Introduction to the Premarket Approval Application (PMA) Program

Donna Headlee, RN, BSN, CCRP
Branch Chief, Premarket Programs Branch
Division of Industry and Consumer Education
Office of Communication and Education
Center for Devices and Radiological Health
U.S. Food and Drug Administration

PMA Devices

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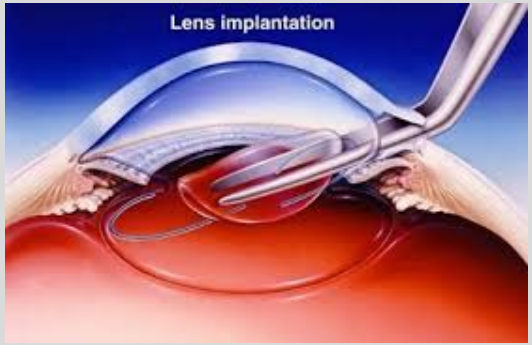

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Learning Objectives

1. Define PMA
2. Describe the contents of a PMA application
3. Describe FDA review process of a PMA
4. Discuss key milestone interactions and actions
5. Identify strategies for a successful PMA application and review process

Class III Medical Devices

- **Highest risk category**
- Subject to **PMA requirements**
- **Support or sustain** human life, substantial importance in **preventing impairmen**t of human health, potential for **unreasonable risk** of illness or injury
- **Unable to solely rely on general and special controls** to assure safety and effectiveness

Content of PMA

Contents of PMA

- Name and address of applicant
- Table of contents
- Indications for use
- Description of device and functional components or ingredients
- Reference to performance standards
- Environmental assessment

21 CFR 814.20

www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=814.20

Contents of PMA

- Manufacturing
- Bibliography
- Sample of device, if practical
- Proposed labeling
- Financial certification or disclosure
- Information concerning uses in pediatric patients

21 CFR 814.20

www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=814.20

Contents of PMA
Pre-Clinical Studies

- Test reports, summaries and conclusions
- Example Categories include:
  - Bench and animal testing
  - Biocompatibility
  - Software
  - Engineering
  - Electromagnetic Compatibility (EMC)
  - Electromagnetic Interference (EMI)

21 CFR 814.20
www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=814.20

Contents of PMA
Clinical Studies

- Any clinical experience, within and outside United States
- Support safety and effectiveness
- Support benefit-risk determination
- Include all data, whether adverse or supportive:
  - methods
  - results
  - conclusions

➢ *Reasonably obtainable by applicant*

21 CFR 814.20

www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=814.20

PMA Review Process

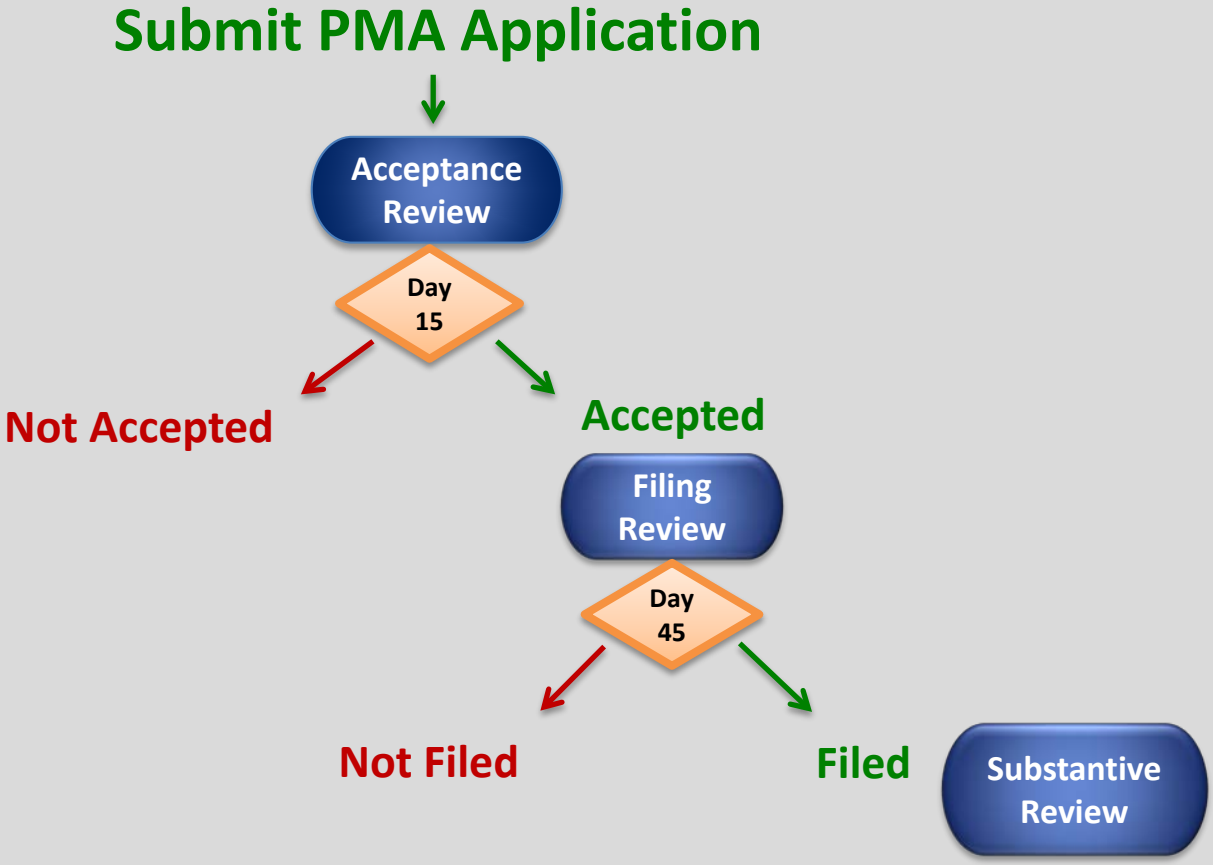
Multi-Disciplinary FDA Review Team

Scientific, Regulatory, Quality System Review

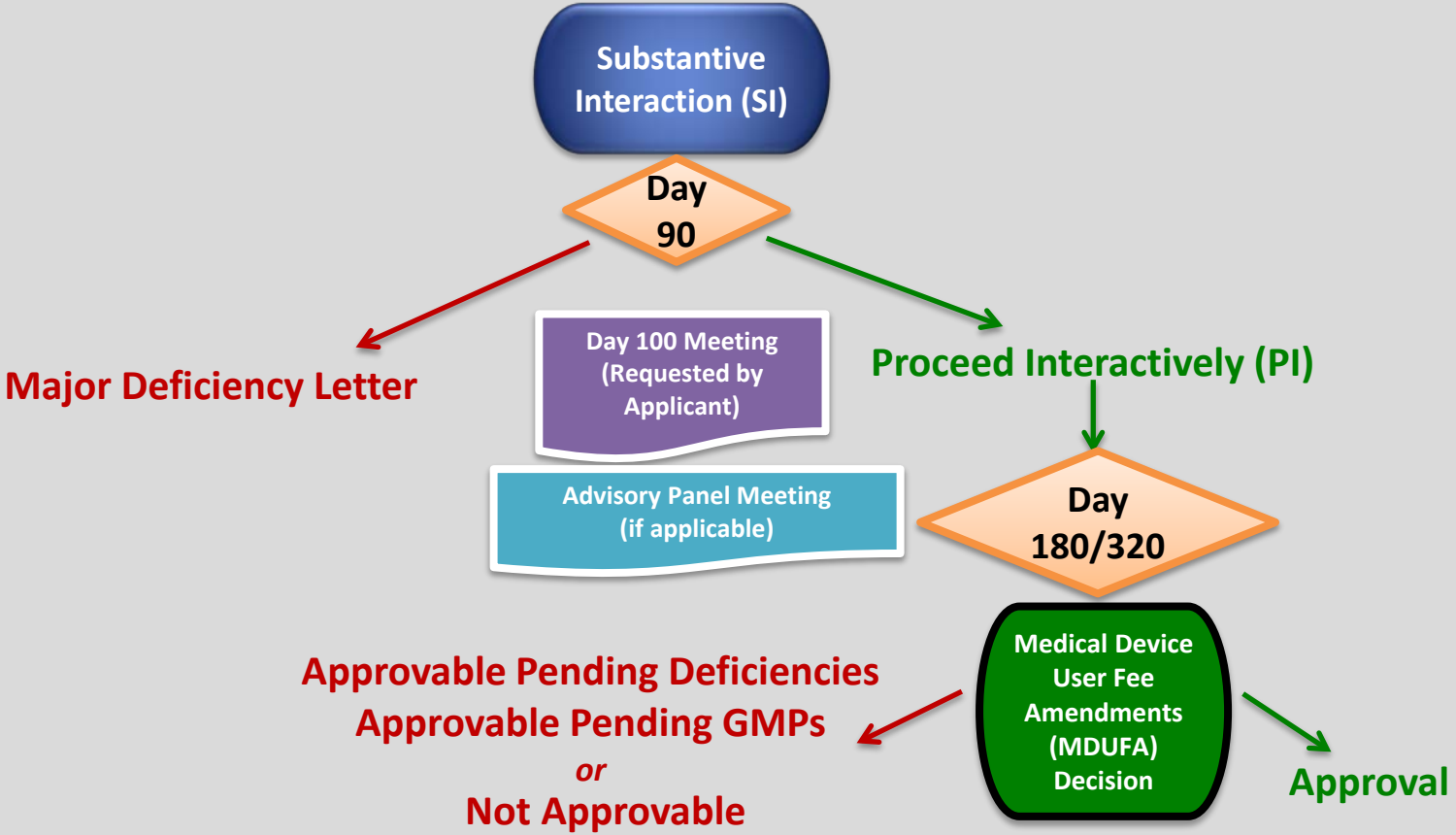
- Team Leader/Lead Reviewer
- Clinical
- Statistical
- Preclinical
- Engineering
- Animal Studies

- Biocompatibility
- Microbiology
- Quality System and Manufacturing
- Bioresearch Monitoring
- Patient Labeling
- Epidemiology

PMA Review Process (1/2)



PMA Review Process (2/2)



Acceptance Review

- **Purpose**
  - Assess administrative completeness of application
  - Does Application **contain required elements** per 21 CFR 814.20?

- **FDA Action:**
  - FDA sends Applicant email notification
  - Decision Options: Accepted or Not Accepted (identify missing elements)
  - Completed within **15 calendar days** of FDA's receipt of PMA

Acceptance and Filing Reviews for PMAs
www.fda.gov/regulatory-information/search-fda-guidance-documents/acceptance-and-filing-reviews-premarket-approval-applications-pmas

Filing Review

- **Purpose**
  - Threshold determination that application is sufficiently complete to review
    - Adequacy of technical elements allow for substantive review
  - Evaluate whether data are consistent with protocol, final device design, and proposed indications

- **FDA Action:**
  - FDA sends Applicant notification of filing review
  - Decision Options: Filed or Not Filed
  - Completed within **45 calendar days** of FDA receipt of PMA

Substantive Review

- **Purpose**
  - In-depth Scientific, Regulatory, and Quality System Reviews
- **Interactive Process**
  - Interact with applicant to address deficiencies
    - that can be addressed in appropriate timeframe

Substantive Interaction (SI)

- **Purpose:**
  - FDA to provide a major interaction including feedback/action by **Day 90**

- **FDA Options:**
  1. **Continue to work interactively with applicant**
     - Proceed interactively
     - Application remains under review (i.e., not placed on hold)
  2. **Issue Major Deficiency Letter**
     - Application is placed on **hold** until complete response is made to deficiencies

Advisory Committee Review

- **Independent panel of experts**
  - Clinical practice, academia, statistics, industry, patients and any additional expertise needed
- **Open to the public**

Procedures for Meetings of the Medical Devices Advisory Panel Committee
www.fda.gov/regulatory-information/search-fda-guidance-documents/procedures-meetings-medical-devices-advisory-committee

FDA MDUFA Decisions

FDA Review Decisions

- **Approval Order:**
  - Device may be marketed
  - Identifies conditions of approval

FDA Review Decisions

- **Approvable Pending Deficiencies Letter:**
  - Device can **not** be marketed
  - Identify clarifications/deficiencies to be addressed before PMA may be approved
  - Common issues:
    - unresolved labeling
    - unresolved post-approval study design

FDA Review Decisions

- **Approvable Pending GMP Letter:**
  - Device can **not** be marketed
  - Primary reason: FDA has not confirmed that manufacturing facilities, methods and controls are in compliance with Quality System

Quality System - 21 CFR Part 820
www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820

FDA Review Decisions

- **Not Approvable Letter:**
  - Device can **not** be marketed
  - Identify deficiencies that need to be addressed to make the PMA application approvable
  - May include requests for new clinical and/or preclinical data

Summary of Safety and Effectiveness Data (SSED)

- FDA summarizes basis for PMA Approval
- Provides comprehensive, detailed summary and analysis of PMA:
  - Device and Background Information: device description, indications for use
  - Performance Testing: preclinical, animal, and clinical
  - Review of Panel meeting
  - Benefit/Risk summary

PMA Approval Database
www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

Strategies for a Successful PMA Application

Successful Strategies
3 B's

- **B**e organized
- **B**e prepared
- **B**e responsive

Be Organized

- **Well-organized** application
- Administratively and scientifically **complete** application

Be Prepared

- Have your team ready to **answer questions**
- Have **copies of PMA** and make available any previously submitted information (e.g., IDE, Q-submission)
- Be **ready for** manufacturing (Quality System) and bioresearch monitoring (BIMO) **inspections**

Be Responsive

- **Be upfront and responsive**
  - Answer FDA's questions when you say you will
  - If you don't understand a question, call/email and ask for clarification
  - Plan a Day 100 meeting - you can always cancel if it is not needed
- **Start early to develop your post-approval study plan**
  - Work with FDA study team to gain agreement on post approval study

References

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

  www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-premarket-approval-and-de

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

  www.fda.gov/regulatory-information/search-fda-guidance-documents/balancing-premarket-and-postmarket-data-collection-devices-subject-premarket-approval

References

- **Acceptance of Clinical Data to Support Medical Device Applications and Submissions Frequently Asked Questions**

  www.fda.gov/regulatory-information/search-fda-guidance-documents/acceptance-clinical-data-support-medical-device-applications-and-submissions-frequently-asked

- **Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices**

  www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices

References

- **The Least Burdensome Provisions: Concept and Principles**
  www.fda.gov/regulatory-information/search-fda-guidance-documents/least-burdensome-provisions-concept-and-principles

- **Guidance on PMA Interactive Procedures for Day 100-Meetings and Subsequent Deficiencies**
  www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-pma-interactive-procedures-day-100-meetings-and-subsequent-deficiencies-use-cdrh-and

- **FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Goals**
  www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-and-industry-actions-premarket-approval-applications-pmas-effect-fda-review-clock-and-goals

Summary

- A PMA is a marketing application for the **highest risk** of medical devices that FDA regulates
- A PMA application includes **valid scientific evidence** to support the reasonable assurance of safety and effectiveness of the device for the intended use
- The PMA review process is a **multidisciplinary, collaborative, and interactive** process

Providing Industry Education

1. **CDRH Learn – Multi-Media Industry Education**
   - Videos, audio recordings, power point presentations, software-based "how to" modules describing aspects of medical device and radiation emitting product regulations: **www.fda.gov/CDRHLearn**

2. **Device Advice – Text-Based Education**
   - Text-based resource that explains many aspects of medical device laws, regulations, guidances, and policies: **www.fda.gov/DeviceAdvice**

3. **Division of Industry and Consumer Education (DICE)**
   - If you have a question - Email: **DICE@fda.hhs.gov**
   - Phone: 1(800) 638-2041 or (301) 796-7100 (Live Agents 9am – 12:30 pm; 1-4:30 pm EST)

Your Call to Action

- **Work** with the Agency before and during the PMA review process
- Submit a **well-organized** PMA
- Provide **valid scientific evidence** to support the reasonable safety and effectiveness of the medical device for the intended use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