have the same intended use and technological characteristics as the predicate.
- Premarket Approval (PMA)
- FDA Clearance
- Risk Assessment

**Pathways Taken (2016)...**

Anually >4,000 510(k) notifications and ~40 original PMA applications.

**Federal Food, Drug and Cosmetic Act 1997...**

- Generally speaking, under the Federal Food, Drug and Cosmetic Act (FFDCA), manufacturers:
  - Are prohibited from selling an adulterated product;
  - Are prohibited from misbranding a product;
  - Must register their facility with FDA and list all of the medical devices that they produce or process;
  - Must file the appropriate premarket submission with the agency at least 90 days before introducing a nonexempt device onto the market; and
  - Must report to FDA any incident that they are aware of that suggests that their device may have caused or contributed to a death or serious injury.
Medical Device User Fees ($)...  

<table>
<thead>
<tr>
<th>Year</th>
<th>Review Path</th>
<th>Large Business (&gt;$10m Revenue)</th>
<th>Small Business</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>510(k)</td>
<td>5,228</td>
<td>2,614</td>
</tr>
<tr>
<td></td>
<td>513g</td>
<td>3,529</td>
<td>1,765</td>
</tr>
<tr>
<td></td>
<td>PMA</td>
<td>261,388</td>
<td>65,347</td>
</tr>
<tr>
<td>2017</td>
<td>510(k)</td>
<td>4,690</td>
<td>2,345</td>
</tr>
<tr>
<td></td>
<td>513g</td>
<td>3,166</td>
<td>1,583</td>
</tr>
<tr>
<td></td>
<td>PMA</td>
<td>234,495</td>
<td>58,624</td>
</tr>
<tr>
<td>2018</td>
<td>510(k)</td>
<td>10,566</td>
<td>2,642</td>
</tr>
<tr>
<td></td>
<td>513g</td>
<td>4,195</td>
<td>2,098</td>
</tr>
<tr>
<td></td>
<td>PMA</td>
<td>310,784</td>
<td>77,691</td>
</tr>
</tbody>
</table>

Premarket Approval (PMA)  

- A *Investigational Device Exemption* is required before the clinical study (unless exempt). Must have *Institutional Review Board (IRB)* approval.  
- Summaries of nonclinical and clinical data supporting the application and conclusions drawn from the studies.  
- Device description including significant physical and performance characteristics.  
- Indications for use, description of the patient population and disease or condition that the device will diagnose, treat, prevent, cure, or mitigate.  

- Description of the foreign and U.S. marketing history, including if the device has been withdrawn from marketing for any reason related to the safety or effectiveness of the device.  
- Proposed labeling.  
- Description of the manufacturing process.  
- FDA may order a post-approval study.  
- *PMA Supplements* are required to make a change to an approved PMA device.  
- FDA approval does not imply Medicare coverage.
**Clinical Studies…**

- **Required:**
  - Randomized Controlled Trial (RCT).
  - Blinded Clinical Trial.
- **Issues:**
  - Use of surrogate end point (e.g. low cholesterol lab) value vs direct patient benefit (less death from heart disease).
  - Reporting bias.
  - Failure to timely publish clinical results (or substantially different than was submitted).
  - Accessibility to patients of data the FDA used in the PMA.
  - Lack of clinical data in the PMA Supplement.

---

**Good Clinical Practices (21 CFR)**

- Investigational Device Exemptions (812)
  - Covers the procedures for the conduct of clinical studies with medical devices including application, responsibilities of sponsors and investigators, labeling, records, and reports.
- Protection of Human Subjects (50)
  - Provides the requirements and general elements of informed consent;
- Institutional Review Boards (56)
  - Covers the procedures and responsibilities for institutional review boards (IRBs) that approve clinical investigations protocols;

---

- Financial Disclosure by Clinical Investigators (54)
  - Covers the disclosure of financial compensation to clinical investigators which is part of FDA’s assessment of the reliability of the clinical data.
- Design Controls of the Quality System Regulation (820 Subpart C)
  - Provides the requirement for procedures to control the design of the device in order to ensure that the specified design requirements are met.
**Investigational Device Exemption (IDE)**

- Allows the device to be used in an a clinical study in order to collect safety and effectiveness data.
- Usually in support of the PMA.
- An investigational plan 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 stating that the device is for investigational use only;
- Monitoring of the study and;
- Required records and reports

**Do not require PMA, 510(k), establishment registration or listing. Exempt form Quality System.**

---

**Humanitarian Device Exemption (HDE)**

- Diseases or conditions that affect fewer than 4,000 individuals in the United States per year.
- Exempt from the effectiveness requirements to encourage manufacturers to develop devices for these small markets.
- IRB approval required.
- Potential insurers may not cover the device.
- Cannot be another similar legally marketed device.
510(k) Notification

- Required for a moderate-risk medical device that is not exempt from premarket review.
- Typically Class II, rarely Class III.
- Must be substantial equivalence with a predicate device.
  - Previously cleared Class I or II device that does not require a PMA.
- Three types: Traditional, Special, and Abbreviated.
- De Novo - novel devices without a predicate.

Substantial Equivalence Defined:

- A device is substantially equivalent if, in comparison to a predicate it:
  - has the same intended use as the predicate; and
  - has the same technological characteristics as the predicate; or
  - has the same intended use as the predicate; and
  - has different technological characteristics and does not raise different questions of safety and effectiveness; and
  - the information submitted to FDA demonstrates that the device is at least as safe and effective as the legally marketed device.

Traditional 510(k)

- Name of the device, a description of the device, a comparison with a predicate device, the intended use of the device, and the proposed label, labeling, and advertisements for the device and directions for use.
- Generally do not require premarket inspection and post market studies.
Abbreviated 510(k)
- Uses guidance documents developed by FDA to communicate regulatory and scientific expectations to industry.
- FDA can either develop performance or consensus standards or ‘recognize’ those developed by outside parties.
- The manufacturer describes what guidance document, special control, or performance standard was used, and how it was used to assess performance of their device.
- Requires a product description, representative labeling, and a summary of the performance characteristics.

Special 510(k)
- Used for a modification to a device that has already been cleared under the 510(k) process.
- Typically uses the design control requirement of the Quality System (QS) regulation.
- The QS regulation describes the good manufacturing practice (GMP) requirements for medical devices.

De NOVO 510(k)
- Under the FFDCA, novel devices lacking a legally marketed predicate are automatically designated Class III.
- FDAMA amended FFDCA Section 513(f) to allow FDA to establish a new, expedited mechanism for reclassifying these devices based on risk, thus reducing the regulatory burden on manufacturers.
- The de novo 510(k), though requiring more data than a traditional 510(k), often requires less information than a premarket approval (PMA) application.
FDA Clearance for Class I and II Devices...

FDA's perspective on additively manufactured medical products:
- Center for Devices and Radiological Health (CDRH).
  - Cleared additively manufactured devices for over a decade within the existing medical device regulations.
- Center for Drug Evaluation and Research (CDER).
  - Approved the first 3D printed drug within the existing chemistry, manufacturing and control standards that all other drug products are regulated by.
- Center for Biologics Evaluation and Research (CBER).
  - Following the literature and interacting with stakeholders.

3D Printing

Office of Cellular, Tissue and Gene Therapies
- Works with Office of Combination Products
- Regulates, reviews and develops policy on:
  - Tissues,
  - Cellular and tissue based products,
  - Gene therapies,
  - Xenotransplantation,
  - Combination products containing living cells or tissues,
  - Unique assisted reproduction (ooplasm transfer).
Not Needing Approval...

- Cell, tissue and gene therapy do not need PMA if:
  - There is minimal manipulation.
  - There is homologous use.
  - They are not combined with a drug or device.
  - They exert no systemic effect.
  - They exert a systemic effect, but they are not:
    - Autologous
    - Allogenic in a first or second-degree relative
    - For reproduction use.

FDA: Title 21 Food & Drugs...

- 3D bioprinting is regulated by existing laws, mainly those concerning medicinal products and medical devices.
- Part 1271: Human Cells, Tissues and Cellular and Tissue-Based Products.
  - An electronic registration and listing system for establishments that manufacture human cells, tissues, and cellular and tissue-based products.
  - To establish donor-eligibility, current good tissue practice, and other procedures to prevent the introduction, transmission, and spread of communicable diseases. (Safety and quality control.)

Not Needing Approval...

- Cell, tissue and gene therapy do not need PMA if:
  - There is minimal manipulation.
  - There is homologous use.
  - They are not combined with a drug or device.
  - They exert no systemic effect.
  - They exert a systemic effect, but they are not:
    - Autologous
    - Allogenic in a first or second-degree relative
    - For reproduction use.

FDA: Title 21 Food & Drugs...

- 3D bioprinting is regulated by existing laws, mainly those concerning medicinal products and medical devices.
- Part 1271: Human Cells, Tissues and Cellular and Tissue-Based Products.
  - An electronic registration and listing system for establishments that manufacture human cells, tissues, and cellular and tissue-based products.
  - To establish donor-eligibility, current good tissue practice, and other procedures to prevent the introduction, transmission, and spread of communicable diseases. (Safety and quality control.)

Currently, products that use stem cells or are derived from stem cells are treated by the FDA as somatic cellular therapies and are regulated as “biologics” under Section 351 of the Public Health Act.

Bioprinted tissues typically used in research do not require FDA approval during animal and in vitro testing because they are not intended for use on humans.

Title 21 of the Federal Code of Regulations defines certain restrictions with regard to shipping and disposal of these products.
FDA: Draft Guidance...

- In May 2016, the US Food and Drug Administration (FDA) released draft guidance for medical device manufacturers working with additive manufacturing.
  - Technical considerations.
  - Characterizing and validating devices.
  - Type of information to be submitted – premarket submissions.
  - Does not address the use or incorporation of biological, cellular, or tissue-based products.

FDA: Combination Product

- Biological products are defined as combination products under 21 CFR 3.2(e) if they are produced as a single entity but are physically or chemically combined with at least one integral constituent, independently regulated part.
  - The FDA classifies these combination products according to the claimed primary mode of action (MoA), the characteristics of the active substance, and the way in which it is combined in the finished product.
  - This includes medical devices that consist of biological materials, medical technologies, and drugs of different compositions.

Summary

- FDA Authority
  - Premarket Requirements
    - Product Classification – Type I, II or III
    - Premarket Approval (PMA)
    - PMA Supplements
    - Evaluations of the PMA and PMA Supplement Process
    - Humanitarian Device Exemption (HDE)
    - 510(k) Notification – Substantially Equivalent Device
      - Traditional 510k
      - Abbreviated 510k
      - Special 510K
      - De Novo 510K
  - 3D Printing & Combination Products