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FDA Authorization Pathways for High Risk or Novel Devices (Premarket Approval and More)

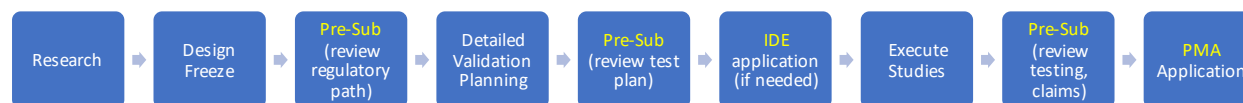
Context

Class III medical devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential for unreasonable risk of illness or injury. Many NIH innovators are developing new technologies with some or all of these attributes in order to offer patients additional diagnostic or treatment options. Class III medical devices are regulated by the U.S. Food and Drug Administration (FDA) through the Premarket Approval (PMA) pathway. The PMA is the most rigorous market authorization pathway required by FDA in which the safety and efficacy of a new medical device is demonstrated through clinically, statistically, and scientifically rigorous methods. This document provides an overview of the steps leading up to a PMA application and the application itself.

Devices that do not have an existing FDA classification for the technology or intended use are designated as Class III with PMA requirement by legislation. However, it is increasingly common for lower-risk, first-of-a-kind, devices to pursue a De Novo classification, which reclassifies them prior to market access as either Class II (moderate risk) or Class I (low risk). Eligibility for the De Novo pathway depends on the risk of the device. The “Other Paths” section of this document includes more information on De Novo and presents some additional paths for consideration.

Before PMA Application

Innovators spend significant time performing research, development, and validation of a new device before applying for approval. It’s the innovator’s responsibility to ensure the data collected will demonstrate safety and effectiveness to expert FDA reviewers. An example flowchart is shown below.



Note that in this example there are multiple [pre-submissions](#) with FDA. Pre-submissions are optional and some manufacturers opt to submit more or fewer than what is shown above. Before embarking on a time consuming or expensive milestone, it is wise to engage with the agency via a pre-submission to obtain direct written feedback with or without a teleconference to inform future work plans.

Due to the nature of class III devices, PMA applications often require clinical study. Depending on their risk, clinical studies often require a form of authorization from FDA called an [Investigational Device Exemption](#) (IDE). Be sure to review the types of studies that require an IDE, the IDE approval process, and IDE reporting requirements while planning for a clinical study and working with your Institutional Review Board (IRB).

In addition to development of the device itself, innovators should develop a well-informed regulatory strategy. Prior to preparing a PMA, some other potential options can be considered by asking these questions:

- Is there a comparable Class II device? Consider [510\(k\)](#).
- Is this a totally new device with manageable risk? Consider [De Novo](#).
- Is there a small patient population affected in the US? Consider [HDE](#).
- Is there a comparable Class III device? Then add context to your PMA strategy by reviewing the Summary of Safety and Efficacy and other information made available by FDA in the [PMA database](#).

There is also a wealth of knowledge in guidance documents and information pages available from FDA that can inform your unique regulatory roadmap. A good place to start is [Device Advice: Comprehensive Regulatory Assistance](#)

During and After Your PMA Application

FDA's website includes a [comprehensive walkthrough](#) of PMA review processes, application contents, clinical studies, frequently asked questions, and more. There even is a checklist provided to ensure each part of the PMA documentation is complete.

The PMA process formally begins with a Filing Review performed by FDA to ensure an in-depth review is warranted. Within 45 days, FDA will make a determination to file and proceed or refuse to file and provide a written rationale to the applicant describing the deficiencies noted in the initial filing.

Starting from the filing date, FDA has 180 days to review the information provided and make an approval decision. The steps within this substantive review period are [also listed](#) on FDA's website. Note that there is an option for a [day 100 meeting](#) with the FDA review team to discuss the status of the application. Additional information sent to FDA to support an ongoing review is called a [PMA Amendment](#). Amendments can be requested by FDA to allow applicants an opportunity to revise existing or provide additional information; unsolicited additional information can also be provided by applicants.

After 180 days, FDA will determine whether the device is:

- Approved
- Approvable – if specific conditions are agreed to with applicant.
- Not Approvable – because key information is lacking.
- Denied – because non-compliance was identified.

Upon receiving approval, congratulations, but interactions with FDA about the device are only just beginning! At a minimum, manufacturers of a PMA approved device [will register, list, pay fees](#), as well as submit a detailed **PMA Annual Report** every year. The report [needs to document](#) every change to the device's manufacturing or labeling, any related findings in scientific literature and other items.

If there is a substantial update or change to the device, manufacturers are required to file a **PMA Supplement**. PMA Supplements can be just as laborious as an original PMA, as short as a 30-day notice, or may fall somewhere in between. [More details](#) on Supplements can be found on FDA's website.

Other Paths

[FDA states](#) the "PMA is the most stringent type of device marketing application required by FDA." As discussed earlier, it is important to first consider whether other regulatory pathways could apply. Here, we provide some additional details about these less "stringent" paths to market. However, if there is an existing classification for your device (technology and intended use) as a Class III PMA, then a PMA is required.

De Novo: If there is no existing classification, and the risks associated with your device can be adequately controlled, the De Novo pathway may be an option. This directly classifies your new device as Class II, enabling future devices to submit a 510(k) using your device as a predicate. For more information check the FDA website on [De Novo Classification](#), as well as the following NIH SEED resources:

- [CASE STUDY: Medical Device – De Novo marketing path example](#)
- [De Novo Pre-Submission Meetings](#)
- [FDA Medical Device Databases: Reviewing De Novo Summaries](#)

Humanitarian Device Exemption (HDE): If fewer than 8,000 Americans are affected by the condition your device helps treat, diagnose, or mitigate – then the HDE may apply. For more information check the FDA website on [Humanitarian Use Devices](#), as well as the following NIH SEED resource:

- [Humanitarian Use Devices](#)

510(k): While 510(k) does not strictly apply for high-risk devices, some implantable devices are considered Class II (for example a knee replacement). Also, it is possible for a device to be substantially equivalent to an existing, legally marketed device, while also exhibiting novel functionalities or additional clinical claims. The key is for those differences to not affect the intended use, or to raise new questions of safety or effectiveness. For more information check the FDA website on [510\(k\)](#), as well as the following NIH SEED resources:

- [510\(k\) Documentation and Application](#)
- [510\(k\) Pre-Submission Meetings](#)
- [CASE STUDY: Software as a Medical Device \(SaMD\) – 510\(k\) marketing path example](#)
- [Finding a Predicate Device - FDA Database Navigation \(Recording\)](#)
- [Mapping Your Way Through FDA's 510\(k\)](#)