

Overview of Premarket Approval (PMA) Program

**FDA Small Business
Regulatory Education for Industry (REdI)
Silver Spring, MD
September 27, 2016**

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



Poll Question

DEV-D1S7-1

View Votes

Edit

End Poll

Have you had any prior experience with a Premarket Application (PMA)?

<input type="radio"/> Yes	<div></div>	0%	(0)
<input type="radio"/> No	<div></div>	0%	(0)
<input checked="" type="radio"/> No Vote			

☒ Broadcast Results

Poll Question

DEV-D1S7-2

View Votes

Edit

End Poll

What role did you have with PMAs?

<input type="radio"/> Developer	<div></div>	0%	(0)
<input type="radio"/> Clinical Researcher	<div></div>	0%	(0)
<input type="radio"/> Non-clinical testing	<div></div>	0%	(0)
<input type="radio"/> Quality Assurance	<div></div>	0%	(0)
<input type="radio"/> Regulatory, Consultant	<div></div>	0%	(0)
<input type="radio"/> None	<div></div>	0%	(0)
<input checked="" type="radio"/> No Vote			

☒ Broadcast Results

Learning Objectives

- Define PMA and what should be included in a PMA application
- Describe the FDA review process
- Understand the Post Approval regulatory requirements
- Identify some best practices for a successful PMA submission and review process

Regulatory Background

Regulatory Framework: Law & Regulations

- **Section 515**, Federal Food, Drug, and Cosmetic Act (FD&C Act)
- **Part 814**, Title 21 Code of Federal Regulations (CFR)



Class III Medical Devices: Highest Risk

- Insufficient information exist to assure safety and effectiveness, solely through general or special controls
- Class III is the highest risk category
- Support or sustain human life, substantial importance in preventing impairment of human health, potential for unreasonable risk of illness or injury
- Subject to PMA Approval

Examples of Class III Medical Devices



**Implantable Cardioverter
Defibrillator (ICD)**



**Left Ventricular
Assist Device
(LVAD)**



Knee System



Cochlear Implants



Gastric Band

Content of PMA

Contents of PMA

- Name and address of applicant
- Table of contents
- Summary including:
 - Indication for use
 - Device description
 - Alternative practices and procedures
 - Marketing history
 - Conclusions
 - Summary of studies clinical and nonclinical



21 CFR 814.20

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

Contents of PMA (cont.)

- **Complete description of device and functional components or ingredients including:**
 - Diagrams
 - Properties
 - Principles of operations
- **Reference to performance standards**
- **Manufacturing**

Contents of PMA (cont.)

- Test reports, summaries and conclusion of all applicable **non-clinical studies** including :
 - Microbiological
 - Toxicological
 - Biocompatibility
 - Stress, wear
 - Shelf life
 - Other laboratory or animal tests as appropriate

Contents of PMA – Clinical Data

- Results of **clinical studies** including:
 - Clinical protocols
 - Number of investigators and subjects per investigator
 - Subject selection and exclusion criteria
 - Study population
 - Safety and effectiveness data
 - Adverse reactions and complications

Contents of PMA – Clinical Data (cont.)

- Patient discontinuation
- Patient complaints
- Device failures and replacements
- Tabulations of data from all subjects
- Case report form for each subject who died during a clinical investigation or who did not complete the investigation
- Results of statistical analyses
- Any other appropriate information

Contents of PMA (cont.)

- Bibliography
- Sample of device – if practical
- Proposed labeling
- Environmental assessment
- Financial certification or disclosure
- Information concerning uses in pediatric patients

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
 - Weighing any probable benefit against any probable risk.

513(a) Federal Food, Drug, and Cosmetic Act (FD&C Act)

[www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/
FDCActChapterVDrugsandDevices/default.htm](http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterVDrugsandDevices/default.htm)

Quiz

DEV-D1S7-3

View Votes

Edit

End Poll

Which of the following is NOT an example of valid scientific evidence?

<input type="radio"/> A well-controlled, randomized multicenter study conducted outside the US and conducted without an IDE	<div></div>	0%	(0)
<input type="radio"/> A well-controlled, randomized multicenter study with sites within and outside the US and conducted under an IDE	<div></div>	0%	(0)
<input type="radio"/> An isolated case report	<div></div>	0%	(0)
<input type="radio"/> A partially controlled, well-documented study	<div></div>	0%	(0)
<input checked="" type="radio"/> No Vote			

☐ Broadcast Results

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:

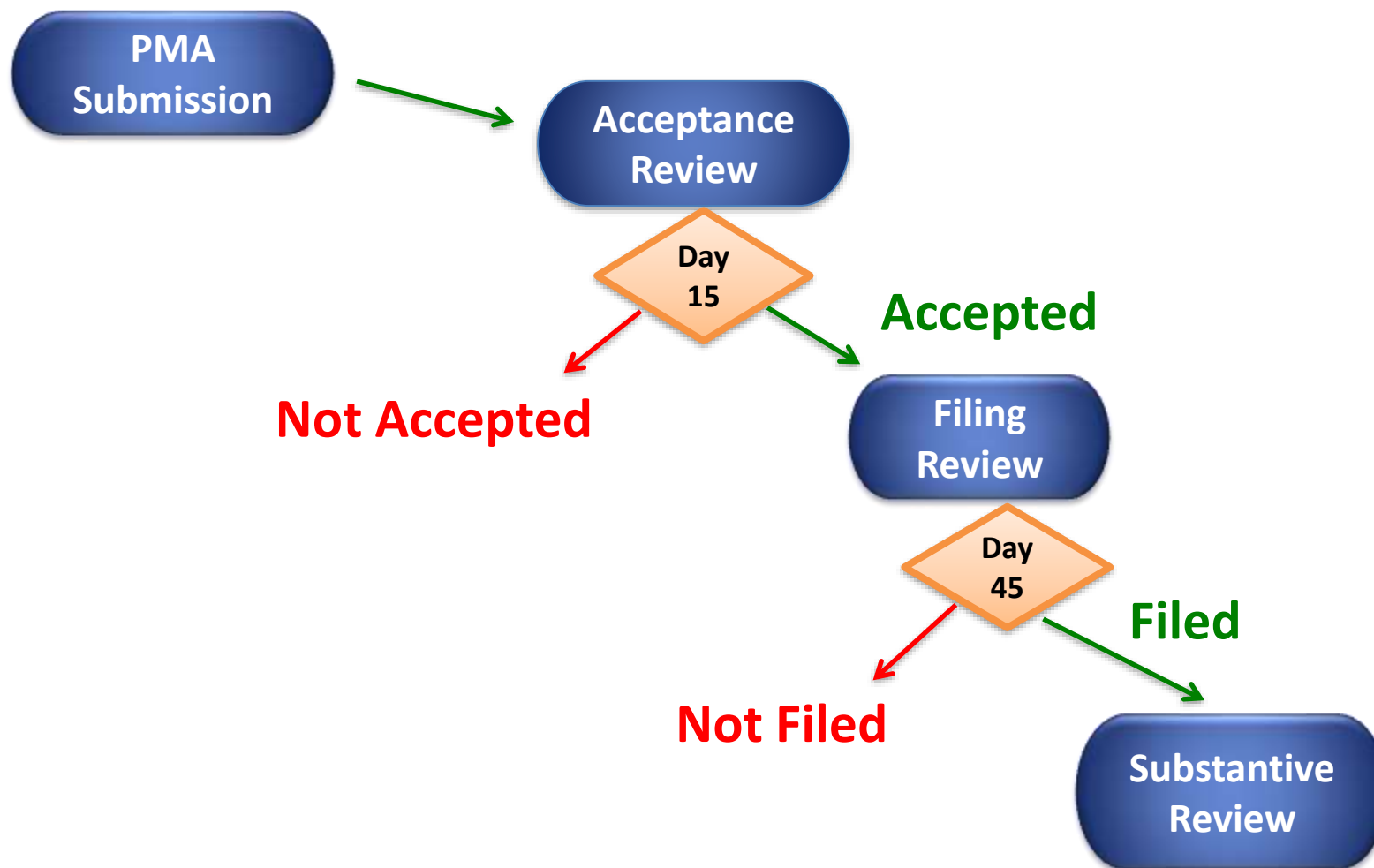
www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm267829.htm

PMA vs 510(k)

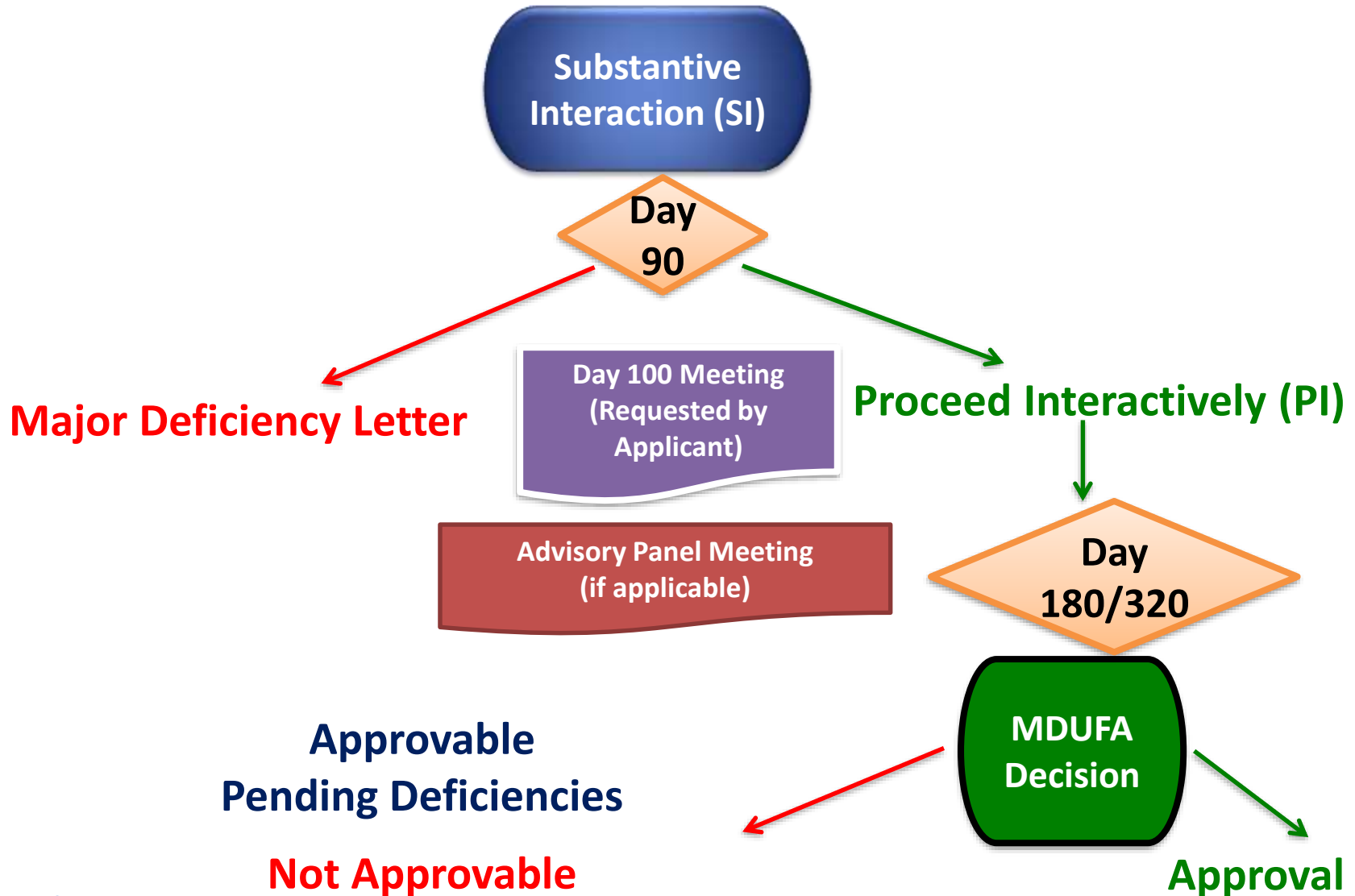
	PMA	510(k)
Device Class	Class III	Class I or Class II
Application	Stand-Alone	Substantial Equivalence (SE) to Predicate Device
Clinical Evidence	Almost 100% have Clinical Evidence	Approximately 10% have Clinical Evidence
FDA Review Days (calendar days)	180 days – no panel 320 days– if panel	90 days
Final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

PMA Review Process

PMA Review Process (1/2)



PMA Review Process (2/2)



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

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**
 - 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:**
 - FDA Team performs the in-depth Scientific, Regulatory, and Manufacturing Reviews
- **Interactive Process**
 - interact with applicant to address deficiencies that may likely be addressed by applicant in an appropriate timeframe
 - does not affect FDA review clock

Interactive Review: Applicant Best Practices

- Submit **well-organized** submission
- Provide complete and accurate **contact information**
 - List alternate contact
 - Foreign applicant should have a U.S. representative
- Provide a **complete response** to all deficiencies
 - Within FDA-allotted timeframe

**Guidance: Types of Communication During the Review of
Medical Device Submissions**

www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm341918.htm#s4

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

Day 100 Meeting

- **Purpose:**
 - Discuss review status
 - Discuss/Clarify outstanding deficiencies
- **Applicant Requests Meeting**
 - With original PMA or as amendment within 70 days of filing
 - Specify format of meeting (in person, teleconference, etc.)
- **FDA provides list of outstanding deficiencies**
 - Prior to meeting

Advisory Committee Review

- **Independent panel of experts**
Clinical practice, academia, statistics, industry and patients
- **Provide recommendations:**
 - 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
- Approvable Pending Deficiencies Letter:
 - Device can **not** be marketed
 - Identify clarifications/deficiencies that need to be addressed to make PMA application approvable
 - Common reasons: unresolved labeling; unresolved post-approval study design; and/or FDA has not determined that the manufacturing facilities, methods and controls are in compliance with the Quality System



FDA Review Determinations

- **Major Deficiency Letter:**
 - Device can **not** be marketed
 - Identifies deficiencies that cannot be adequately addressed interactively
- **Not Approvable Letter:**
 - Device can **not** be marketed
 - Identify deficiencies that need to be addressed to make the PMA application approvable
 - New clinical/preclinical data

PMA Approvals

www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/default.htm

The screenshot shows the FDA website header with the U.S. Department of Health & Human Services logo and the FDA logo. The main navigation bar includes links for Home, Food, Drugs, Medical Devices, Radiation-Emitting Products, Vaccines, Blood & Biologics, Animal & Veterinary, Cosmetics, and Tobacco Products. The page title is "Innova Vascular Self-Expanding Stent System - P140028". Below the title, there is a breadcrumb trail: FDA Home > Medical Devices > Products and Medical Procedures > Device Approvals, Denials and Clearances. The page is dated "Issued July 21, 2015". A list of links is provided: Approval Order, Summary, Labeling (Part 1), Labeling (Part 2), and Other Consumer Information. A note states: "This document is in a Portable Document Format (PDF). Acrobat Reader is required to read this document." The page was updated on August 27, 2015.

U.S. Department of Health & Human Services

U.S. Food and Drug Administration
Protecting and Promoting Your Health

A to Z Index | Follow FDA | En Español

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

Innova Vascular Self-Expanding Stent System - P140028

FDA Home > Medical Devices > Products and Medical Procedures > Device Approvals, Denials and Clearances

Issued July 21, 2015

- Approval Order
- Summary
- Labeling (Part 1)
- Labeling (Part 2)
- Other Consumer Information

This document is in a Portable Document Format (PDF). Acrobat Reader is required to read this document.

Updated August 27, 2015

Summary of Safety and Effectiveness (SSED)

- Summarizes basis for FDA's Decision and Review Analysis
- Provides comprehensive, detailed summary information of valid scientific evidence in application:
 - Device description
 - Engineering
 - Preclinical
 - Animal data
 - Clinical study

Conditions of Approval

- **General conditions**
 - Mandatory annual reporting
 - Mandatory reporting of medical device reports (MDRs) and product defects

- **Specific conditions that may be mandated on case by case basis**
 - Specific reporting requirements
 - Clinical updates to clinicians
 - Post-Approval Studies

Post-Approval Studies (PAS)

- **May be required as a condition of approval**
- **Reasons/Examples 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**
- **May be reviewed by Office of Surveillance and Biometrics (OSB) and/or Office of Device Evaluation (ODE)**

What happens after the PMA is approved?

Post-Approval Annual Reports

- Due **annually** on date of approval
 - E.g., if February 29, 2016 due by February 29, 2017; 2018
 - 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 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 Requiring a PMA Supplement

Changes affecting safety and/or effectiveness of the PMA-approved device

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 manufacturing process
- Revisions to a post-approval study plan/protocol

Types of Supplements

- **Panel-Track Supplement**
 - Indications for use
 - Contraindication changes that require minimal or no preclinical testing
- **Normal 180-Day Supplement**
 - Device design or performance
 - Labeling
- **Real-Time Supplement**
 - Minor device change
 - Review involves a single scientific discipline

**Guidance: Modifications to Devices Subject to Premarket Approval (PMA):
The PMA Supplement Decision-Making**

[www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/
guidancedocuments/ucm089360.pdf](http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm089360.pdf)

Types of Supplements

- **30-Day Notice, 135-Day Supplement**
 - Modifications to manufacturing process
- **Special PMA Supplement: Changes Being Effected**
 - Changes that enhance the safety of device
 - Can be implemented prior to FDA approval

Guidance for Industry and FDA Staff - 30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes

[www.fda.gov/medicaldevices/deviceregulationandguidance/
guidancedocuments/ucm080192.htm](http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm080192.htm)

Strategies for a Successful Submission



Successful Submission Strategies

3Bs

- Be organized
- Be prepared
- Be responsive



Be Organized

- **Well-organized submission**
- **Administratively and scientifically complete submission**
- **Contain:**
 - comprehensive table of contents
 - detailed sections
 - all test reports
 - labeled graphs/tables
 - consecutive pagination

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
- **Be in touch**
 - Discuss questions, concerns with lead reviewer
 - Have your subject experts available for consult with FDA as well
 - Plan on a Day 100 meeting- you can always cancel if it is not needed

Be Responsive

- **Be ready to interact on labeling**
 - Have your decision makers available for quick turnaround
- **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 class III medical devices in the United States.
- A PMA should contain all the content necessary to demonstrate the reasonable safety and effectiveness of the device.
- The PMA review process is a multidisciplinary collaborative interactive process.

Summary

- There are continued regulatory requirements for an approved PMA
 - Post approval reports
 - Supplements
- A well organized, complete application will assist the review process

Questions



Please complete the session survey:

surveymonkey.com/r/DEV-D1S7

Call to Action



