**Premarket Approval (PMA)**

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| What is the Premarket Approval (PMA) Process |

1. **Definition**
   1. 21 CFR 814.42(e)
   2. The most rigorous approval process for medical devices by FDA.
   3. Applies to all Class III medical devices (almost exclusively).
   4. A PMA must be supported by valid scientific evidence to demonstrate the *safety and effectiveness* of the device for its intended use.
   5. Typically includes the results of:
      1. Extensive clinical trials
      2. Bench tests
      3. Laboratory studies
      4. Animal studies
      5. References to any standards relevant to a device’s safety or effectiveness
2. **Decision Options that FDA Can Make About PMA Application**
   1. Accept
   2. Refuse to Accept (RTA)
   3. File
   4. Not File

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| Contents of a PMA |

1. **21 CFR Part 814.20: Information and format required in PMA**
   1. Identifying Information
      1. Applicant’s name and address
      2. Detailed table of contents
   2. Table of Contents
   3. Summary
      1. A detailed summary to provide FDA reviewer a general understanding of the data and information in application
   4. Device Description and Manufacturing Information
      1. A complete description of:
         1. Device: Include pictorial representations
         2. Each of the functional components or ingredients of the device if the device consists of more than one physical component or ingredient
         3. The properties of the device relevant to the diagnosis, treatment, prevention, cure or mitigation of a disease or condition
         4. The principles of operations of the device and
         5. The methods used in, and the facilities and controls used for, the manufacture, processing, packing, storage, and a detailed explanation about where instillation of the device happens so that the person reviewing the PMA, who as the familiar and current good manufacturing practice background, can make a knowledgeable judgment about the quality control used in the manufacturing of the device
   5. Performance Standards
      1. Explain how your device meets any existing performance standards established by the FDA or recognized standards development organizations (SDOs) relevant to your device type.
      2. If there are no existing standards, describe how you established the performance criteria for your device and the methods used to demonstrate the device meets those criteria.
      3. Reference any performance standard under section 514 of the FDCA or Radiation Control for Health and Safety Act of 1968 (442 USC 263b et seq) that has to do with safety or effectiveness of the device. This should include known to or should reasonable be known to applicant
   6. Technical Information
      1. This section provides detailed engineering drawings, schematics, and other technical data that describe the design, construction, and operation of your device.
      2. Ensure the information is clear, concise, and allows the FDA reviewer to understand the technical aspects of your device.
      3. *Nonclinical Laboratory Studies*
         1. This section should include results of the device, including:
            1. Microbiological
            2. Toxicological
            3. Immunological
            4. Biocompatibility
            5. Stress
            6. Wear
            7. Shelf life
            8. And other laboratory or animal tests as appropriate
      4. *Clinical Investigation Section*
         1. Includes human subjects with the device including
            1. Clinical protocol
            2. Number of investigators and subjects per investigator
            3. Subject selection
            4. Exclusion criteria
            5. Study population
            6. Study period
            7. Safety and effectiveness data
            8. Adverse reactions and complications
            9. Patient discontinuation
            10. Patient complaints
            11. Device failures and replacements
            12. Tabulations of data from all individual subject report forms and copies of such forms for each subject who died during a clinical investigation or who did not complete the investigation
            13. Results of statistical analyses of the clinical investigations
            14. Device failures and replacements
            15. Contraindications and precautions for use of the device
            16. Include any other appropriate information from clinical investigations
            17. Include any IDE information
   7. Sole Investigations
      1. If a single investigator acquired the data for a PMA, a justification showing that data and other information from a single investigator are sufficient to demonstrate the safety and effectiveness of the device and to ensure reproducibility of the test results.
   8. Bibliography
      1. This section lists all the references cited throughout the PMA document.
   9. Device Samples
      1. Explain how many and what types of device samples you are submitting to the FDA for review.
      2. Include details on labeling, packaging, and instructions for handling the samples.
      3. If submission of any portion of the sample device is impractical, the applicant can name the location that the FDA can visit so that they can examine and test the sample devices.
   10. Labeling
       1. Explain how many and what types of device samples you are submitting to the FDA for review.
       2. Include details on labeling, packaging, instructions for handling the samples, installation and any information, literature, or advertising that constitutes labeling under section 201(m) of the Act.
   11. Environmental Assessment
       1. PMA’s are categorically excluded from requiring an environmental assessment (EA) or environmental impact statement (EIS) if the device is of the same type and for the same use as a previously approved device.
          1. 21 CFR Part 25.34(d)
       2. Describe the potential environmental impact of your device throughout its lifecycle, including manufacturing, use, and disposal.
       3. Address any potential environmental hazards associated with materials, energy use, or waste generation.
   12. Financial Disclosure and Information
       1. A financial certification and/or disclosure statement as required by 21 CFR Part 54
   13. Pediatric Use
       1. Address the use of your device in pediatric populations. Give a description of the number of affected pediatric patients that suffers from the disease or conditions that the device is intended to treat, diagnose, or cure.
   14. Additional Information
       1. Any other information the FDA may request.
   15. Benefit Risk Assessment
       1. Include the benefit/risk analysis

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| PMA Review Process |

1. **Acceptance Review (15 days):**
   1. You submit your PMA application to the FDA.
   2. FDA will accept the application for filing to permit a substantive review if the PMA is sufficiently complete.
   3. If that is the case, the FDA will accept the application for filing within 15 days of receipt
   4. Note: The FDA will use the RTA checklist to decide if the application will be approved or denied.
2. **Application Filing (45 days):**
   1. The FDA conducts a preliminary review to ensure the application contains all the required elements as outlined in the regulations (21 CFR Part 814).
   2. Once accepted, FDA completes a more in-depth filing review within 45 days. This includes the time spent on the acceptance review.
   3. Within 45 days of receiving your application, the FDA will notify you if it's accepted for filing or if there are deficiencies that need to be addressed.
3. **Substantive Review (180 days with a possible 90-day extension):**
   1. If your application is accepted for filing, the FDA initiates a comprehensive review of the technical and scientific data to assess the *safety and effectiveness* of your device.
   2. This review can involve multiple reviewers from various disciplines like engineering, toxicology, and clinical specialists.
   3. On Day 90 (or earlier), the FDA may issue a deficiency letter outlining any missing information or unresolved issues identified during the review. These letters can be categorized as major or minor depending on the severity of the deficiencies. The letter will detail the additional information needed to complete the review of the application.
   4. On Day 100, the FDA can schedule a meeting to go over the deficiencies flagged in the PMA application, overall review of the of the pending PMA, and if an advisory panel is needed.
   5. The application is now placed on hold at this point once the deficiency letter is issued.
   6. The review timeframe is typically 180 days, but the FDA can request additional information or studies during this period, though the hold period may be extended a further 180 days upon request if applicants need more time for the response.
4. **Communication and Meetings:**
   1. You can request a pre-submission meeting with the FDA before filing your application to discuss your device and the PMA process.
   2. You can also request a meeting (100-Day Meeting) within 70 days of filing to discuss the status of your application and any potential issues identified by the FDA during the initial review.
5. **FDA Decision:**
   1. After the review is complete, the FDA will issue a decision on your PMA application:
   2. Approved: You can market your device in the U.S.
   3. Approvable: The FDA identifies deficiencies that can be addressed through amendments to your application.
   4. Not Approvable: The FDA outlines reasons for non-approval, and you may need to conduct further studies or make significant changes to your device before resubmitting the PMA.

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| What the IRB Looks for in the PMA |

1. **Reference Link**
   1. [IDE Institutional Review Boards (IRB) | FDA](https://www.fda.gov/medical-devices/investigational-device-exemption-ide/ide-institutional-review-boards-irb)
2. **Subject Protection**
   1. Minimizing Risk
   2. Informed Consent
   3. Subject Selection
   4. Data Security and Confidentiality