Introduction to the Premarket Approval (PMA) Program

FDA Small Business
Regulatory Education for Industry (REdI)
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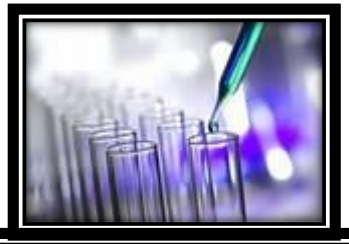
Impact



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
- **Unable to solely rely on general and special controls** to assure safety and effectiveness
- Subject to PMA Approval

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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

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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 for person prescribed,
      - With respect to the conditions of use prescribed

513(a) Federal Food, Drug, and Cosmetic Act (FD&C Act)
www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterVDrugsandDevices/default.htm

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

Guidance: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and de novo Classifications:
www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm267829.htm

Use of Real World Evidence

- **Real World Evidence (RWE)**
  - Derived from collection and analysis of real-world data (RWD)
  - May augment understanding of benefit/risk profile
  - In proper context, may be considered valid scientific evidence
  - Need to consider overall relevance and reliability of data
- **CDRH Strategic Priority 2016-17**
  - Increase access to real-world evidence to support regulatory decision making
  - Draft 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' view of benefits and risks
  - patient perspective studies and data
- **CDRH Strategic Priority 2016-17**
  - Increase use and transparency of patient input as evidence in decision making
  - 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

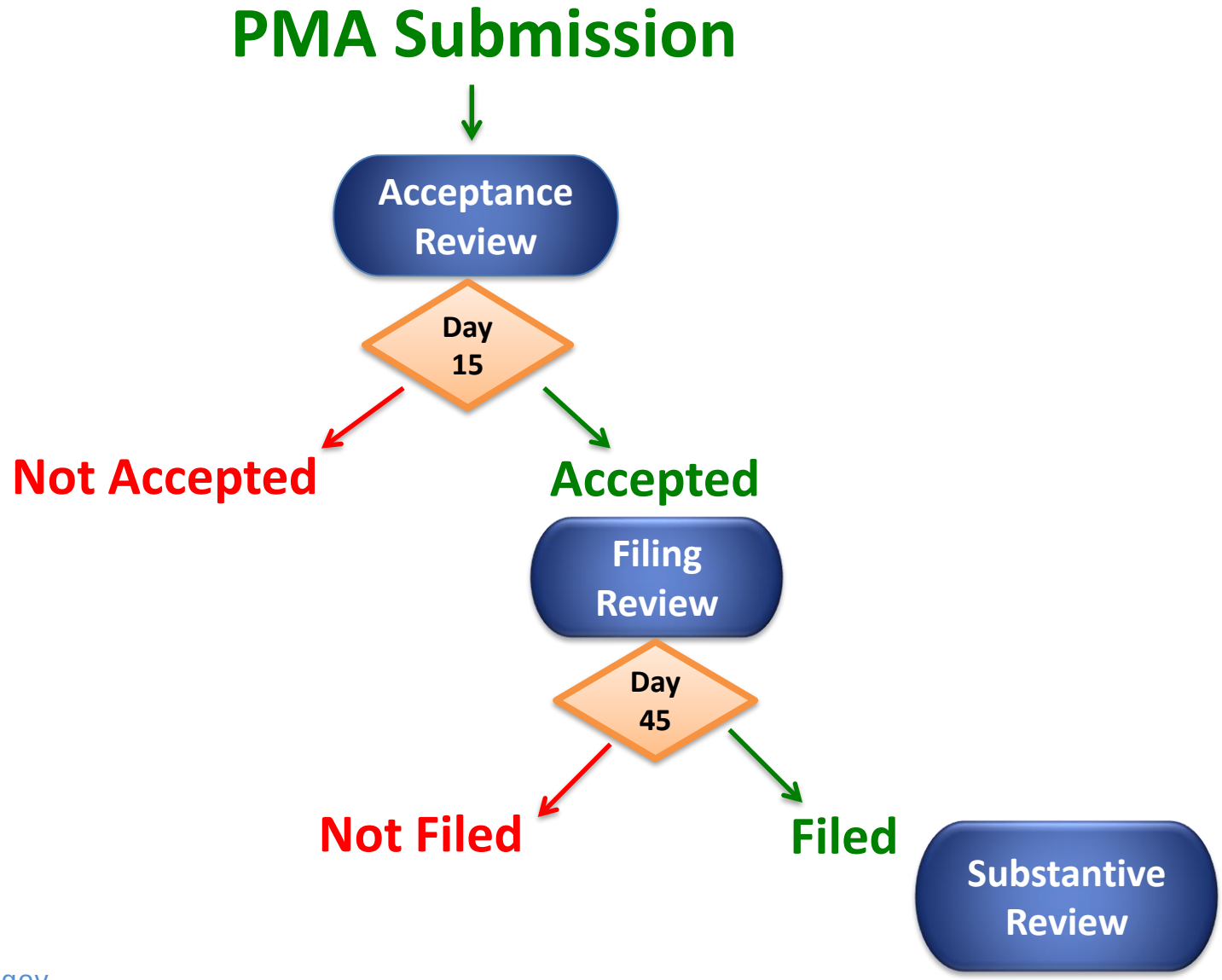
Multi-Disciplinary FDA Review Team

Scientific, Regulatory, Quality System Review

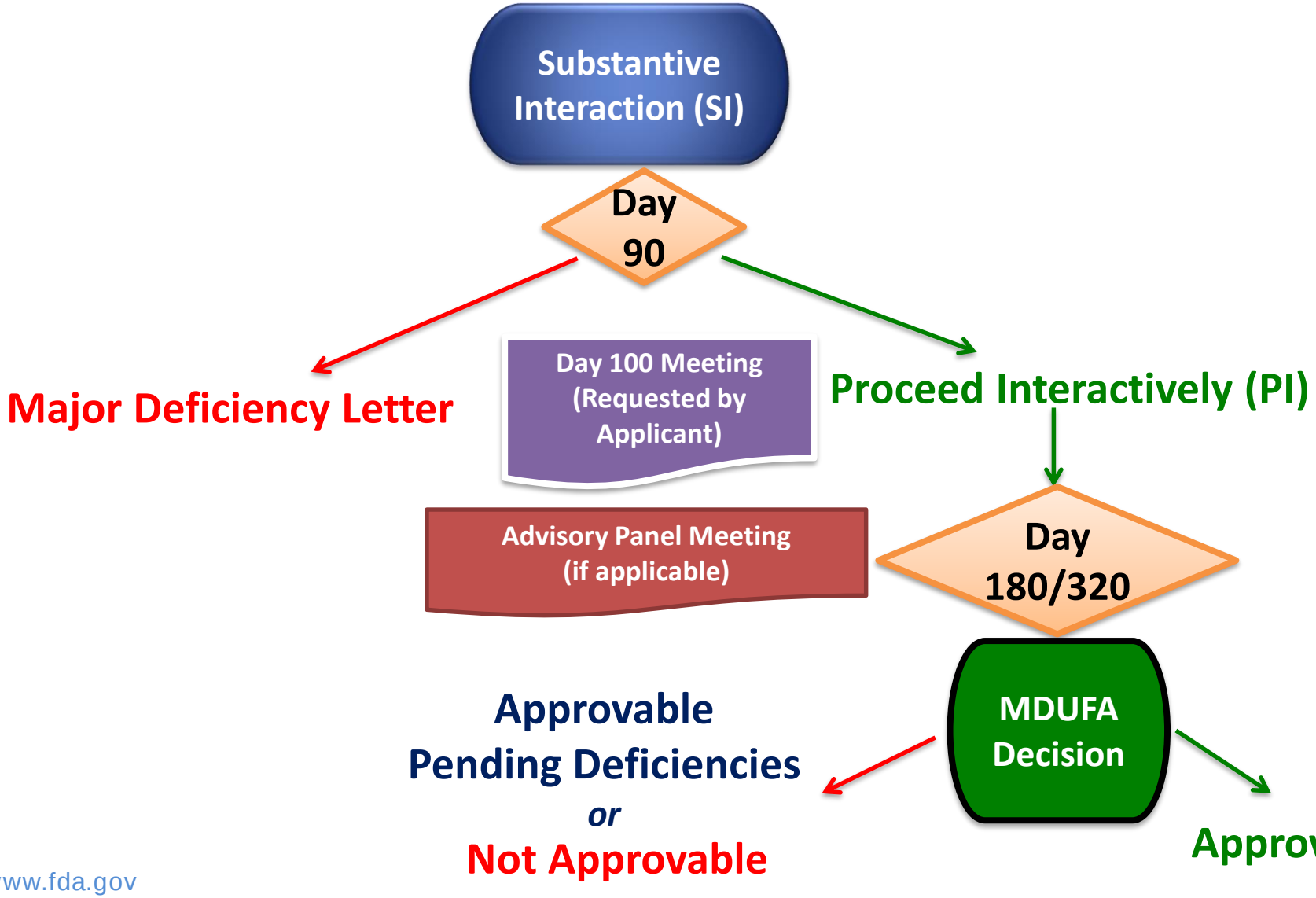
- Team Leader/Lead Reviewer
- Clinical
- Statistical
- Preclinical
- Engineering
- Animal Studies
- Biocompatibility

- 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

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
- **Open to the public**

Guidance: Amended Procedures for Advisory Panel Meetings

www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073722.htm

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 (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

What happens after the PMA is approved?

Post-Approval Annual Reports

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

21 CFR 814.84

Guidance: Annual Reports for Approved Premarket Approval Applications (PMA)

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

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

Guidance: Modifications to Devices Subject to Premarket Approval (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

- Be organized
- Be prepared
- Be 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***
  www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm296379.pdf

- **Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval**
  www.fda.gov/Downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm393994.pdf

Selected References

- **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**

  www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313368.pdf

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

  www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080190.htm

Summary

- A PMA is a marketing application for the highest risk of medical device that FDA regulates.
- A PMA provides reasonable assurance of safety and effectiveness of the device.
- A successful PMA review process involves a number of individuals and features collaboration between FDA and the applicant.

Summary

- There are continued regulatory requirements for an approved PMA
  - Post approval reports
  - Supplements
- A well-organized, complete application leads to an efficient review process.

Questions

Please complete the session survey:

surveymonkey.com/r/DEV-D1S07

Call to Action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