REVIEW ARTICLE

Comparative Study of Pre-Market Approval Process and *De novo* Process for Medical Devices

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ABSTRACT

FDA's Center for Devices and Radiological Health (CDRH) is responsible for regulating firms who manufacture, repackage, relabel, and/or import medical devices sold in the United States. Regulatory control increases from class I to III. Most class I devices are exempt from Premarket Notification 510(k); most class II devices require pre-market notification 510(k); and most class III devices require Pre-market Approval.The Food and Drug Administration Modernization Act of 1997 (FDAMA) added the De Novo classification option as an alternate pathway to classify novel medical devices that had automatically been placed in class III after receiving a "not substantially equivalent" determination in response to a pre-market notification [510(k)] submission.Class III Devices are those considered as high risk along these lines requiring the regularly lengthier Pre-market approval (PMA) process. The new De Novo process was designed to usher through any new device that was both Unprecedented (novel) and Low to moderate risk (or with a risk that was easily mitigated). The most inventive gadgets are considered high-hazard due to the non-attendance of equivalent items and follow either the De Novo or PMA path. Truly high-risk devices, in which deficient data exists to decide if general and special controls are sufficient to give sensible attestation of the item's safety and effectiveness, follow the PMA pathway. Novel devices that do not have a predicate are classified in the highest risk class,despite the level of genuine risk it postures or the capacity of general and special controls to guarantee safety and effectiveness. The De Novo process allows these novel devices with low to moderate risk to be reclassified from a high-risk class, which requires a PMA.

Keywords: *De novo*, Risk, Devices, 510(k), Class III pre-market approval (PMA).

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INTRODUCTION

PMA

Pre-market approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices, and the most stringent of the device marketing applications. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. Due to the level of risk associated with Class III devices, FDA has determined that general and special controls alone are insufficient to assure the safety and effectiveness of Class III devices. Therefore, these devices require a PMA application under section 515 of the FD&C Act in order to obtain marketing clearance. Some Class III pre-amendment devices may also require a

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Class III 510(k). PMA applications will include technical sections, usually divided into non-clinical laboratory studies and clinical investigations. PMA approval typically requires a facility inspection to confirm compliance to 21 CFR 820 prior to approval.[1]

The PMA is the most stringent type of device marketing application required by the FDA. The applicant must receive FDA approval of its PMA application prior to marketing the device. PMA approval is based on a determination by FDA that the application contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). An approved PMA is, in effect, a private license granting the applicant (or owner) permission to market the device. The PMA owner, however, can authorize the use of its data by another.[3]

The PMA applicant is usually the person who owns the rights or otherwise has authorized access to the data and other information to be submitted in support of FDA approval. This person may be an individual, partnership, corporation, association, scientific or academic establishment, government agency or organizational unit, or other legal entity. The applicant is often the inventor/developer and, ultimately the manufacturer.[3]

When PMA is Required?

PMA requirements apply to Class III devices, the most stringent regulatory category for medical devices. Device product classification is provided in the Product Classification Database. The database search provides the name of the device, classification, and a link to the Code of Federal Regulations (CFR) if any. The CFR provides the device type name, identification of the device, and classification information.

A regulation number for Class III devices marketed before the 1976 Medical Device Amendments is provided in the CFR. The CFR for these Class III devices that require a PMA states that the device is Class III and will provide an effective date of the requirement for PMA. If the regulation in the CFR states that "No effective date has been established of the requirement for PMA," a Class III 510(k) should be submitted.

The PMA devices often involve new concepts, and many are not of a type marketed prior to the medical device amendments. Therefore, they do not have a classification regulation in the CFR. In this case, the product classification database will only cite the device type name and product code.

If it is unclear whether the unclassified device requires a PMA, use of three-letter product code to search the PMA database, and the 510(k) Pre-market Notification database is recommended. These databases can also be found by clicking on the hypertext links at the top of the product classification database web page. The three-letter product code in the product code box will de. If there are 510(k)'s cleared by FDA and the new device is substantially equivalent to any of these cleared devices, in that case, the applicant should submit a 510(k).

Furthermore, a new type of device may not be found in the product classification database. If the device is a high-risk device (supports or sustains human life, is of substantial importance in preventing impairment of human health, or presents a potential, unreasonable risk of illness or injury) and is not substantially equivalent (NSE) to a Class I, II, or III [Class III requiring 510(k)] device, then the device must have an approved PMA before marketing in the U.S. Some devices that are found to be not substantially equivalent to a cleared Class I, II, or III (not requiring PMA) device, they may be eligible for the de novo process as a Class I or Class II device. De Novo sections of Device advice will provide additional information. [3]

De novo

The De Novo pathway for device marketing rights was added to address novel devices of low to moderate risk that do not have a valid predicate device. Upon successful review of a De Novo submission, FDA creates a classification for the device, a regulation if necessary, and identifies any special controls required for future pre-market submissions of substantially equivalent (SE) devices. Companies with novel devices of low to moderate risk have two options when considering the De Novo pathway: the company can submit a 510(k) to the FDA, and upon receipt of a "Not Substantially Equivalent" (NSE) determination, the De Novo request can be made; or the company can submit a De Novo request without first submitting a 510(k). Devices that are classified through the De Novo process may be marketed and used as predicates for future 510(k) submissions.[1]

In accordance with section 513(f)(2) of the FD & C Act, applicant may submit a De Novo request for FDA to make a classification determination for the device according to the criteria in section 513(a)(1) of the FD&C Act. The De Novo request must include a description of the device and detailed information and reasons for any recommended classification (see section 513 (f) (2) (A) (v) of the FD & C Act). FDA must make a classification determination for the device that is the subject of the De Novo request by written order within 120 days of the request (see section 513 (f) (2) (A) (iii) of the FD & C Act).[4]

If the requester demonstrates that the criteria at section 513(a)(1)(A) or (B) of the FD&C Act are met, FDA will grant the De Novo request, in which case the specific device and device type is classified in Class I or II. The granting of the De Novo request allows the device to be marketed immediately, creates a classification regulation for devices of this type, and permits the device to serve as a predicate device. FDA will publish a notice in the Federal Register announcing the classification and the controls necessary to provide reasonable assurance of safety and effectiveness. The classification, including any special controls, is effective on the date the order letter is issued granting the De Novo request. If the De Novo request is declined, the device remains in Class III and may not be marketed, unless the device is found substantially equivalent to an existing legally marketed class I, class II, or pre-amendment device, the device is reclassified under section 513 (f) (3) of the FD & C Act, a PMA is approved, or a new De Novo request is granted.[4]

When may the De Novo Classification Process and may not be used?

FDA will review De Novo requests for devices that are not within a device type that has been classified under the criteria at section 513 (a) (1) of the FD & C Act. This includes devices that do not fall within any existing classification regulation, where the De Novo requester either determines that there is no predicate device or has received an NSE determination on a 510 (k) submission. If the device is within a type for which there is an existing classification regulation or one or more approved PMAs, the appropriate mechanism for classification into Class I or II would be reclassification under section 513(e) or section 513 (f) (3) of the FD & C Act.[4]

In addition, the following criteria should be met for a device for which a De Novo request is submitted:

- The device should appear, based on what is known about the device, to meet the statutory standards for classification into Class I or Class II under section 513 (a) (1) of the FD&C Act, i.e., general controls or general and special controls would provide reasonable assurance of the safety and effectiveness of the device; and
- Applicant should sufficiently understand and be able to explain all of the probable risks to health and probable benefits of the device, explain the measures needed to effectively mitigate all probable risks, and explain how device safety and effectiveness can be assured through the application of general controls or general and special controls.[4]

OBJECTIVE

To compare and differentiate between De Novo and Premarket Approval Process for Medical Devices in USA

DISCUSSION

De novo Request

Pre-Submission (Pre-Sub)

A Pre-Sub may be submitted early in the development process for a device; however, FDA believes it is most useful after the applicant has identified the proposed intended use and key aspects of the device design sufficient to permit a meaningful discussion. A pre-Sub related to a future anticipated De Novo request should contain sufficient information to enable for providing guidance on the test methods and protocols that should be used for the collection of non-clinical and/or clinical data.

In addition to the recommended content for all Pre-Subs (device description, proposed intended use/indications for use, previous submissions, etc.), a Pre-Sub is not required to obtain FDA review of a De Novo request. Still, it is a useful way for requesters to obtain early feedback from FDA. A pre-sub allows FDA to provide feedback on whether a device may be eligible for the De Novo classification process, including whether a potential predicate device exists, and/or to advise on the documentation needed in a subsequent De Novo request.[4]

De Novo Request

A De Novo request may be submitted with or without a preceding 510 (k). the success of De Novo's request that is filed without a Pre-Sub will depend more heavily on the search process for a Potential predicate device, identify the risks to health and special controls (if applicable), and provide adequate valid scientific evidence to support granting the De Novo request.

The De Novo request should include all information and evidence that the applicant is aware of regarding the safety and effectiveness of the device, including the general controls or general and special controls that belief would provide reasonable assurance of safety and effectiveness. The De Novo request should establish the risk profile of the device, establish the benefits of the device use, and provide valid scientific evidence demonstrating the performance characteristics of the device.[4]

FDA Review Process for De Novo Requests

510 (k) Followed by De Novo Request

If, at the end of a review of a 510 (k), if determined that a device is NSE due to lack of a predicate, new intended use or different types of technical issues, it may indicate that the device may be suitable for review under the De Novo classification process. The 510(k) review will occur as per standard review practices for 510(k)s and in accordance with current performance goals.

If general controls or general and special controls may provide reasonable assurance of safety and effectiveness, it may indicate in the NSE letter that the product may be appropriate for the De Novo classification process under section 513(f)(2) of the FD &C Act.[4]

De Novo Request

Once a De Novo request is received, whether or not it is preceded by a 510(k), FDAwill verify that another submission for the same device (same technological characteristics and same indication (s) for use) from the same requester is not under review (e.g., Pre-sub, 510(k) or PMA). FDA will not review two submissions for the same device from the same requester simultaneously. If FDA identifies another submission for the same device, FDA will place the applicant file on administrative hold. FDA will not begin a review of the De Novo request and will notify applicant, that to start the review, the applicant needs to withdraw the other submission.[4]

FDA will also check the content of the De Novo request which includes the information required by section 513 (f) (2) of the FD &C Act., in order to submit a Direct De Novo request, the submitter must determine that there is no legally market device upon which to base a determination of substantial equivalence.

Under Section 513 (f)(2)(A)(i) of the FD &C Act, a *De novo* request preceded by a 510(k)Must be for a device type that has not been previously classified; thus if applicant submit a *De novo* request after receipt of an NSE determination, an applicant should confirm that no device has the same ty pe

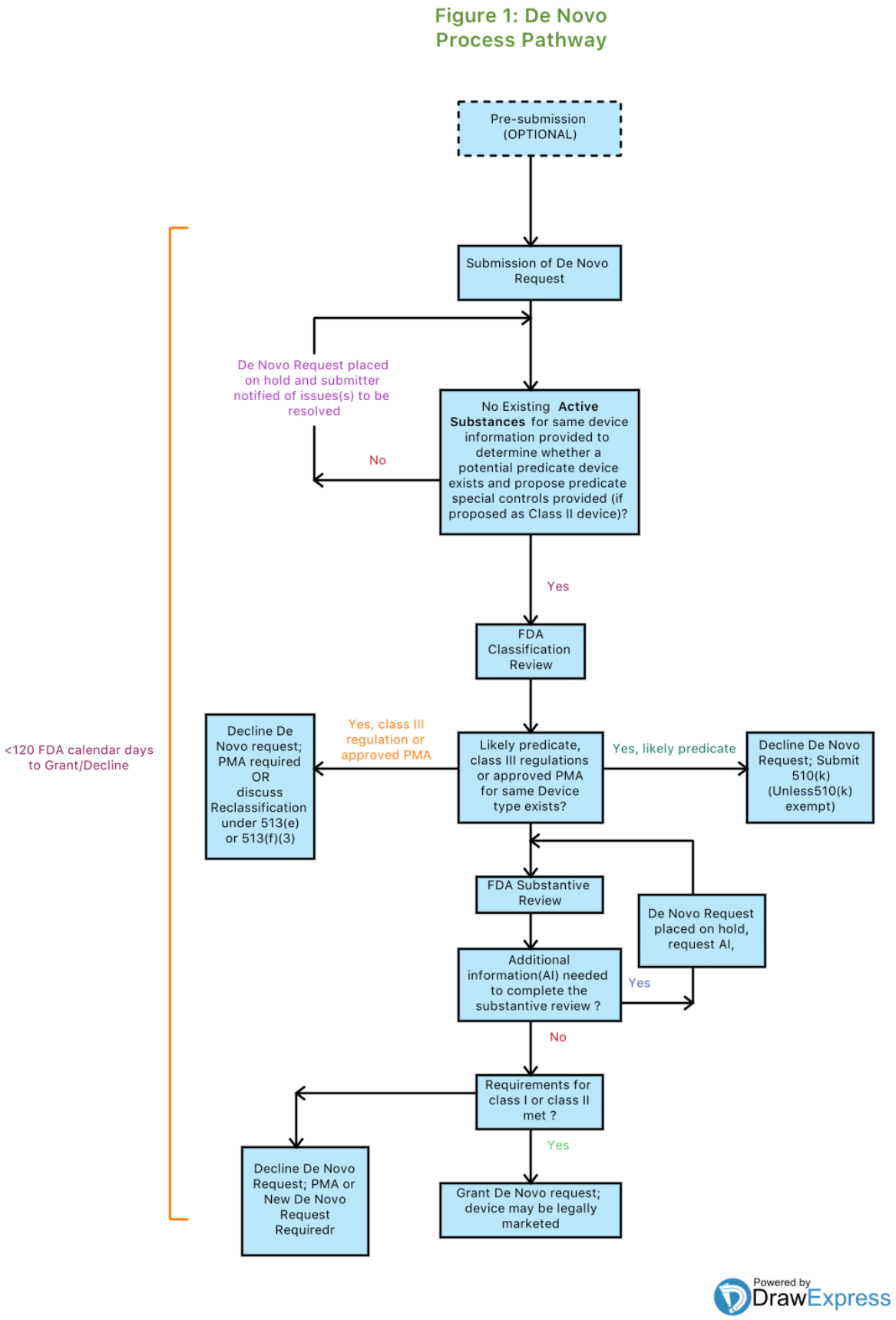

Figure 1: FDA Review of De Novo Request[2]

of has legally entered the market since the time of the NSE determination.[4]

De Novo request that lack information to determine whether a potential predicate device exists may be placed on hold. As provided by section 513 (f) (2) (v) of the FD & C Act, if applicant is recommended that their device be regulated as Class II device, they must also submit an initial draft proposal for applicable special controls.

If the applicant De Novo request is placed on hold, the review clock stops, and FDA will notify the applicant that it is on hold, pending receipt of information regarding potential predicates or a draft proposal for special controls. In the event if applicants do not provide the requested information within 180 calendar days, FDA will consider applicant De Novo request to be withdrawn.

In the next step, FDA will conduct a classification review of legally marketed device types. FDA will analyze whether an existing legally marketed device of the same type exists (e.g., whether the proposed device likely falls under an existing Class II classification regulation), including whether a predicate has been recently established through the De Novo classification process. If a likely predicate device exists or the proposed device falls under a class III classification, FDA intends to decline applicant De Novo request and notify the applicant of the basis for their decision. If the device falls within a class III classification regulation or there is one or more approved PMAs for the same type of device and FDA believe general and/or special controls are adequate to provide a reasonable assurance of safety and effectiveness, the appropriate mechanism for classification into Class I or II would be reclassification under section 513 (e) or 513 (f) of the FD & C Act. If no existing legally market device of the same type is identified, FDA will continue the review.[4]

FDA does not anticipate that De Novo requests for the same device type will frequently be under review concurrently. However, in cases where a De Novo request is granted while another device of the same type is under review in a separate de Novo request after the first De Novo request is granted, FDA intends to notify the submitter of the other De Novo request still under review that a predicate has been established and that the De Novo request still under review will be declined. The submitter of the declined De Novo request may leverage all information in the De Novo request by incorporating it by reference in a new submission but will still be required to demonstrate substantial equivalence in a subsequent 510 (k) including conformity with the newly established special controls for the device type (if Class II)[4]

Upon successful completion of the submission and classification review, FDA will begin the substantive review of the De Novo request. If the De Novo request is missing, information and/or data necessary to determine whether general controls or general and special controls can provide reasonable assurance of safety and effectiveness, FDA may issue additional information (AI) letter or request information via interactive review. Issuance of AI letter stops the review clock, and once an applicant provides a complete response, the clock will resume, and review will continue.

If an applicant fails to provide a complete response within 180 calendar days of the date of the AI request, FDA will consider the De Novo request to be withdrawn. If a De Novo request is withdrawn due to failure to submit adequate information, a new De Novo is required in order to reinitiate the review of the device under the De Novo classification process.

FDA regulations provide 180 days to review the PMA and make a determination. In reality, the review time is normally longer. Before approving or denying a PMA, the appropriate FDA advisory committee may review the PMA at a public meeting and provide FDA with the committee's recommendation on whether FDA should approve the submission. After FDA notifies the applicant that the PMA has been approved or denied, a notice is published on the Internet.[4]

- Announcing the data on which the decision is based, and
- Providing interested persons an opportunity to petition FDA within 30 days for reconsideration of the decision.

The regulation governing pre-market approval is located in Title 21 CFR Part 814, Premarket Approval. A class III device that fails to meet PMA requirements is considered to be adulterated under section 501(f) of the FD&C Act and cannot be marketed.

Pathway 1: 510(k) → De Novo[2]

- Attempt 510(k) route with the proposed predicate device
- Submission found NSE, but a candidate for De Novo

Pathway 2: Direct De Novo[2]

- Useful if the applicant believes proposed device is viable De Novo candidate (especially with feedback from Pre-Sub program)

Pathway 1: 510(k) → *De novo*

Steps Involved

- *Sponsor submits 510(k) submissions:* this should be a complete 510(k) submission
- *FDA reviews 510(k) submission:* makes NSE finding due to lack of predicate
  - Lack of predicate = proposed predicate device does not have the same intended use and technological characteristics as a new device.
  - FDA may choose to indicate in NSE letter that new device may be appropriate De Novo candidate (based on risk-benefit profile, not the adequacy of data submitted)[2]
- *Sponsor submits De Novo application*
  - Reference prior 510(k)
  - Provide additional evidence to demonstrate the safety and effectiveness of a new device, as appropriate
  - Address any differences and evidence gaps between 510(k) device and De Novo; provide added testing, Safety, and Effectiveness information as needed
  - Characterize risks to health associated with the use of a new device
  - Characterize how the risks may be mitigated

- Provide a rationale for why a device does not fit into an existing regulation
- If propose Class II classification, then identify the special controls to mitigate the risks to health
- May interact with a sponsor, ask for additional information
- Render final De Novo decision: grant or decline.[2]

Pathway 2: Direct *De novo*

Steps Involved

- *Sponsor submits De Novo application:*
  - Evidence that establishes reasonable assurance of safety and effectiveness of new device most information typically submitted in traditional 510(k) submission, device description, labeling, Performance testing (bench, animal, clinical)
  - Characterize risks to health associated with the use of a new device
  - Characterize how the risks may be mitigated
  - Provide a rationale for why the device does not fit into existing regulation (either 510(k) or PMA
  - If proposed Class II classification, then identify the special controls to mitigate the risks to health.[2]
- *FDA reviews De Novo application*
  - May interact with a sponsor, ask for additional information
  - Render final De Novo decision: grant or decline.[2]

PRE-MARKET APPROVAL

The PMA application consists of scientific, regulatory documentation to the FDA to evaluate the safety and effectiveness of a class III device. The PMA review process is a 4-step process of 180 days.[7]

Step 1: Filing a review

In this step, the application is reviewed by using a checklist; if it is complete, it will be filed issuing a PMA reference number. In the case of refusal, the applicant can request a review again to the director, who will make the final decision.

Step 2: In-depth Scientific Review

After filing the application, in case of any deficiency, a notification will be given to the applicant within 90 days; otherwise, the status of the application will be given within 100 days. If required, by request of the applicant, a meeting will be conducted on day 100, followed by a quality research inspection and bioresearch audit.

Step 3: Panel Review

The PMA is forwarded to the appropriate member of the advisory panel. In case of any queries, they are forwarded to the applicant through the FDA, and after receipt of a response by the panel members, followed by review issues, final report is sent to the FDA. Based on the report, and if any recommendations are given by the advisory committee, a final decision is made by the FDA

Table 1: Comparison of PMA and De Novo Process.[5,6]

Parameter	*Pre-market Approval*	*De Novo Process*
Definition	Pre-market approval (**PMA**) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices.	Classify new devices without predicate as Class I or Class II.
Pathway	*PMA* is the Complex pathway to market	*De Novo* is the simplest pathway to market
Regulatory Burden	Offers less advantage in terms of review time and data burden for a De Novo are close to those of a PMA, a PMA affords a higher regulatory barrier to competition.	*De Novo* pathway offers an advantage in terms of reduced review time and data collection burden, then a lesser degree of competitive protection may be acceptable.
Clinical Data	Amount of Clinical data required to support PMA Submission is more as compared to De Novo submission	Amount of Clinical data required to support a *De Novo* submission is less as compared to PMA
Study Set up	PMA process does not afford more flexibility in study design	De Novo process affords more flexibility in study design
Study Design	Randomized, Controlled Investigation support PMA	De Novo is supported by single-arm Studies
Device Classification	PMA is used for the highest risk devices	De Novo is used for Novel Devices of low to Moderate devices
Review Period	Timeline: 180 days	Timeline: 150 days
Risk	High	Low or moderate
Control	General controls special controls pre-market Authorization	General controls Special controls
Safety	Reasonable assurance of safety	Reasonable assurance of safety
Effectiveness	Reasonable assurance of effectiveness	Reasonable assurance of effectiveness
Clinical Data	Yes	Yes
Annual reporting requirement	Yes	No
Medical device reporting requirements	Yes	Yes
Application fee	$322,147	$96,644

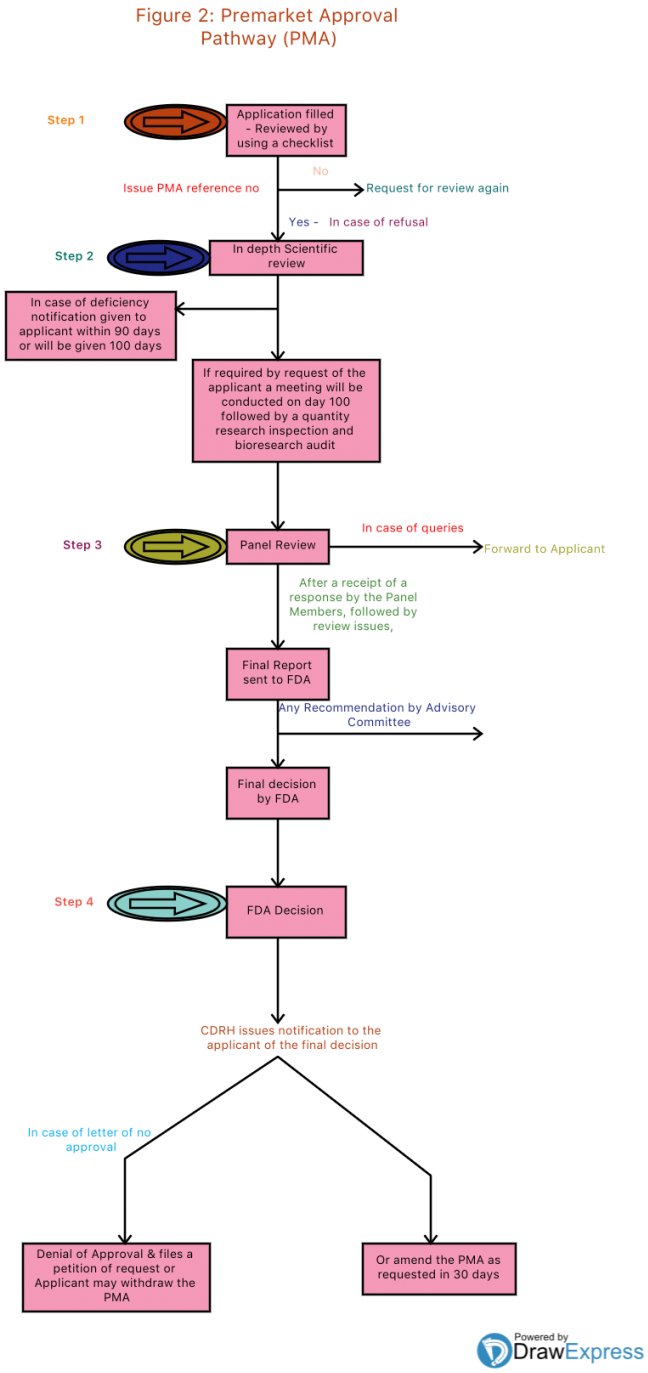

Figure 2: Pre-market approval pathway (PMA)[7]

Step 4: FDA Decision

In this step, the CDRH issues a notification to the applicant of the final decision. In case of a letter of no approval, the applicant can consider it as a denial of approval and files a petition of request, or the applicant may withdraw the PMA or amend the PMA as requested in 30 days.

CONCLUSION

The amount of data required to support a *de novo* submission may, in some cases, be reduced compared to a PMA, while in other instances, the amount of data required has approached that of a PMA. There is some indication based on prior *de novo* clearances that the process affords more flexibility in study design compared to a PMA, with a number of *de novo* clearances supported by single-arm studies, rather than randomized, controlled investigations, as would typically be required for PMA approval. There are, however, other benefits of a *de novo* pathway compared to a PMA, particularly as related to post-market reporting and compliance.

Overall, while the *de novo* program may provide a useful regulatory approach as an alternative to a PMA application for some products, the reforms implemented under Food and Drug Administration Safety and Innovation Act (FDASIA) have not yet produced meaningful and consistent streamlining of the procedure.

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