FDA Device Regulation:

510(k), PMA

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Topic Relevance by Time

Summary

- In the U.S., medical devices are classified into one of three groups based on potential risk to patients and this plays an important role in determining the appropriate FDA regulatory pathway.
- The three most common regulatory pathways through which the FDA clears or approves devices are: 1) exemption status, 2) 510(k), and 3) premarket approval (PMA).
- Early understanding of likely pathways is essential for planning device design and research strategy.
- All devices with more than a low or non-significant risk potential must be granted clearance, approval, or an Investigational Device Exemption (IDE) from the FDA prior to use in human subjects.
- Pre-submission, or Q-sub meetings, allow innovators and device companies to meet with the FDA for free and obtain feedback on the potential pathway and research protocols in an effort to have higher success with a future formal application.
- Early involvement of a regulatory expert or consultant can lead to a reduction in time to market and important cost savings.

Introduction

Understanding the fundamentals of FDA regulation is essential for all innovators interested in bringing a product or idea forward in the medical device space. Innovators who consider the regulatory pathway and develop a regulatory strategy earlier in the process of device design or development will put themselves at a clear advantage, potentially saving critical time and money

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that frequently makes the difference between success and failure for a product reaching the market. FDA regulation hinges on the invasiveness and risk level of the device, which places it in a specific class. Depending on device class, the regulatory process may be straightforward with exempt status or more laborious, requiring formal application through premarket clearance using the 510(k) process or the premarket approval (PMA) pathway. While the 510(k) pathway is often quicker, less costly, and requires less robust, if any, clinical evidence, this pathway depends upon the device having a predicate (a similar device with similar proposed indications for use) that has already received FDA approval. The average reported costs for a 510(k) is $20 million USD. Novel or high-risk devices usually require the PMA pathway, which often is longer and requires larger clinical trials (which are often randomized controlled trials [RTCs]) at costs exceeding $100 million USD, on average. While the basics of FDA regulation are critical for all innovators to learn, navigating the intricacies and complexities of the regulatory landscape almost always requires the guidance of experts or consultants, who should be involved as early as possible to improve the likelihood of success.

Background on FDA Regulation

In 1906, Congress passed the Pure Food and Drugs Act, which initiated the modern regulatory functions of what would become the U.S. Food and Drug Administration (FDA) by requiring that drugs be held to standards of strength, purity, and quality. After several public health concerns in the 1930s, including over 100 deaths (many in children) from the new "wonder drug" elixir sulfanilamide, Congress passed the Food, Drug, and Cosmetics Act in 1938 (Office of the Commissioner). This act legally mandated that drugs be proven to be safe before being marketed to consumers, and the FDA was given authority over inspections and control of advertising, including prohibiting false claims. Furthermore, for the first time, the FDA's control was extended to devices, but its power was limited to reviewing devices already on the market for safety, efficacy, and proper labeling. This limited role changed the following passage of the Medical Device Amendment in 1976, which was triggered, in part, by the Dalkon Shield intrauterine device catastrophe, and thus began the FDA's current era of medical device regulation (Office of the Commissioner).

Under this new amendment, the FDA was given authority to ensure the safety and effectiveness of medical devices by requiring device manufacturers to register with the FDA and follow quality control procedures (Yock et al.). The FDA's role in device regulation was further expanded by the Safe Medical Device Act in 1990, which required post-market surveillance and adverse event reporting. In 1997, the FDA Modernization Act was passed, which attempted to improve the FDA review of devices by setting time limits for the steps along the approval process (Adamovich et al.; Maisel).

These laws have helped shape the FDA's role in medical device regulation, which is overseen by a branch of the FDA called the Center for Devices and Radiologic Health (CDRH). In 1980, the

FDA became part of the Department of Health and Human Services and is currently headquartered in Silver Spring, Maryland at the White Oak Federal Center.

Definition of Medical Device

In the United States, a medical device is defined by the FDA as:

- "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is … intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes" (Center for Devices and Radiological Health, "Is The Product A Medical Device?").

In situations when a question arises about whether an innovation or technology is truly a medical device, the inventor or company can file a request for designation (RFD) with a proposed recommendation. RFDs are reviewed by the Office of Combination Products (OCP) at the FDA, which makes the final decision on the product's primary mode of action (e.g. if it is a medical device) within 60 days of filing and then assigns the product to the appropriate FDA regulatory center. While a lead division will always oversee this process (i.e., Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), or CDRH), cross consultation within divisions can occur if needed to make the final determination for approval.

Classification of Medical Devices

After determining that the product is a medical device, the next step is to correctly classify the device based on the FDA's three-tiered system, which considers the level of risk posed to the patient. Proper classification of the device is essential; the device class helps to determine the level of FDA review, along with the appropriate regulatory pathway, including the level of control necessary to establish safety and efficacy (Table 1). Class I devices are considered low risk (minimal potential harm to patients) and often have a long history of clinical safety and effectiveness (e.g.: bandages, surface electrodes, gloves, and surgical instruments). Class II devices pose a moderate risk; they are often, but not always, non-invasive and have more complex designs than class I; these devices must demonstrate that they can perform as expected without causing harm to patients (e.g. surgical sutures and needles, CT scanners or MRI machines, guidewires and angiography catheters). Class III devices are considered high risk and are capable of supporting or sustaining human life; they are of substantial importance in preventing impairment of human health or are new devices or technologies with the potential for high risk of harm or injury to the patient for

which no predicate or similar device exists (e.g. heart valves, cardiac stents, spinal cord stimulators, and pacemakers).

Table 1. Risk and Class.

	Class 1	Class 2	Class 3
Risk Based	Low Risk	Medium Risk	High Risk
Most probable route to market	No formal	510(k) Clearance	PMA
Example	• Surface Electrodes • Band-aids • Surgical scissors • Drapes	• Guidewires • Hip Implant • Sutures	• Heart Valves • Stents • Spinal Cord Stimulator

The importance of early and proper classification of a new device cannot be overemphasized, as device class will determine the regulatory pathway that, in many ways, determines the time and cost necessary (including the type and rigor of preclinical and clinical evidence) to bring the device to the market (see the chapter "Strategic planning and costs of FDA Device regulation"). To help with this process, one can search the FDA website for the classification of similar products that are already on the market; doing so can give hints as to the potential classification and pathway required. Additionally, early engagement with a regulatory expert consultant can be invaluable.

Regulatory Pathways

Three basic pathways exist for medical devices to obtain FDA marketing approval: 1) exempt devices, 2) the 510(k) pathway, and 3) the premarket approval (PMA) pathway (Figure 1). While these three regulatory processes are based on the device's level of risk, there is unfortunately no direct match between device class and regulatory pathway. The vast majority (~75%) of class I devices, and a small percentage (~10%) of class II devices, qualify for exempt status and do not require FDA clearance prior to market entry. These devices do not need proof of safety or efficacy because they are low risk. On the other hand, no class III device can receive exempt status. Despite "exemption status," these class I devices, as well as all class II and III devices, must comply with a set of FDA requirements called "general controls." These requirements require the device company to register their facility with the FDA, list their device and classification on a submitted form, comply with FDA labeling and packaging requirements, and follow the FDA's quality systems

regulation (QSR), which are a set of design and manufacturing guidelines to ensure safety. Not all regulations are mandatory for exempt devices.

Figure 1. FDA Approval Pathway.

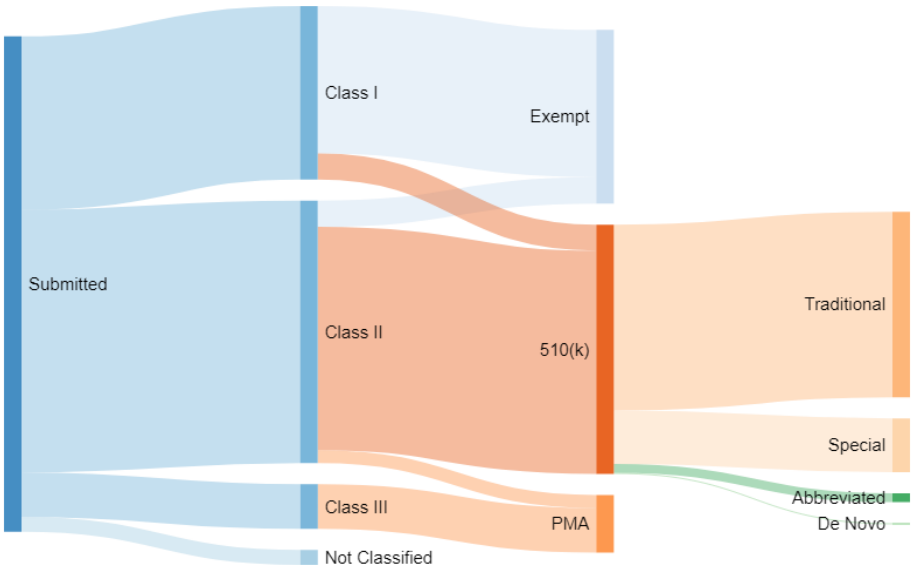

Figure courtesy of Stephen Mckenna

Most class II devices will require the premarket notification 510(k) pathway, which is based on the existence of a similar device that has already been FDA-approved and is in use (as described below). The PMA pathway is the most intricate and complicated regulatory process, and it is required for almost all class III, and some class II, devices. In general, the 510(k) pathway is utilized more often than the PMA. In fiscal year 2016, the FDA received 71 PMA submissions, compared to 3,204 510(k) submissions. Although PMAs represent only 2% of all premarket submissions these numbers reflect a 39% increase in PMA applications, compared to the prior five year average; the number of 510(k) applications in 2016 reflect a 16% decrease ("FY 2015 MDUFA Performance Report").

A fourth regulatory pathway called the Humanitarian Device Exemption (HDE) can be used for certain devices that treat rare diseases (defined as <4,000 patients per year). This process allows for the FDA to encourage companies to develop devices for rare disease and is similar to the PMA pathway, but it requires less clinical data or proof of effectiveness, because properly powered studies for rare diseases could take years to complete in part due to the limited number of patients with the rare disease. These devices must first be approved by an IRB before an application is submitted. The total review period by the FDA is 75 days after the date of filing of the application.

510(k) and de novo 510(k)

The 510(k) pathway is a premarket submission made by a company or institution to the FDA for a medical device (most often class II, occasionally class I or III) that has a predicate device on the market already approved by the FDA previously through the 510(k) process. A device that has gone through the PMA pathway may not be used as a predicate, unless it has been reclassified down to a class II device. The new device must be at least as safe and effective (i.e. "substantially equivalent") to the already approved device. The FDA considers a device substantially equivalent when the new device has (Center for Devices and Radiological Health):

a. the same intended use as the predicate and the same technological characteristics as the predicate, or
b. the same intended use as the predicate, different technological characteristics, but does not raise new questions of safety and effectiveness.

As defined by the FDA, substantial equivalence "does not mean the new and predicate devices must be identical," but rather they should be similar with "respect to intended use, design, energy used or delivered materials, chemical composition, manufacturing process, performance, safety, effectiveness, labeling, biocompatibility, standards, and other characteristics, as applicable" (Center for Devices and Radiological Health). Ultimately, the FDA will decide if the device satisfies substantial equivalence.

A 510(k) must be submitted if a company is introducing a new device to the market for the first time, changing the indications for use of a previously cleared device, or significantly modifying a previously cleared device. The 510(k) pathway is typically faster and less expensive than the PMA pathway and requires less robust clinical evidence. The majority of 510(k) clearances are obtained with only bench and preclinical animal studies (see the chapter "Pre-Clinical Animal Models"). Currently ~10% of submissions require clinical data, although this number is increasing (Yock et al.). In addition to following the requirements for "general controls," all devices that obtain 510(k) premarket notification clearance must also follow a set of FDA requirements called special controls. Special controls are usually device-specific and may include patient registries, premarket data requirements, performance standards, special labeling requirements, QSR design controls, and post-market surveillance. By law, the timeframe for review of a 510(k) submission is 90 days, and in fiscal year 2016, this performance requirement was met for 95% of 510(k) submissions ("FY 2015 MDUFA Performance Report").

In addition to the traditional 510(k) pathway, in 1997 the de novo 510(k) pathway was created in 1997 for devices that do not have the high risks associated with class III, but for which no predicate device exists. This pathway can also be used if the FDA determines non-substantial equivalence for a device going through the traditional 510(k) process because of a new intended use or different technological characteristics that raise questions about safety and effectiveness. The de novo

510(k) pathway typically requires higher standards of evidence or data for safety and efficacy than a traditional 510(k) but less than what is required for a PMA (Center for Devices and Radiological Health, "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program").

Premarket Approval (PMA)

PMA is the strictest FDA device regulatory pathway and is required for any device for which there is no existing predicate and/or almost all class III devices, which are frequently life-sustaining or life-altering (for comparison to 510(k) process see Table 2). The PMA application requires FDA scientific, regulatory review and quality system review by a special advisory panel of physicians, statisticians, and other topic experts. Approval requires reasonable assurance of safety and effectiveness based on the intended use and clinical evidence. The level of clinical evidence for PMA is substantially higher than for a 510(k), and most PMAs require a pivotal study, usually consisting of large, randomized, controlled trials. These studies often take longer to run and cost significantly more than those required for 510(k) submissions. Study design and protocol, including the determination of appropriate endpoints, are critical to support the device's safety and efficacy for its intended use. While costly, PMAs do offer additional protection to innovators, as they cannot be used as a predicate in a 510(k), ensuring follow-up products have the same high threshold to cross.

Table 2. Comparison of PMA vs. 510(k) Pathways in Terms of Challenges and Requirements.

	PMA	510(k)
Requirements	• Manufacturing section • Bibliography of published reports and discussion of all other relevant information – published or not, supportive or not • Device samples, if requested • Environmental assessment	• Typically cheaper • Typically does not require expensive and lengthy clinical trials
Challenges	• More expensive • Typically takes longer	• Predicate-derived intended use can be challenging for differentiation • Intended use statement form • Executive summary • Substantial equivalence discussion

The full PMA application includes the proposed labels, compliance with manufacturing and QSR, especially in regards to design controls, which are a framework of quality practices and procedures that must be followed during the design and development process. Additionally, the PMA application includes preclinical and clinical data (to support the safety and effectiveness of the device),

device description, post-market surveillance plan (i.e. post-approval studies), and a full literature review and bibliography. While the traditional PMA pathway is used when clinical studies are already completed and the application is submitted in its entirety, an alternate pathway called the modular PMA exists and is being used more frequently. In this PMA route, the areas and contents of the PMA application are broken down into modules or components that are pre-defined, and the sponsor submits paperwork for each module as it is completed in real-time. In this way, the completed PMA is compiled over time, and the FDA can provide feedback as the process is ongoing to allow for changes or modifications, reducing the risk and costs associated with a negative decision late in the review process (Yock et al.).

The FDA has a 180-day timeframe to complete a PMA review, although at the conclusion of this period, the FDA may request additional information. Once the sponsor submits this information, the FDA can take an additional 180 days before a decision or before requesting more information. Typically, at least two cycles of requests and responses occur before a decision; the entire process may take over a year. The average time to decision by the FDA for PMA applications in fiscal year 2014 was 330 days ("FY 2015 MDUFA Performance Report").

Investigational Device Exemption (IDE)

Prior to testing a medical device in human subjects as part of a clinical trial to collect safety and efficacy data, the FDA requires the device be granted an Investigational Device Exemption (IDE). IDEs are usually obtained to support either a future 510(k) or PMA application. Devices that are considered to have low or non-significant risks by an Internal Review Board (IRB) at the sponsoring or supporting institution do not require an IDE and can be used in the proposed study without FDA involvement. For devices with significant risk, as determined by the IRB, the FDA must first approve IDE status and patient counselor forms prior to enrolling patients in clinical trials. The IDE application process is substantially less burdensome than the 510(k) and PMA processes, although the FDA still requires data to support the safety of the device in humans from laboratory experiments, preclinical studies, and any clinical studies from outside the United States (if available). A stringent and well thought out clinical study plan is important for an IDE submission, and the sponsors can meet with the FDA prior to submitting an application in order to review the study protocol.

Post-Approval Requirements

Post-approval or post-marketing studies are becoming increasingly common as part of the requirements set forth by the FDA when approving a PMA. In general, 510(k) clearances have fewer post-marketing requirements. PMA post-approval requirements may include on-going clinical trials, registry or periodic reporting of safety, reliability, and efficacy of the device as it expands to a larger patient population. The FDA requires manufacturers to report all serious adverse reactions or events. Furthermore, federal regulations require hospitals, health care professionals, and any

user of a medical device to report any patient incidents or adverse events (including serious injury or death) involving the device to the manufacturer and the FDA (Van Norman).

The FDA is also in the process of establishing the unique device identifier (UDI) system as part of a final rule released in 2013. The final rule requires that device labelers include the UDI on device labels and packages. Doing so will allow the FDA to better monitor the distribution and use of all medical devices, and improve patient safety and post-market surveillance (Center for Devices and Radiological Health, "Unique Device Identification System (UDI System)").

Breakthrough Devices Program

In addition to the standard FDA application process, the FDA has a mechanism for expedited review with the aim of reducing the time and cost necessary to move a device from development to the market (see the chapter "Strategic planning and costs of FDA Device regulation"). Prior to January 2018, several programs offered this service, including the Expedited Access Pathway (EAP), the Innovation Pathway, and the Priority Review Program, and existed with various guidance rules and requirements. However, in response to the 21st Century Cure Act, the FDA, at the end of 2017 announced the Breakthrough Devices Program (BDP), which supersedes these prior programs in order to help patients have more timely access to devices with breakthrough technologies while preserving the statutory standards of the regulatory process.

The BDP defines breakthrough devices as those that provide "more effective treatment or diagnosis" of life-threatening or irreversibly debilitating diseases and which incorporates breakthrough technologies (U.S. FDA Breakthrough). To qualify as "breakthrough technology," the device must have the potential for clinical improvement in diagnosis, treatment, cure, mitigation, or prevention of a specific disease or condition. In addition, to meet the criteria of a breakthrough device, there must be no approved or cleared alternatives, or the new device must offer "significant advantages" over existing approved or cleared alternatives.

The BDP program, like the previous expedited review programs, covers PMA, de novo, and IDE applications, and for the first time, expands coverage to qualifying 510(k) applications. In addition to undergoing priority review (i.e., placement at the top of the review queue), the benefits of the BDP program include earlier communication between the FDA and applicants, more flexibility in clinical study designs and the possibility of considering additional post-market data in lieu of premarket data, along with expedited manufacturing inspections. Each device in the BDP will be assigned to an FDA review team for additional guidance and support. To obtain breakthrough device designation, the device sponsor is required to submit a pre-submission application, and the FDA will make a decision within 60 days of receipt (Center for Devices and Radiological Health, "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program").

Conclusion

The FDA regulation of medical devices protects and promotes public health and patient safety. The regulatory pathway is risk-based, and all medical devices can be classified into one of three risk classes. Risk class then, for the most part, determines which of the traditional three pathways the device will proceed along to obtain FDA clearance or approval. Class I devices are typically exempt from clearance, class II devices usually require 510(k) clearance, and class III devices almost always require premarket approval. The regulatory strategy also depends on the existence of an appropriate predicate device, which can save a device company significant time and money if the PMA process can be avoided. Consideration of the regulatory process and engagement with a regulatory consultant should begin at the initial phases of device design, as all components of device development, especially the research plan, are influenced by class type and regulatory pathway.

Resources

1. Biodesign: The Process of Innovating Medical Technologies
    a. In the book *Biodesign: The Process of Innovating Medical Technologies*, written by Paul Yock, Stefanos Zenios, and Josh Makower, the chapters "4.2 Regulatory Basics" and "5.4 Regulatory Strategy" present an excellent overview of regulatory pathways in the U.S. and worldwide, especially in the European Union, Canada, China, India, and Japan.
    b. Book available on Amazon: https://www.amazon.com/Biodesign-Process-Innovating-Medical-Technologies/dp/110708735X/ref=sr_1_1?s=books&ie=UTF8&qid=1517864373&sr=1-1&keywords=Biodesign%3A+The+Process+of+Innovating+Medical+Technologies.
    c. Book's accompanying website: http://ebiodesign.org/.
2. Drugs, Devices, and the FDA: Part 2: An Overview of Approval Processes: FDA Approval of Medical Devices
    a. The article "Drugs, Devices, and the FDA: Part 2: An Overview of Approval Processes: FDA Approval of Medical Devices" in *J Am Coll Cardiol Basic Trans Science* provides a concise overview of FDA regulatory processes with helpful figures and flowcharts to determine the appropriate regulatory pathways for different device types.
    b. Article available here: https://www.sciencedirect.com/science/article/pii/S2452302X16300183.
3. Pre-submissions and Meetings with FDA Staff
    a. The presentation "Pre-submissions and Meetings with FDA Staff" by the U.S. Food and Drug Administration is an extremely helpful guide on the pre-submission or Q-sub process, explaining the types of meetings and how and when to request them. It also includes a list of best practices for meeting with the FDA at the end of the powerpoint.
    b. Presentation available here: https://www.fda.gov/media/93740/download.

4. Product Classification Database
    a. The "Product Classification Database" hosted by the U.S. Food and Drug Administration and the Department of Health and Human Services is an important resource to use early during device ideation or development. Users can identify the classifications of current devices on the market, and it offers a guide for the likely classification of their new device.
    b. Database available here: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm.
5. History of the U.S. Food and Drug Administration
    a. "History," on the U.S. Food and Drug Administration's website, gives a detailed history of the FDA and the motivation behind its evolution over the years as an overseer of medical devices and an advocate for patient safety.
    b. Webpage available here: https://www.fda.gov/about-fda/history-fdas-fight-consumer-protection-and-public-health.

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