MEDICAL DEVICES:

FDA regulatory pathways for medical devices

The regulations, developed as a result of the 1976 Medical Device Amendments to the Food, Drug, and Cosmetic Act of 1938, share a common goal with the pharmaceutical regulations: they both strive to ensure that new medical treatments reach the public as quickly as possible while protecting patients and ensuring that the new treatments have a positive benefit–risk balance. However, they approach this goal in different ways. This continuing professional development supplement explains the fundamentals of the FDA regulatory pathways for medical device manufacturers that wish to bring their products to the US market.

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KEYWORDS: FDA; Medical devices; Pre-market approval (PMA), 510(k); Humanitarian Device Exemption (HDE); United States.

In 1976, amendments to the Federal Food Drug and Cosmetics (FD&C) Act expanded the US FDA's responsibility to also oversee medical devices, in addition to its drug role,[1] under the Center for Devices and Radiological Health (CDRH). There are many similarities between the medical device and the pharmaceutical regulations. However, the pace of innovation in these two fields is different. Whereas a new drug approval takes an average of 10 to 15 years, moving a new medical device from concept to market takes an average of three 3 to seven 7 years.[2]

According to the FD&C Act, a device is "an instrument, apparatus, implement, machine, implant or an *in vitro* reagent or other similar or related article, including a component part, or accessory" that meets three conditions:[3]

1) Recognised in the official National Formulary or the US Pharmacopoeia;
2) Intended for use in the diagnosis of disease or other conditions, or the cure, mitigation, treatment, or prevention of disease, or;
3) Intended to affect the structure or function of the body of humans, and which does not achieve its primary intended purposes through chemical action or by being metabolised.[4]

The range of objects that falls under the FDA definition of medical devices is broad, for example, tongue depressors, stethoscopes, laboratory equipment, surgical instruments, pacemakers and ventilators. Some products that contain biological material are inert (eg, acellular dermatologic fillers) and can also be considered devices.[5,6]

Bringing a device to market

The development of an entirely new device typically begins with a concept by a physician or a bioengineer for a solution to a medical problem. A preliminary prototype of the device is built and simultaneously a patent process is initiated. Preliminary bench testing is then followed by animal testing, and the device enters a cycle of testing and redesign.

Although portrayed as a compartmentalised process with distinct phases, such as preclinical and clinical, steps in device development overlap and portions may need to be repeated as testing and user experience are incorporated into product modifications and the device moves closer to its marketed form. There are at least three key steps that developers should follow to bring their device to the US market:[7] Step 1: Classify the device; Step 2: Select the appropriate regulatory pathway; and Step 3: Register the establishment and list the device.

Step 1: Classify the device

The first step, after determining that the product is a device, is to classify the device. Because medical devices vary widely in their complexity and benefits or risks, they do not require the same degree of regulation. Thus, the FD&C Act established the risk-based device classification system for medical devices. Each device is assigned to a regulatory class based on the level of control necessary so that there is a reasonable assurance of its safety and effectiveness. Device classification depends on intended use and indications for use. All devices are classified into three groups by the FDA:[8–10] Class I or "low risk"; Class II or "medium risk"; and Class III or "high risk" devices.

Class I devices have the least regulatory requirements. Under current law, Class I devices are defined as those for which general controls "are sufficient to provide reasonable assurance of the safety and effectiveness of the device".[11] Many Class I devices are exempt from the pre-market notification and/or the quality system (QS) regulation requirements.[12,13]

Unless the manufacturer obtains a reclassification, all new devices that are not Class I or II are automatically designated as Class III

KEY LEARNING POINTS

- In the US, devices are classified based on the level of risk in Class I or "low risk," Class II or "moderate risk" and Class III, or "high risk"
- There are four basic paths that manufacturers can use to bring new medical devices to the US market: the PMA, the 510(k), the De Novo, and the Humanitarian Device Exemption (HDE) pathways
- The US FDA requires all medical device manufacturers to register their facilities, and list their devices with the agency
- Once a medical device is on the US market, the manufacturers must comply with various post-marketing regulations on labelling and advertising, manufacturing and surveillance.

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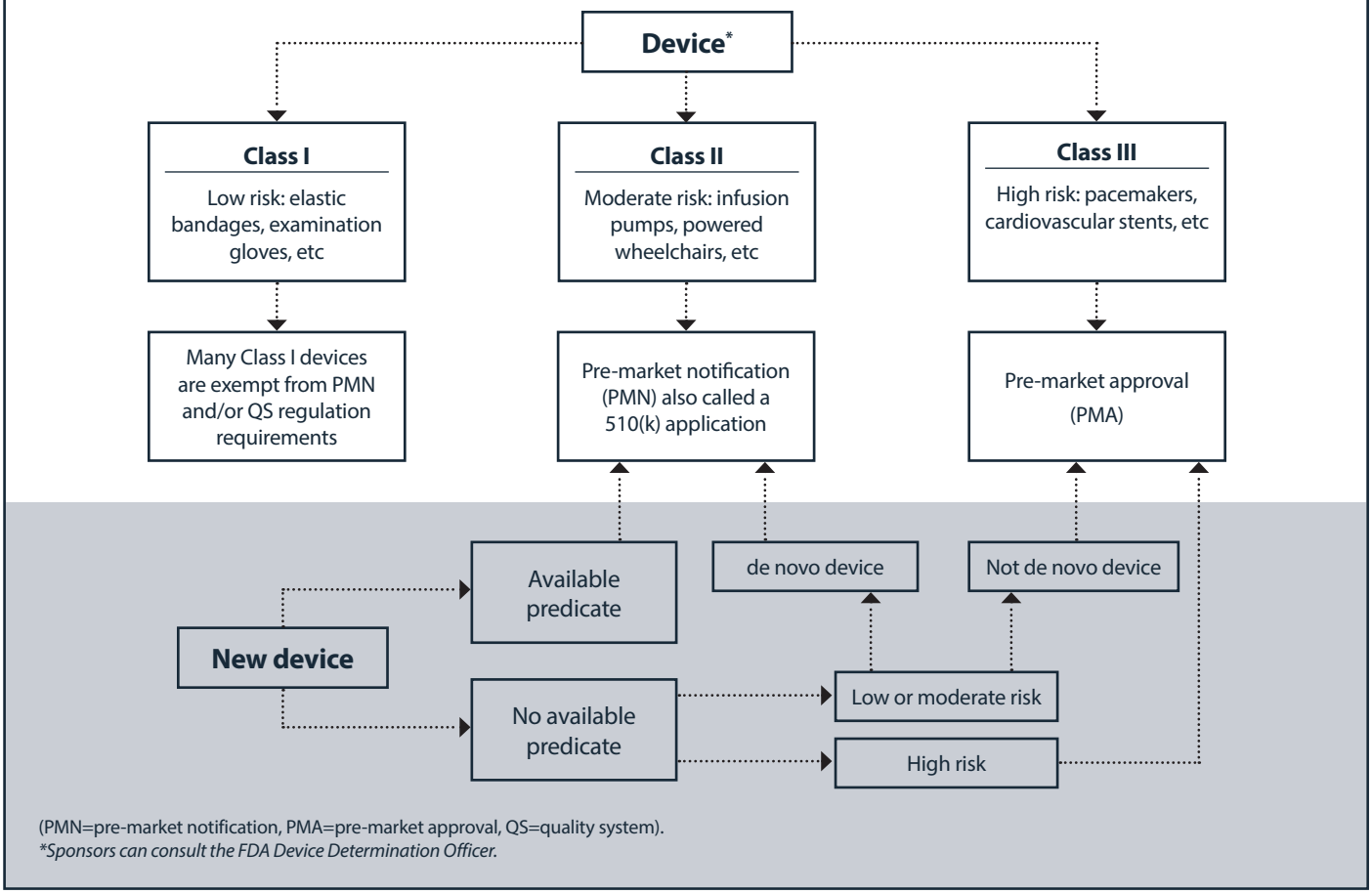
Figure 1: Overview of FDA regulatory pathways for medical devices.



(PMN=pre-market notification, PMA=pre-market approval, QS=quality system).
**Sponsors can consult the FDA Device Determination Officer.*

Class II devices are defined as those "which cannot be classified as class I because the general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness of the device".[14] Class II devices can only be marketed after providing the FDA with a "pre-market notification", also called a "510(k)" submission.[15] Only a few Class II products require studies in humans to support claims of performance or safety. For the majority of Class II products, requirements can be satisfied by bench and animal testing.

Class III devices include devices which are life-supporting or life-sustaining and present a high or potentially unreasonable risk of illness or injury to a patient. Unless the manufacturer obtains a reclassification, all new devices that are not Class I or II are automatically designated as Class III.[16] Before a Class III device is marketed it must be approved by the FDA. This is different than for Class II devices, which are "cleared" by the agency.

Once a device is classified, an appropriate regulatory pathway needs to be conducted. The summary of regulatory pathways for medical devices by the FDA is described in Figure 1.

Step 2: Select the appropriate regulatory pathway

Pathway 1—Pre-market approval (PMA)

A PMA is a stringent type of marketing application required by the agency for new or high-risk devices. The PMA approval is based on a determination by the FDA that the application contains sufficient evidence to provide reasonable assurance that the device is safe and effective for its intended use(s).[17] PMAs generally require some clinical data before an approval decision. All clinical evaluations of investigational devices (unless exempt) must have an investigational device exemption (IDE) before the clinical study is initiated.[18] An IDE allows an unapproved device to be used in a clinical study to collect the data required to support a PMA submission.

The content of the PMA includes: (1) summaries of nonclinical and clinical data; (2) a device description; (3) indications for use; (4) a description of the foreign and US marketing history; (5) the proposed labelling; and (6) a description of the manufacturing process. Approval is based not only on the strength of the scientific data but also on the inspection of the manufacturing facility to ensure that the facility and the manufacturing process comply with the quality system (QS) regulation.[19] The PMA process can be described in 4 steps as depicted in Table 1.

Pathway 2—Pre-marketing notification (PMN), also known as 510(K) application

In general, a 510(k) submission is required for a moderate-risk medical device that is not exempt from pre-market review. The standard for clearance of a traditional 510(k) is substantial equivalence with a predicate device, which can be either a previously cleared Class I or II device that does not require a PMA, or a pre-amendment Class III for which the agency has not issued regulations requiring a PMA. There are three types of 510(k) submissions for pre-market clearance: traditional, special, or abbreviated.

A traditional 510(k) application includes the device's name, description, intended use, proposed label, as well as a comparison with a predicate device, and the device's advertisement and directions for use,[20] supported by preclinical studies. The term substantial equivalence, in many cases, means simply that the device performs in a similar fashion to the predicate under a similar set of circumstances. Many Class II devices that are cleared via a 510(k) submission do not have to demonstrate safety and effectiveness through clinical studies with human subjects.

A special 510(k) application is appropriate when the manufacturer is planning device modifications to its own legally marketed device (predicate device). Such modifications may not affect the intended use or the fundamental scientific technology of the device.

An abbreviated 510(k) is appropriate when the manufacturer is planning to rely solely on the use of guidance documents, special controls, and recognised standards.

Some novel devices without a predicate have another alternative pathway available called *de novo*. Under the FD&C Act, novel devices lacking a legally marketed predicate are automatically designated Class III. In 1997 the act was amended to allow the FDA to establish a new, expedited mechanism for reclassifying these devices based on risk. The amendment resulted in a reduction of the regulatory burden on manufacturers. The *de novo* application, although requiring more data than a traditional 510(k), often requires less information than a PMA application.[21] Devices approved as *de novo* can serve as predicates for other devices.

Table 1: Application timeline for 510(k) and PMA.	
Pre-market notification (PMN) – 510(k)	**Pre-market approval (PMA)**
Day-1 FDA receives 510(k) submission	**Day-1** FDA receives PMA submission
Day-7 FDA sends Acknowledgement Letter or Hold Letter if unresolved issues with User Fee and/or eCopy	**Day-45** FDA verifies if the application is administratively complete. Or else, the application will be returned
Day-15 FDA conducts Acceptance Review or FDA informs sponsor if 510(k) is accepted for Substantive Review or placed on RTA Hold	**Day-120** FDA completes the Initial Review and determines if an advisory committee meeting is necessary
Day-60 FDA conducts Substantive Review of FDA communicates via a Substantive interaction to inform the sponsor that the FDA will either proceed with Interactive Review or that the 510(k) will be placed on hold and Additional Information is required.	**Day-180 (+)** FDA regulations allows 180 days to review and make a determination. However, the total review time can be much longer. There are four options for the final deliberation: a) approval order b) approvable letter c) not approvable letter d) order denying approval
Day-90 FDA sends final MDUFA Decision on 510(k)	
Day-100 If MDUFA Decision is not reached by Day 100, FDA provides Missed MDUFA Decision Communication that identifies outstanding review issues	
(RTA=refuse to accept, MDUFA=medical device user fee amendments)	

Pathway 3—The Humanitarian Device Exemption

The Safe Medical Devices Act of 1990 authorised the Humanitarian Device Exemption (HDE)[22] to encourage the development of devices that aid in the treatment and diagnosis of diseases or conditions affecting less than 4,000 individuals in the United States per year. To encourage manufacturers to develop devices for these small markets, the HDE application is similar to a PMA but it is exempt from the effectiveness requirements. The device sponsor is only required to demonstrate that there is a probable benefit to health and that the probable benefit outweighs the risk of injury or illness caused by the device. In other words, the HDE requires demonstration of device-related safety, but not device efficacy.[23]

However, there are some important restrictions such as, for example, a 4,000-unit limit per year on the number of devices shipped. In addition, the use of an HDE device requires approval by an institutional review board (IRB) at the institution where the device is to be used.

Step 3: Register the establishment and list the device

The FDA requires all medical device manufacturers to register their facilities and list their devices with the agency. Manufacturers and initial distributors of medical devices must register their establishments with the FDA. All establishment registrations must be submitted electronically unless a waiver has been granted by the FDA. All registration information must be verified annually. In addition to registration, foreign manufacturers must also designate a US agent.[24]

Post-market regulations and processes

Once their product is approved or cleared for marketing, manufacturers of medical devices must comply with various regulations on labelling and advertising, manufacturing, and post-marketing surveillance. The iterative nature of medical device development adds a layer of complication. It is challenging to create post-market requirements for a product that may be replaced by the next-generation product before the start of, for example, a post-market surveillance study.

The current US medical device post-market surveillance system depends primarily on the following sources for detecting potential problems with medical devices:[25]

- **Medical device reporting (MDR)** The FDA annually receives several hundred-thousand reports of suspected medical device-related malfunctions, serious injuries, and deaths
- **Medical Product Safety Network (MedSun)** The FDA receives about 5,000 higher quality reports each year on device use and adverse outcomes from a network of 280 US hospitals
- **Post-approval studies** Such studies may be ordered by the FDA as a condition of approval for a PMA device
- **Post-market surveillance studies** The FDA may order a manufacturer of a Class II or Class III device to conduct post-market surveillance studies
- **FDA discretionary studies** The FDA conducts its own research to monitor device performance, investigate adverse event signals and characterise device-associated benefits and risks to patient subpopulations.

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Conclusion

Although the FDA's process to bring new medical devices to the US market can be daunting, the agency has implemented activities to increase the transparency and predictability of the process. Numerous guidance documents and the FDA policies and procedures are available on the FDA's website. Medical device developers and manufacturers are also 'encouraged to take advantage of the opportunities available for meetings with FDA officials.

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Case study: **Eluvia: a drug-eluting stent**

Peripheral arterial disease (PAD) affects around 8–12 million people in the US.[1] The strong association with ageing, tobacco smoking, and diabetes means that the prevalence of PAD will continue to increase in the coming years. Although 20–50% of patients with PAD are asymptomatic, they are still at significant risk of adverse outcomes due to the co-prevalence of coronary, renovascular and cerebrovascular diseases. Five-year mortality approaches 30% in the population and five-year lower extremity amputation risk is 2–5 % or higher in particular patient subsets, such as those with diabetes or who are smokers.[2] Most of the PAD lesions are located in the femoropopliteal arteries.

The Eluvia drug-eluting vascular stent system is a self-expanding metal (nitinol) stent intended to treat PAD. It was developed by Boston Scientific as the counterpart of Zilver PTX from Cook Medical for femoropopliteal lesions treatment. The Eluvia stent first obtained the CE Mark approval in February 2016, which allowed the company to distribute the product in the European market. To seek approval in the US market, the company submitted a pre-market approval (PMA) and obtained FDA approval for the Eluvia stent system in September 2018.[2]

The CE Mark approval was primarily based on data from the MAJESTIC trial, a head-to-head study comparing the clinical performance of Eluvia and Zilver PTX in femoropopliteal lesions. This prospective, single arm, multicenter trial assessed the safety and performance of the Eluvia stent system and reflected a primary patency rate of more than 96% (57 patients were involved). Although MAJESTIC was considered as a small trial, it showed the highest patency rate reported among prior drug-eluting system (DES) trials.[3]

To generate the clinical data in support of the PMA for the FDA submission, a global, prospective, multicenter IMPERIAL clinical trial was initiated in early 2016. The study compared the safety and effectiveness of the Eluvia DES versus Zilver PTX for the superficial femoral or proximal popliteal artery lesions up to 140mm in length. It randomised 309 patients with occlusive lesions of the superficial femoral or proximal popliteal arteries to the polymer-coated, paclitaxel-eluting Eluvia stent and 156 to paclitaxel-eluting Zilver PTX, which is the only drug-releasing stent approved in the US for the indication.[4]

There are several factors that influence the length of time it takes for a medical device to reach its end user in a specific jurisdiction. Companies that manufacture medical devices frequently face a challenging decision whether they should try to bring their products to the European or US market first. From a timeline perspective, there used to be a delay in launching new medical devices in the US compared with Europe. This was partly due to the fact that, before the new medical device regulation in Europe, the European regulatory process used to be less bureaucratic and more predictable than the one in the US.

For a class III device such as the Eluvia drug-eluting vascular stent system, the timeline for obtaining a CE Mark was typically much shorter than the one for obtaining FDA approval of a PMA. A comparative study concerning FDA approvals versus European CE mark (from 2000 to 2011) for the innovative and potentially risky medical technologies suggested that the same devices have been approved and made available to patients in Europe three or more years before devices are approved in the US.[5,6] These data, although interesting from a historical perspective, are not necessarily relevant anymore. With the new medical device regulation in Europe coming into force in 2020, things will probably change dramatically. New research will need to be conducted to compare the typical timelines needed to receive FDA approvals versus CE mark.

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