AdvaMed Accel | Regulatory Best Practices Guide

INTRODUCTION & OVERVIEW

An original **Premarket Approval Application (PMA)** is a stringent premarket submission, intended for Class III medical devices. Such devices often are used to treat life-threatening conditions, and they may pose significant risks to human health with improper use. For this reason, the product manufacturer must reasonably assure the safety and effectiveness of the device utilizing appropriate standards, guidance documents, and other required testing. Class I and Class II devices do not require a PMA because they are low to moderate risk.

The Class III product manufacturer often must also provide detailed Quality System information. Under most circumstances, products eligible for a PMA must undergo clinical and non-clinical testing as well as facility inspections by the Agency. FDA recommends that manufacturers request a meeting prior to testing to establish a common understanding with the FDA review team of the evidence required.

PMA Application Checklist

- ☐ Cover letter: Must clearly identify the submission type
- ☐ Summary
- ☐ Device Description
- ☐ Manufacturing Information
- ☐ References to performance standards or voluntary standards
- ☐ Non-clinical testing/laboratory study results
- ☐ Clinical trial results
- ☐ Bibliography of all published reports pertaining to the device
- ☐ Proposed labeling, including all promotional materials if available at the time of submission
- ☐ Financial certification or disclosure statement

Types of PMA Submissions

1. A **Traditional PMA** may be used for any Class III device. All required contents are submitted in a single application.
2. A **modular PMA** allows companies to submit an application in sections, or modules. FDA collaborates with manufacturers to develop a customized PMA "shell" that outlines the plan for modular submissions, including suggesting timelines and contents for each module.

During the review process, companies may modify their applications or provide additional information in a **PMA Amendment**. Once FDA grants approval, all changes must be submitted as PMA Supplements, 30-day Notices or in the Annual Report.

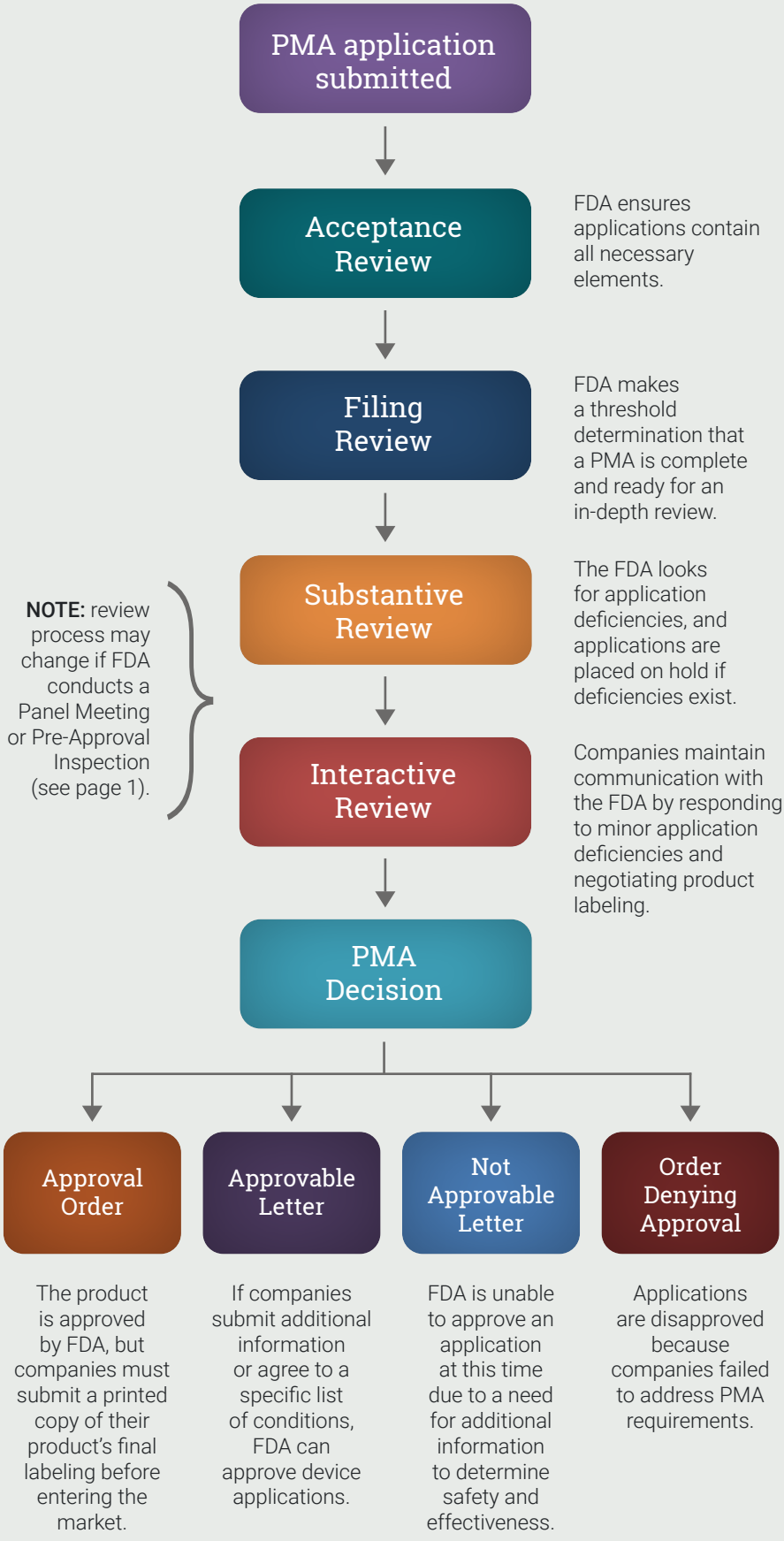
Panel Meetings

FDA may request a **Panel Meeting** of the applicable device **Advisory Committee**, for example, if a device is the first of its kind. In this case, applications are sent to an advisory committee, or panel of experts, for review. Advisory Committees hold public meetings where the company presents highlights of its application, FDA presents its perspective on the application, and the panel asks questions about the device and submits reports to FDA with specific recommendations and the criteria on which they were based.

Pre-Approval Inspections

In some cases, FDA may request a **Pre-Approval Inspection** to evaluate a company's facilities and manufacturing practices to confirm they comply with (1) Quality System regulations and (2) the information that was written in their PMA submissions.

PMA Submission Review Process



MDUFA Time Commitments

DAY 1

Company submits PMA application to the FDA.

DAY 15

FDA conducts an Acceptance Review.

DAY 15

FDA conducts Acceptance Review and informs companies if their applications have been accepted for Substantive Review or placed on RTA hold.

DAY 45

FDA notifies the company if its application has been filed, and, if so, Substantive Review begins.

DAY 70

Deadline for requesting a Day 100 Meeting.

DAY 90

FDA completes Substantive Review and Interactive Review begins.

DAY 100

Meeting with FDA review team if requested.

Companies may request a Day 100 Meeting (a type of Q-Submission) to review the status of PMA applications (either for original PMAs or amended applications).

DAY 180

FDA completes Interactive Review and issues a decision letter to the company.

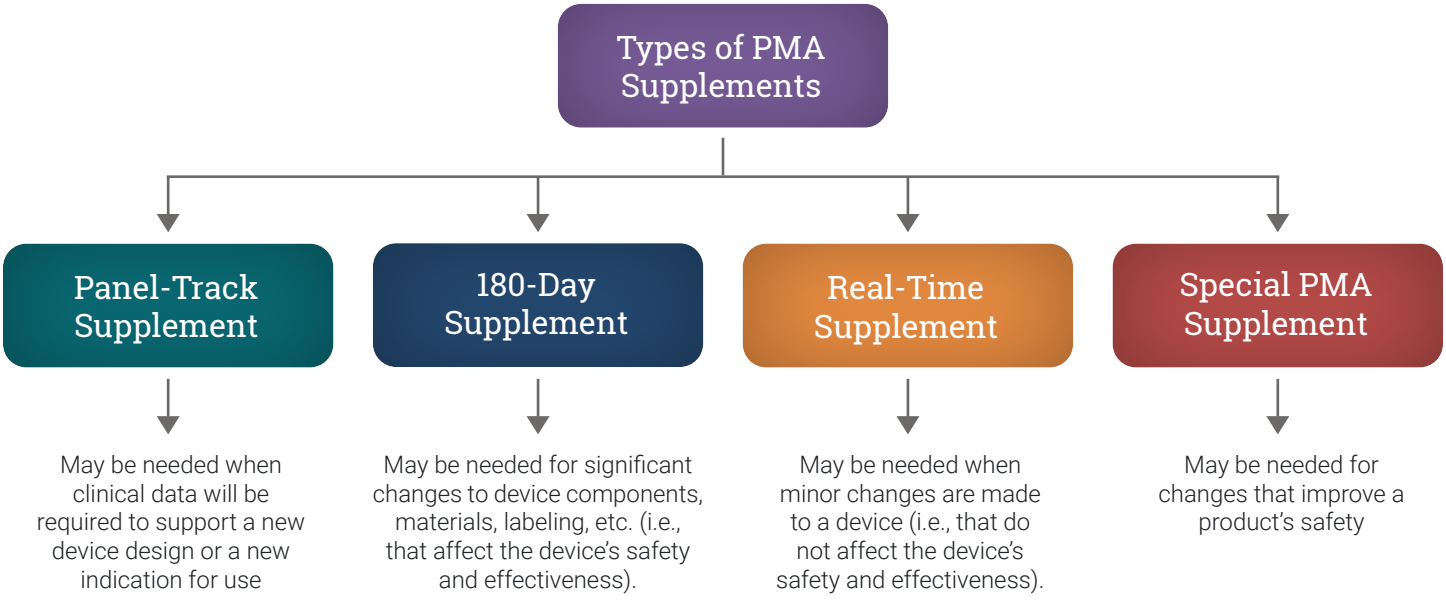
DAY 320

FDA issues a decision letter for PMAs requiring a Panel Meeting.

POST-APPROVAL

PMA Supplements

Once a device has been approved by FDA, companies are required to submit supplementary applications to make changes that affect product safety and effectiveness. Changes are not permitted until such applications are approved by the Agency. Also, the type of PMA supplement that a company submits is based on the type of change that needs to be made to the device.



NOTE: *FDA may convert any supplement, notice, or report to another type and require additional information about the change.*

30-Day Notice

Sponsors may need to submit another report type—a **30-Day Notice**—if changes need to be made to a device's manufacturing methods and/or procedures (see examples on page 24 of this **Guidance**). Changes can be implemented once FDA provides approval of the 30-day notice.

Annual Reports

Annual reports, including information on changes to the device, performance, labeling, and manufacturing, are required for all PMA devices.

Post-Approval Studies

FDA requires post-approval studies for most Class III devices to ensure continued safety and effectiveness. The Agency will inform companies during the PMA review process if their products will require post-approval studies. If so, companies work together with FDA to establish study protocols for their devices. If both parties are unable to reach an agreement before a PMA is approved, then the final protocol must be submitted as a PMA supplement. If an established protocol needs to be modified, then the modifications must also be submitted as a PMA supplement. FDA reserves the right to revoke product approval if post-approval studies indicate non-compliance with appropriate post-market requirements.

▲ **Results typically must be reported every 6 months for the first 2 years and annually thereafter.**

▲ **Companies must submit a final report to the FDA no later than 3 months after a post-approval study is complete.**

FDA GUIDANCE DOCUMENTS

Pre-Approval

Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions

Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications

User Fees and Refunds for Premarket Approval Applications and Device Biologics License Applications

Premarket Approval Application Modular Review

FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Goals

Acceptance and Filing Reviews for Premarket Approval Applications (PMAs)

Guidance on PMA Interactive Procedures for Day-100 Meetings and Subsequent Deficiencies

The Review and Inspection of Premarket Approval Application Manufacturing Information and Operations

Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations

Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval

Post-Approval

Procedures for Handling Post-Approval Studies Imposed by PMA Order

Modifications to Devices Subject to Premarket Approval (PMA) – The PMA Supplement Decision-Making Process

Real-Time Premarket Approval Application (PMA) Supplements

30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes

Annual Reports for Approved Premarket Approval Applications (PMA)

Quality System Information for Certain Premarket Application Reviews

Additional Resources

Premarket Approval (AdvaMed.org)

FDA/CDRH Webinar – Regulatory Overview for Developers and Sponsors of Neurological Devices: An Introduction to Premarket Approvals (PMA) (July 26, 2017)

Tips from the Experts

1. **Use the Q-Sub (Pre-Submission) process for Class III devices.** Companies frequently request these meetings to discuss preclinical testing, clinical trial design, and data from clinical trials prior to submitting a premarket application. Multiple Pre-Submission meetings are typical for the PMA process.
2. **Establish a relationship with the reviewer and, if possible, the review team** to facilitate more informal communications throughout the PMA process.
3. **Prepare the PMA application carefully and be very thorough** in describing the device, its intended use and indications for use, protocols and results for testing performed, design of clinical trials and results. Use graphics, flow charts, or videos to illustrate complex product description, testing, or trial aspects that may be difficult to understand.
4. **Organize the application so that FDA reviewers will not become frustrated by errors** like misspelling, incomplete or inaccurate references, incorrect page numbering, and similar factors.
5. **FDA may divide up the sections of the PMA application among reviewers.** Provide a brief device description and other information at the beginning of each section that will enable the reviewer to understand whatever is needed to review his or her section.
6. **Request a Day 100 Meeting if needed** to gain clarification on application deficiencies.
7. **Ask FDA to schedule the pre-approval inspection as soon as the company is ready.** Otherwise, it may delay PMA approval. FDA may waive the inspection if the facility in which the new device will be made has been inspected recently and makes similar types of devices using similar processes.
8. **Be friendly and cooperative** when FDA investigators inspect manufacturing practices and facilities.
9. **During an inspection, document all records and other information provided to FDA.** Respond to any inspectional observations as quickly as possible.
10. **Engage appropriate experts in preparing for a panel meeting.** Even the largest companies seek assistance in developing a presentation, anticipating and responding to questions, and learning about the panel members. A dress rehearsal (or several) for the panel meeting is a valuable use of time.

AdvaMed Working Groups

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