

Introduction to the Premarket Approval Application (PMA) Program

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Hello, my name is Donna Headlee. I am the Branch Chief of the Premarket Programs Branch, in the Division of Industry and Consumer Education. Welcome to CDRH learn, CDRH's resource for multimedia industry education. The title of this presentation is "Introduction to the Premarket Approval Application Program." A Premarket Approval Application is often referred to as PMA. The purpose of this presentation is to provide you with an introduction to the PMA Program and the FDA's review process of a PMA.

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I am going to begin with examples of Class III PMA devices. The first device pictured on this Slide is a valve implanted in the lung to help decrease over inflation of the lung in patients with emphysema. The second device is a lens implanted in the eye after cataract surgery, to help a patient see. The third device is a diagnostic test that can detect a specific receptor or gene to guide cancer treatment. The fourth and final device is a pump to assist the heart to pump blood to the vital organs of the body. As you can see by these examples, Class III PMA devices can pose high risks and have a significant impact on public health and a patient's quality of life.

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After watching this module, I hope that you will have a better understanding of the PMA program and the FDA's review process. In order to accomplish these objectives, the topics I am going to discuss are: First, what is a PMA? Second, the contents of a PMA application. Third, the FDA's review process of a PMA. Fourth, key milestone interactions and actions during the FDA review process. And lastly, I will conclude with a discussion of strategies for a successful PMA application submission and review process.

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Let's begin with a discussion of Class III medical devices. This is critical, because the regulatory pathway to market a class III medical device is the PMA pathway. CDRH classifies devices into 3 Classes: Class I is the lowest risk, Class II is moderate risk and Class III is the highest risk. Class III devices are devices that support or sustain human life, are of substantial importance in preventing or diagnosing illness or disease or present a potential unreasonable risk for illness or injury. For these types of devices, there is insufficient information to assure the reasonable assurance of safety and effectiveness solely with general and special controls. A PMA is the most stringent marketing application for a medical device in the United States.

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Now that we understand the types of devices that require a PMA, in this next section, I am going to discuss the contents of a PMA application.

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The contents of a PMA application are described in 21 Code of Federal Regulation, referred to as CFR, 814.20. Over the next three Slides, I have highlighted some of the contents of an application. The sections of a PMA application include: The name and address of the applicant; a table of contents that specifies the volume and page number of the contents; indications for use statement that contains a description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate and a description of the patient population for which the device is intended; a complete description of the

device and functional components or ingredients; reference to performance standards; and an environmental assessment under 21 CFR 25.20(n).

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Additional sections include the methods used in, and the facilities and controls used for, the manufacturing, processing, packaging, storage, and, where appropriate, installation of the device; a bibliography of all published reports; a sample of the device, if practical; copies of all the proposed labeling; copies of the financial certification or disclosures of the clinical investigators; and information concerning uses in pediatric patients.

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There are 2 significant sections I have not discussed - the pre-clinical and clinical study sections. They make up a large portion of the application and include a significant amount of the valid scientific evidence to support the safety and effectiveness of the device for the intended use. The pre-clinical study data section includes pre-clinical test reports and summaries, such as bench and animal testing; biocompatibility; software; engineering; Electromagnetic Compatibility, referred to as EMC, and Electromagnetic Interference, referred to as EMI.

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In addition, the application should include information related to any clinical experience from the United States and Outside the United States to support the safety and effectiveness, including the benefit risk determination. The data should include summaries, conclusions and results of all clinical experience or investigations reasonably obtainable by the applicant, whether adverse or supportive. As you can see, this is an extensive application, which includes a significant amount of data, summaries and analyses.

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The next topic I am going to discuss is the FDA's review process of a PMA application.

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An applicant assembles a multidisciplinary team to develop a device and gather all the data needed to seek approval. Likewise, when the FDA receives an application, one of the first steps is to assemble a multi-disciplinary team with varying expertise to review the application. They perform a scientific, regulatory, and Quality System review of the PMA.

This list identifies some of the disciplines the FDA may include on the review team. I want to highlight the Team or Lead Reviewer - they will be communicating with the applicant and be the point of contact. A typical review team could include 10 to 15 members. At any time during the review, if additional expertise is needed, additional consults will be obtained.

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Sometimes visualizing something in a diagram assists with clarifying the process. The next couple of Slides show a flow chart, identifying key milestones and actions in the submission and review process. I'll walk you through this diagram and then we'll go into more detail for the key milestones and actions. The blue ovals indicate the FDA key milestones. The diamonds illustrate the day by which the FDA will take action for the key milestone. Red arrows note actions that stop the review clock. Green arrows note actions that continue the review clock. Starting from the top of the flow diagram, we begin with submitting the PMA application to the FDA. Continuing down the flow chart, the first blue oval

milestone is the acceptance review. The diamond notes this should be completed by day 15. Next is the filing review by day 45. If accepted and filed, then the substantive review begins.

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By Day 90, the FDA will render a substantive interaction decision by either proceeding interactively or issuing a Major Deficiency Letter. An applicant may request a Day 100 meeting either in the cover letter of their Original PMA application or a Q-Submission request by Day 70 to discuss the progress of the review and obtain clarification of any deficiencies. Next, the FDA may seek input from an advisory committee. If the FDA obtains input from an advisory committee, they should issue the MDUFA decision by day 320. If the FDA does not obtain input from an advisory committee, they should issue the MDUFA decision by day 180. The possible MDUFA decisions are: Approval, Approvable Pending Deficiencies, Approvable Pending GMPs, and Not Approvable.

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Now I will discuss some of the key milestones and activities in more detail. Once the application is received and passes e-copy and user fee checks - the FDA begins the review process. We begin with the acceptance review. The acceptance review is an administrative review to assess the completeness of the application - that is - are all the required elements included? If any of the required elements are not included there should be a justification for the omission of these items. Within 15 calendar days of the FDA's receipt of the PMA, the FDA will send the applicant an email notification of the decision to accept or not accept the application. If the application is not accepted the notification will include a summary identifying any missing elements.

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The next significant milestone is the filing review. The filing review is a threshold determination that the application is sufficiently complete to begin an in-depth review. Are the data consistent with the protocol, final device design, and proposed indication?

This is not an in-depth review to determine approvability. Within 45 calendar days of the FDA's receipt of the PMA, the FDA will send the applicant a notification of the decision to file or not to file the application. If the PMA is filed, the applicant will receive an email notification with the filing decision. If the PMA is not filed, the applicant will receive a dated and signed letter, via email, with a statement or summary of the reasons for not filing the PMA.

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Once the PMA is filed, the FDA Review Team begins the substantive review of the application. This will consist of the in-depth scientific, regulatory, and quality system reviews. During the review, the FDA may interact with the applicant to address and resolve deficiencies found during the reviews that can be addressed within an appropriate timeframe.

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The next key milestone is that the FDA will provide a major interaction including feedback by Day 90. This is the Substantive Interaction. This interaction is either one of two options: One, continue to work interactively to resolve any outstanding deficiencies. Proceeding interactively allows the application to continue under review. Or the second option, issue a major deficiency letter identifying the deficiencies. This action places the application on hold until a complete response to all the major deficiencies is received by the FDA.

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The FDA may seek input from a medical device advisory committee, also referred to as a Panel Meeting. The committee includes experts from clinical practice, statistics, industry, patients, and any additional expertise that is needed. These meetings are open to the public. For information on Medical Device Advisory Panel Meetings, please review the Guidance shown at the bottom of this Slide.

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Once the FDA's review is complete, the FDA will make a MDUFA decision. In this next section, I am going to discuss each of these decisions. I will begin with the decision that all applicants hope to obtain – that is approval.

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Please note the color of the text for the approval order on this slide. Green is for go. If the FDA issues an Approval Order, the device is legally marketed. The approval order lists the approved indication for use and any conditions of approval. This is the only action in which the device is legally marketed.

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If the application is close to approval, but there are minor deficiencies, the FDA will issue an Approvable Pending Deficiencies Letter. Please note the color of the text for approvable Pending Deficiencies letter is red, red notes stop and the device cannot be legally marketed.

Common issues that may be identified in an Approvable Pending Deficiencies Letter are unresolved labeling or lack of resolution of the post-approval study design, if one was required. The FDA letter will identify deficiencies that need to be resolved for the application to be approved. In an effort not to issue this letter, the FDA is striving to resolve labeling and post approval study deficiencies prior to the MDUFA decision.

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If the application is ready for approval, non-clinical and clinical issues are resolved, but the FDA has not determined that the manufacturing facilities, methods and controls are in compliance with the Quality System Regulation, the FDA will issue an Approvable Pending GMP Letter. The device cannot be legally marketed.

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And finally, the last type of MDUFA decision is a Not Approvable Letter. The same as the Approvable Pending Deficiencies and Approvable Pending GMP letters - the device cannot be legally marketed. There are outstanding major deficiencies that may include requests for new clinical and/or preclinical data. The FDA letter will identify deficiencies that need to be resolved in order for the application to be approved.

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The FDA prepares the Summary of Safety and Effectiveness Data document, referred to as the SSED. This document contains relevant information for device users and patients regarding the basis for the decision to approve the device. It consists of a summary of the information included in the PMA application, explains the basis for FDA's approval of the PMA, and the applicant's demonstration that the device is reasonably safe and effective for the intended use. This document contains information such as the device description, preclinical information, clinical information, a summary of the Advisory Committee Meeting, if one was held, and a discussion of the benefit/risk determination. This document

is published on the FDA's website along with a copy of the approval order. One method to locate these documents is by searching for the PMA in the PMA database. A link to the database is located at the bottom of this slide.

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We have discussed the contents and review process of a PMA application. Now I will conclude with some helpful hints and strategies that can lead to a successful PMA application.

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The strategies are organized into 3 B's: Be organized, Be prepared, and Be responsive. I will discuss these concepts in more detail over the next few Slides.

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First: Be organized. Submitting a well-organized, administratively and scientifically complete application can assist in the review process. A PMA application should have a comprehensive table of contents, detailed sections, and include all test reports, graphs/tables that are clearly labeled.

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Second: Be Prepared. Have your team ready to answer questions. Have copies of the PMA application and any other submissions or interactions you have had with the FDA readily available, such as the Investigational Device Exemption, referred to as an IDE, and Q-Submission. Also, be ready for manufacturing and bioresearch monitoring inspections.

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And the last "B" is Be Responsive. Everyone wants to meet the key milestone goals so, please answer the questions when you say you will. If you don't understand the question or cannot meet the deadline, please contact the lead reviewer. Request and plan on a day 100 meeting. You can always cancel it if it is not needed. Be ready to interact on labeling, especially toward the end of the FDA's review. Have your decision-makers available for a quick turnaround. And finally, develop a post-approval study proposal and work interactively with the FDA Review Team to finalize a scientifically sound study.

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The next three slides provide you with some additional guidance documents to assist you with the PMA development and review process.

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To recap key concepts: A PMA is a marketing application for the highest risk of medical devices that the FDA regulates, that is, class III medical devices. A PMA application should include valid scientific evidence to support the reasonable assurance of safety and effectiveness of the device for the indication for use. And a successful PMA review process involves collaboration between the FDA and the applicant.

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CDRH provides multiple opportunities for industry education. On this slide, I have provided you with links to CDRH Learn which consists of numerous learning modules covering a wide range of medical device topics; as well as Device Advice, which is a text-based resource, and lastly, you may contact the Division of Industry and Consumer Education or DICE by phone or email with questions. The web links and contact information to these resources are provided on this Slide.

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Think back to the first slide of this presentation and the devices pictured on that slide. As you can see, Class III PMA devices can pose high risks and have a significant impact on public health and patient's quality of life. Together, we have a common goal, that is, to assist patients and healthcare providers to have access to safe, effective, and high-quality medical devices.

To achieve this goal: Your call to action is to work with the Agency and submit a well-organized PMA application that contains the necessary valid, scientific evidence to demonstrate the reasonable assurance of safety and effectiveness of the device for the intended use.

Thank you for watching "Introduction to the PMA Program." For further information, please consider watching the additional module on PMAs in CDRH Learn and refer to the PMA section in Device Advice.
