Introduction to the Premarket Approval (PMA) Program

FDA Small Business
Regulatory Education for Industry (REdI)
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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

Impact

Learning Objectives

- Define PMA and its contents
- Describe the FDA review process
- Understand the post-approval regulatory requirements
- Identify some best practices for a successful PMA submission and review process

Class III Medical Devices

- **Highest risk category**
- **Support or sustain** human life, substantial importance in **preventing impairment** of human health, potential for **unreasonable risk** of illness or injury
- **Insufficient information** to assure the reasonable safety and effectiveness solely with **general and special controls**
- Subject to **PMA** Approval
  - most stringent marketing application

Content of PMA

Contents of PMA

- Name and address of applicant
- Table of content
- Description of device and functional components or ingredients
- Reference to performance standards
- Environmental assessment
- Manufacturing

21 CFR 814.20

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

Contents of PMA

- **Non-clinical studies**: test reports, summaries and conclusions
- **Clinical studies:** methods, results and conclusions
- Bibliography
- Sample of device – if practical
- Proposed labeling
- Financial certification or disclosure
- Information concerning uses in patients

21 CFR 814.20

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

FDA Review of PMA

FDA Review of PMA

- **Scientific, Regulatory and Quality System Review**
  - Evaluate reasonable assurance of **safety and effectiveness**;
    - For an intended use, defined with respect:
      - person prescribed, and
      - conditions of use prescribed

513(a) Federal Food, Drug, and Cosmetic Act (FD&C Act)
uscode.house.gov/view.xhtml?req=(title:21%20section:360c%20edition:prelim)

FDA Review

- **Valid scientific evidence**
  - **Well/partially-controlled,** clinical investigations or other objective information
  - Not opinions, random reports or un-interpretable data

- **Considerations**
  - **Benefits vs. risks** for indicated **patient population**
  - Conditions of device use
  - Device safety, performance and reliability

21 CFR Part 860.7(C)(2)
www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?FR=860.7

FDA Guidance: Factors to Consider When Making Benefit-Risk Determinations in PMAs
www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm517504.pdf

Use of Real World Evidence

- **Real World Evidence (RWE)**
  - Evidence collected from clinical experience
    - routine course of care and treatment of patients
  - May augment understanding of benefit/risk profile
  - Evidence needs to be of relevant and reliable quality
  - In proper context, may be considered valid scientific evidence

FDA Guidance: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf

Partner with Patients

- **Patient Perspective in Regulatory Decisions**
  - consideration of patient preference information
    - patients live with their condition and make decisions about their care
  - gain a better understanding of benefit-risk perspectives according to the patients themselves

FDA Guidance: Patient Preference Information – Voluntary Submission, Review in PMA Applications

www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM446680.pdf

PMA vs 510(k)

	PMA	510(k)
Device Class	Class III	Class I or Class II
Application	Stand-Alone	Substantial Equivalence (SE) to Predicate Device
Clinical Evidence	Almost 100% have Clinical Evidence	Approximately 10% have Clinical Evidence
FDA Review Days (calendar days)	180 days – no panel 320 days– if panel	90 days
Final Decision	Approval	Clearance

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PMA Review Process

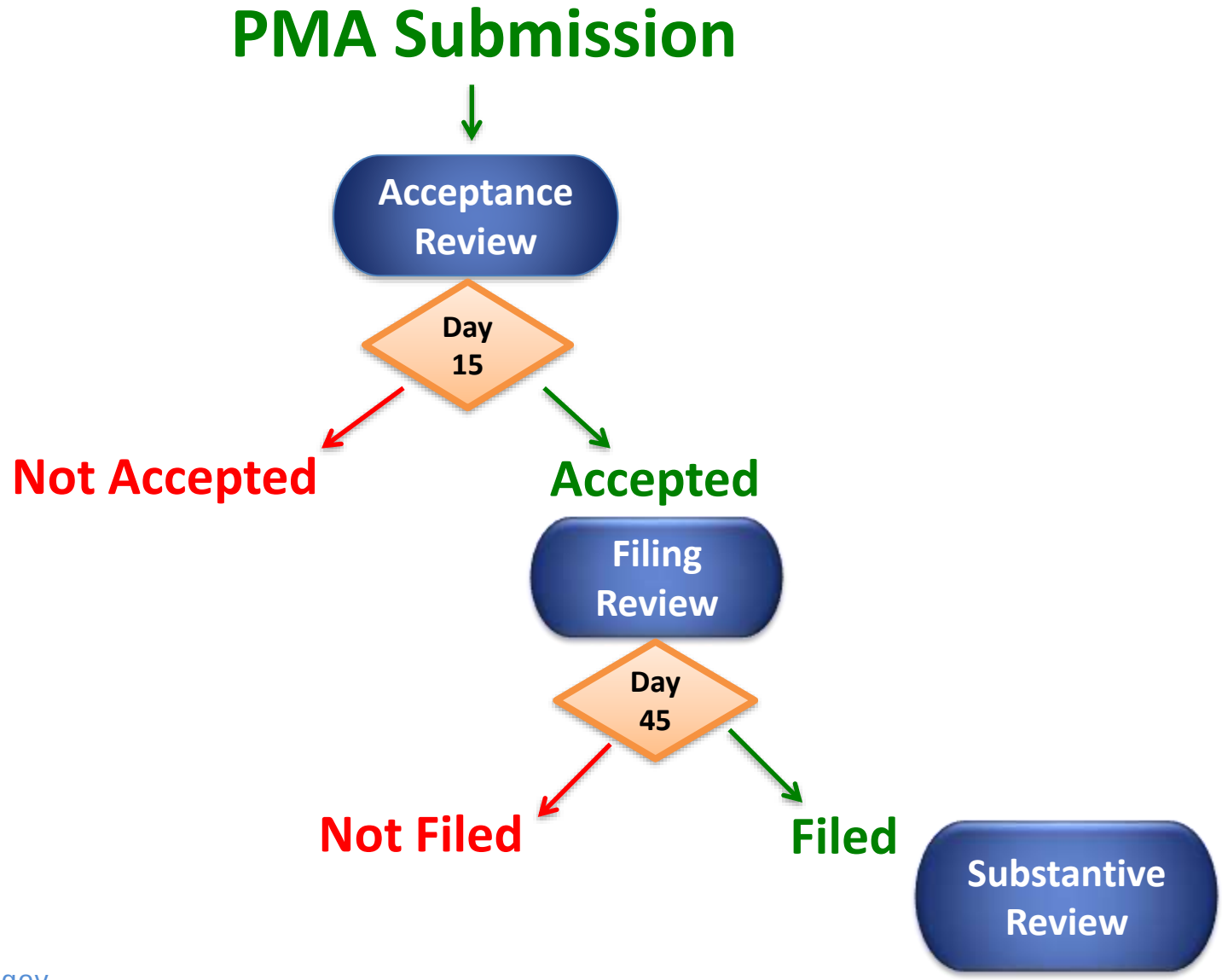
Multi-Disciplinary FDA Review Team

Scientific, Regulatory, Quality System Review

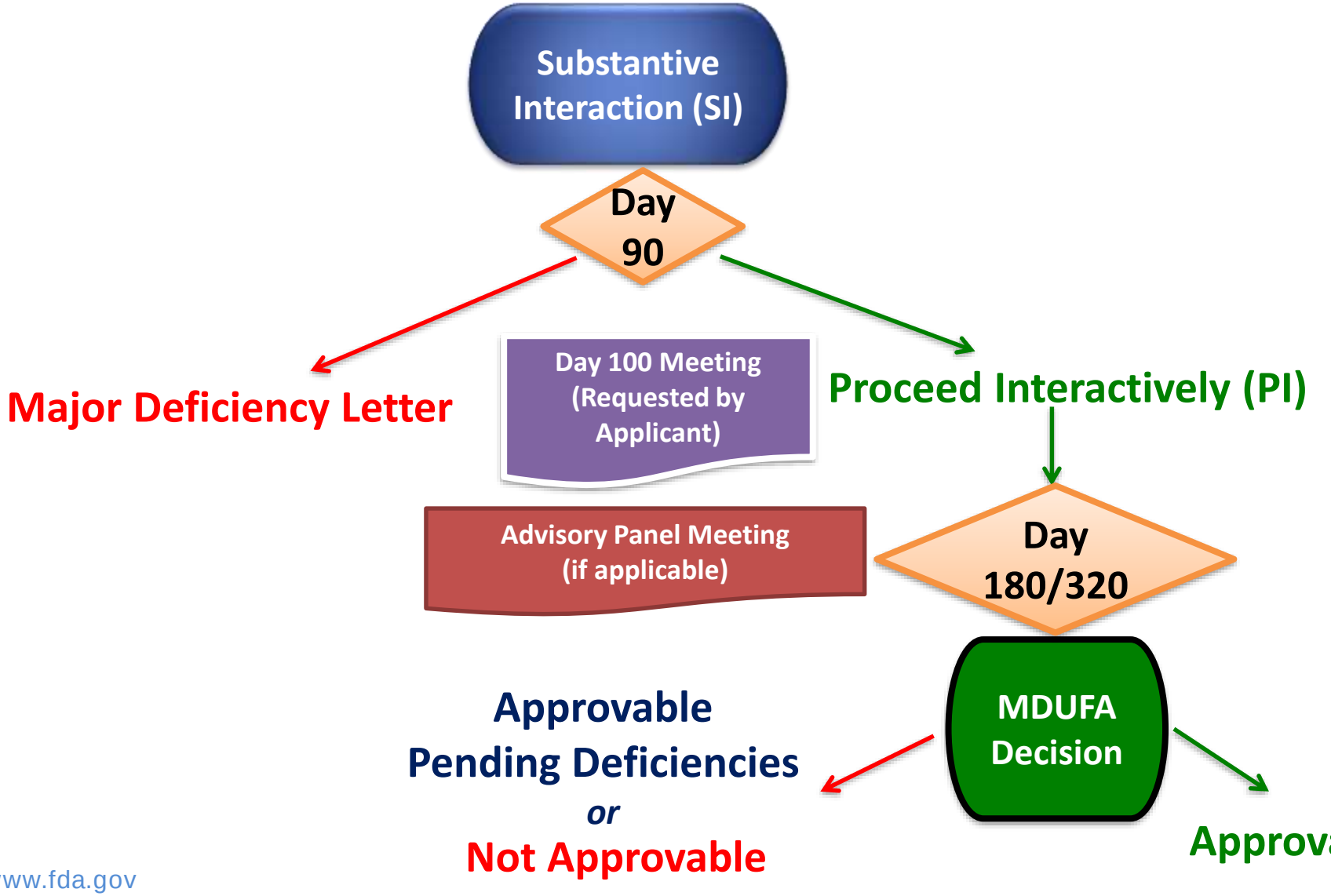
- **Team Leader/Lead Reviewer**
- Clinical
- Statistical
- Preclinical
- Engineering
- Animal Studies
- Biocompatibility

- 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 written notification
  - Decision Options: Accepted or Not Accepted (identify missing elements)
  - Completed within **15 calendar days** of FDA receipt of PMA

FDA Guidance: Acceptance and Filing Reviews for PMAs

www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm313368.pdf

Filing Review

- **Purpose**
  - Threshold determination that the application is sufficiently complete to review.
    - Is the information needed to allow for substantive review?
  - Evaluate whether the data are consistent with the protocol, final device design, and proposed indications

- **FDA Action:**
  - FDA sends Applicant written 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 Manufacturing Reviews
- **Interactive Process**
  - Interact with applicant to address deficiencies
    - that can be addressed in appropriate timeframe
  - FDA Review Clock continues (does not stop)

Substantive Interaction (SI)

- **Purpose:**
  - FDA to provide substantive feedback/action by **Day 90**

- **FDA Options:**

1. **Decide to continue to work interactively with sponsor**
   - Submission remains under review (i.e., not placed on hold)
   - Proceed interactively
2. **Issue Major Deficiency Letter**
   - Submission is placed on **hold** until complete response is made to deficiencies

Advisory Committee

- **Independent panel of experts**
  - Clinical practice, academia, statistics, industry and patients
- **Reasons**
  - Novel technology
  - Input from special expertise
  - Significant public interest
  - Highly controversial
  - Uncertainty of study results
  - Unanticipated serious safety concerns

Advisory Committee Review

- **Provide recommendations:**
  - Address scientific, clinical or public issues
  - Safety and effectiveness
  - Conditions of approval
  - Labeling
  - Post Approval Study (PAS)

- **Open to the public**

FDA Guidance: Procedures for Meetings of the Medical Device Advisory Committee
www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm440348.pdf

FDA Decisions

FDA Review Determinations

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

FDA Review Determinations

- **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
    - manufacturing facilities, methods and controls not confirmed by FDA to be in compliance with the Quality System

FDA Review Determinations

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

Summary of Safety and Effectiveness Data (SSED)

- Summarizes basis for FDA's Final Decision

- 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

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What happens after the PMA is approved?

Post-Approval Annual Reports

- Due **annually** by date of approval
  - e.g., if February 1, 2017 due by February 1, 2018; 2019
- Summarize information pertaining to the original PMA
- Any subsequent PMA supplements
  - Identify changes
- Summary and bibliography of scientific literature
- Unique device identification (UDI)

21 CFR 814.84

FDA Guidance: Annual Reports for Approved PMAs
www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm089398.pdf

Post-Approval Studies (PAS)

- **May be required as a condition of approval**

- **Reasons for PAS:**
  - Understand long-term safety and effectiveness issues
    - Especially for implantable devices (e.g., 5-year)
  - Further evaluate device/component performance
  - Evaluate learning curve or training issues

- **FDA and Applicant agree on PAS protocol/outline prior to PMA approval**

Post-Approval Study Reports

- **Study Information**
  - Purpose of study, study goals, objectives & endpoints, and patient population being studied
- **Summary of study progress:**
  - IRB approvals
  - Number of clinical sites
  - Enrollment status
- Summary of **safety and/or effectiveness data** and an interpretation of study results

FDA Guidance: Procedures for Handling Post-Approval Studies Imposed by PMA Order
www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm

Changes that Require PMA Supplement

- **Changes affecting safety and/or effectiveness of the PMA-approved device require FDA approval prior to implementation**

Examples:

- New indication for use
- Labeling changes
- Use of different manufacturing or sterilization site
- Changes in sterilization procedures
- Changes in performance or design
- Modification to software or hardware
- Changes to manufacturing process
- Revisions to a post-approval study plan/protocol

FDA Guidance: Modifications to Devices Subject to PMA: The PMA Supplement Decision-Making

www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm089360.pdf

Strategies for a Successful Submission

Successful Submission Strategies:
the 3 Bs

1. **B**e organized
2. **B**e prepared
3. **B**e responsive

Be Organized

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

Be Prepared

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

Be Responsive

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

Selected References

- Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo Classifications*
- Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval
- Acceptance and Filing Reviews for Premarket Approval Applications - Threshold determination about whether an application is administratively complete to move forward and conduct a substantive review
- Guidance on PMA Interactive Procedures for Day 100-Meetings and Subsequent Deficiencies

Questions

Please complete the session survey:

surveymonkey.com/r/DEV-D1S07

Call to Action


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