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>
<thead>
<tr>
<th>Table 5.2</th>
<th>Products regulated by the FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood-related biologics; blood substitutes, etc.</td>
<td>Product and manufacturing establishment licensing; safety of the nation’s blood supply; research to establish product standards and develop improved testing methods</td>
</tr>
<tr>
<td>Cosmetics</td>
<td>Safety and labeling</td>
</tr>
<tr>
<td>Drugs (including biological large molecule drugs)</td>
<td>Product approvals; over the counter (OTC) and prescription drug labeling; drug manufacturing standards</td>
</tr>
<tr>
<td>Foods</td>
<td>Labeling; safety of all food products (except meat and poultry); bottled water</td>
</tr>
<tr>
<td>Medical devices</td>
<td>Pre-market approval of new devices; manufacturing and performance standards; tracking reports of device malfunctioning and serious adverse reactions</td>
</tr>
<tr>
<td>Radiation-emitting electronic products</td>
<td>Radiation safety performance standards for microwave ovens, television receivers, diagnostic X-ray equipment, cabinet X-ray systems (such as baggage X rays at airports), laser products; ultrasonic therapy equipment, mercury vapor lamps, and sunlamps; accrediting and inspecting mammography facilities</td>
</tr>
<tr>
<td>Veterinary products</td>
<td>Livestock feeds; pet foods; veterinary drugs and devices</td>
</tr>
</tbody>
</table>

Premarket Requirements

- Device Classification
- Medical Device Marketing Applications
  - 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
## 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</td>
<td>General Controls</td>
<td>Registration only unless 510(k) specifically required</td>
</tr>
<tr>
<td></td>
<td>Examination Glove</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hand-held surgical tools</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>Powered wheelchairs</td>
<td>General &amp; Special Controls</td>
<td>510(k) unless exempt – IDE possible</td>
</tr>
<tr>
<td></td>
<td>Infusion pump</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgical drapes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>Hear Valve</td>
<td>General Controls &amp; Premarket Approval</td>
<td>PMA application – IDE probable</td>
</tr>
<tr>
<td></td>
<td>Silicon implants</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Implanted cerebral stimulators</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metal-on-m hip joint</td>
<td>General Controls</td>
<td>510(k) notification</td>
</tr>
<tr>
<td></td>
<td>Dental implants</td>
<td></td>
<td></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).

To Market

or

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

FDA Approval
Pathways Taken (2016)...

Annually >4,000 510(k) notifications and ~40 original PMA applications.
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;100m 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>310,764</td>
<td>77,691</td>
</tr>
</tbody>
</table>
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.
PMAs (%) Approved 2001–2015

98%
Investigational Device Exemption (IDE)

- Allows the device to be used in 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 from 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.
Medical Device and Diagnostic Industry Qmed, 510(k) Statistical Patterns, December 2012.

Summary of Regulatory Pathways...

Comparison PMA and 510(k) Process...

Table 5.4 Comparison of the PMA and 510(k) processes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PMA submission</th>
<th>510(k) submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to collect data</td>
<td>Several years</td>
<td>Several months</td>
</tr>
<tr>
<td>Submission size</td>
<td>Several thousand pages</td>
<td>Much less</td>
</tr>
<tr>
<td>Manufacturing details</td>
<td>Process, methods, details required</td>
<td>Typically not required</td>
</tr>
<tr>
<td>Pre-approval inspection of device manufacturing facility</td>
<td>Required</td>
<td>Not required</td>
</tr>
<tr>
<td>Clinical trial site review</td>
<td>Often required</td>
<td>Not required</td>
</tr>
<tr>
<td>Review time</td>
<td>1 year</td>
<td>90 days</td>
</tr>
<tr>
<td>Post-approval annual reports</td>
<td>Required</td>
<td>Not required</td>
</tr>
<tr>
<td>Submission availability through Freedom of information (FOI) Act</td>
<td>Not available</td>
<td>Available</td>
</tr>
<tr>
<td>Scientific advisory panels convened to assist FDA in review</td>
<td>Sometimes</td>
<td>Rarely</td>
</tr>
</tbody>
</table>

FDA Clearance for Class I and II Devices...

(a) Regulatory path

1. Register company
2. Establish quality processes
3. Classify device
4. Identify predicate device
5. Substantial equivalence
6. 510(k) application and clearance
7. CLIA categorization

(b) FDA regulatory clearance class I/II diagnostic device (6–9 months)
- Register company as medical device manufacturer with FDA
- Establish quality process – design, packaging, labeling, and manufacturing
- Classify device-Class I exempt, Class I, or Class II for some tests. If exempt, apply directly for “CLIA categorization only”
- Identify predicate devices for application
- Establish substantial equivalence with approved tests
- Pre-market notification (510(k) submission); CLIA categorization request
- Post-marketing reporting
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.
Biologics...

- 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.
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.
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.

Technical Considerations for Additive Manufactured Devices

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.


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.
FDA Authority

Premarket Requirements
- Product Classification – Type I, II or III
- Premarket Approval (PMA)
  - PMA Supplements.
  - Evaluations of the PMA and PMA Supplement Process.
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3D Printing & Combination Products