BEGINNING AT THE BEGINNING
Premarket Approval (PMA)

Quynh Hoang
Senior Regulatory Consultant
FDA & Life Sciences Team
Government Matters Practice

Disclaimer

The views expressed here are solely mine and not of my firm or any of its clients.

Outline

- Definitions
- When does PMA pathway apply?
- Why consider De Novo pathway first?
- What to provide in a PMA?
- How does FDA review a PMA?
- What submissions are required post-approval?

Definitions

- CFR ≡ Code of Federal Regulations (21 CFR)
- CRF ≡ Case Report Form
- FDCA ≡ Federal Food Drug & Cosmetic Act
- FY ≡ Fiscal Year is from Oct. 1st to Sept. 30th
- OCE ≡ Office of Communication and Education
- OPEQ ≡ Office of Product Evaluation and Quality
- OSEL ≡ Office of Science and Engineering Laboratories
- QSR ≡ Quality System Regulation
- Q-Sub ≡ Pre-submission feedback program

PMA Submissions

PATHWAY	FY2022*	
	CDRH	CBER
510(k)	3759	37
De Novo	77	3
Premarket Approval (PMA) Original PMAs and Panel-track Supplements	**45**	**2**
Humanitarian Device Exemption (HDE)**	1	0
Product Development Protocol (PDP) (3 completed since 1976)**	0	0
Device Emergency Use Authorization (EUA)***	~1000 as of May 31, 2022	-

*Fiscal year 2022 is from Oct. 1, 2021 to Sept. 30, 2022. Shown are the numbers received unless otherwise noted, in MDUFA IV Performance Report dated Mar. 31, 2023

**Number approved since pathway is not covered by User Fee Reports (number approved is usually smaller than number submitted.)

***Dr. Shuren on FDA Voices, May 31, 2022

When does PMA pathway apply?

Original PMA (when applicable)

Class III device (FDCA 513(a)(1)(C) and CFR 860.3 (c)(3)):

1. Not Class I: general controls are insufficient;
2. Not Class II: additional special controls are insufficient; and
3. One of the following:
    a. life-supporting,
    b. life-sustaining,
    c. of substantial importance in preventing impairment of human health, or
    d. if presents a potential unreasonable risk.

Original PMA (when applicable)

PMA is the “highest/most controlled” marketing pathway for a novel medical device.

Safety & Effectiveness of Novel Device Can Be Assured With:			
General Controls	X	X	X
Special Controls		X	
PMA-Controls			X
Marketing Pathway	**De Novo (Class I)**	**De Novo (Class II)**	**PMA (Class III)**

Original PMA (when applicable)

PMA is the “highest controlled” marketing pathway for a novel medical device.

PURPOSE	TYPE OF SUBMISSION	
	DE NOVO	PMA
New/Novel Device	ORIGINAL	ORIGINAL
Change to indications	New Indications: New 510(k)	PANEL-TRACK SUPPLEMENT
Manufacturing Change(s) (no fee for site change)	Follows 510(k) Process	30-DAY NOTICE
		135-DAY SUPPLEMENT
Minor Design or Labeling Change(s)		REAL-TIME SUPPLEMENT
Significant Design or Labeling Change(s)		180-DAY SUPPLEMENT
Periodic Reporting	Not applicable	ANNUAL REPORT

Why consider De Novo pathway first?

Why consider De Novo first?

Compared to the PMA pathway, De Novo pathway will require less money over the life span of the device:

PURPOSE	DE NOVO		PMA		
	Standard	Small business*	Type of submission	Standard	Small business*
New/Novel Device	$132,464	$33,116	ORIGINAL	$441,547	$110,387
Change to indications	New Indications: 510(k)		PANEL-TRACK SUPPLEMENT	$353,238	$88,309
Manufacturing Change(s) (no fee for site change)	Follows 510(k) Process		30-DAY NOTICE	$7,065	$3,532
			135-DAY SUPPLEMENT	No fee (already paid with the 30-day notice)	
Minor Design and/or Labeling Changes			REAL-TIME SUPPLEMENT	$30,908	$7,727
Significant Design and/or Labeling Change(s)			180-DAY SUPPLEMENT	$66,232	$16,558
Periodic Reporting	Not applicable		ANNUAL REPORT	$15,454	$3,864

Shown are FY2023 user fees
*Requires a Small Business Designation

What to provide in a PMA?

Original PMA (contents)

Contents (FDCA 515(c) and CFR 814.20)

1. Summary of safety and effectiveness data (SSED);
2. Indications;
3. Device Description;
4. Preclinical data;
5. Clinical data (valid scientific evidence);
6. Labeling;
7. Manufacturing information;
8. Post-approval study proposal;
9. …

Original PMA (contents)

Clinical data-valid scientific evidence (FDCA 513(a)(3) and CFR 860.7(c)(2)):

- well-controlled investigations;
- partially controlled studies (in CFR);
- studies and objective trials without matched controls (in CFR);
- well-documented case histories conducted by qualified experts (in CFR); and/or
- reports of significant human experience with a marketed device (in CFR).

And, data may be from Outside U.S. (CFR 814.15).

How does FDA review a PMA?

Original PMA (FDA review process)

1. Pre-PMA Q-Sub (within 75 days)
2. Acceptance Review (within 15 days – FDA review clock starts here at receipt date if PMA is accepted and filed.)
3. Filing Review (within 45 days of receipt)
4. Substantive Review (within 90 days of receipt)
    a. Major deficiency letter
        i. Stops FDA review clock;
        ii. Requires a Major Amendment with complete response to restart review clock.
    b. Minor deficiency email/call
5. Day 100 Meeting (if applicant requested)
6. Advisory Panel Meeting (as needed)
    a. Major deficiency letter, or
    b. Minor deficiency email/calls
7. Decision
    a. No panel meeting (within 180 days)
    b. Panel meeting (within 320 days)

Original PMA (FDA review process, cont'd)

Advisory Panel Meeting (FDCA Sec. 515(c)(3)(B) & (f)(2)(B) and 21 CFR 814.44 and 814.116)

FDA convenes panel meeting when:

- Device is first of its kind;
- FDA has concerns with performance, outcomes or study conducts; and/or
- PMA applicant requests meeting.

Original PMA (FDA review team)

Engineer (BioMed)

Lead reviewer/ Project manager

Statistician

Engineer (Mechanical)

Scientist (Toxicologist)

Consumer safety officer

OSEL Scientist

Epidemiologist

Medical officer

OCE Communication specialist

Scientist (Microbiologist)

Original PMA (FDA review considerations)

PMA approval is based on (FDCA 515(d)(1)(A)(i) and 814.44 (d)(1)):

1. Reasonable assurance of device safety;
2. Reasonable assurance of device effectiveness;
3. Good manufacturing practices (FDCA 520(f) and CFR 820);
4. True and accurate labeling (per CFR 801 or 809); and
5. …

Original PMA (FDA review considerations, cont'd)

- Reasonable Assurance of Safety: when "it can be determined, based upon valid scientific evidence, that the probable benefits … outweigh any probable risks." (21 CFR 860.7(d)(1))

- Reasonable Assurance of Effectiveness: when "it can be determined, based upon valid scientific evidence that in a significant portion of the target population… the use of the device for its intended uses … will provide clinically significant results." (21 CFR 860.7(e)(1))

Original PMA (FDA review considerations, cont'd)

Other Approval Considerations for PMA Order:

- Extrapolate to pediatric population (FDCA 515A (b))
- Conditions of approval (CFR 814.82)
  - Restrictions of the sale, distribution or use (FDCA 515(d)(1)(B)(ii) and 520(e))
  - Post-approval study
  - Post-market surveillance (522) study (FDCA 522)
  - Tracking (FDCA 519(e) and CFR 821)
  - …

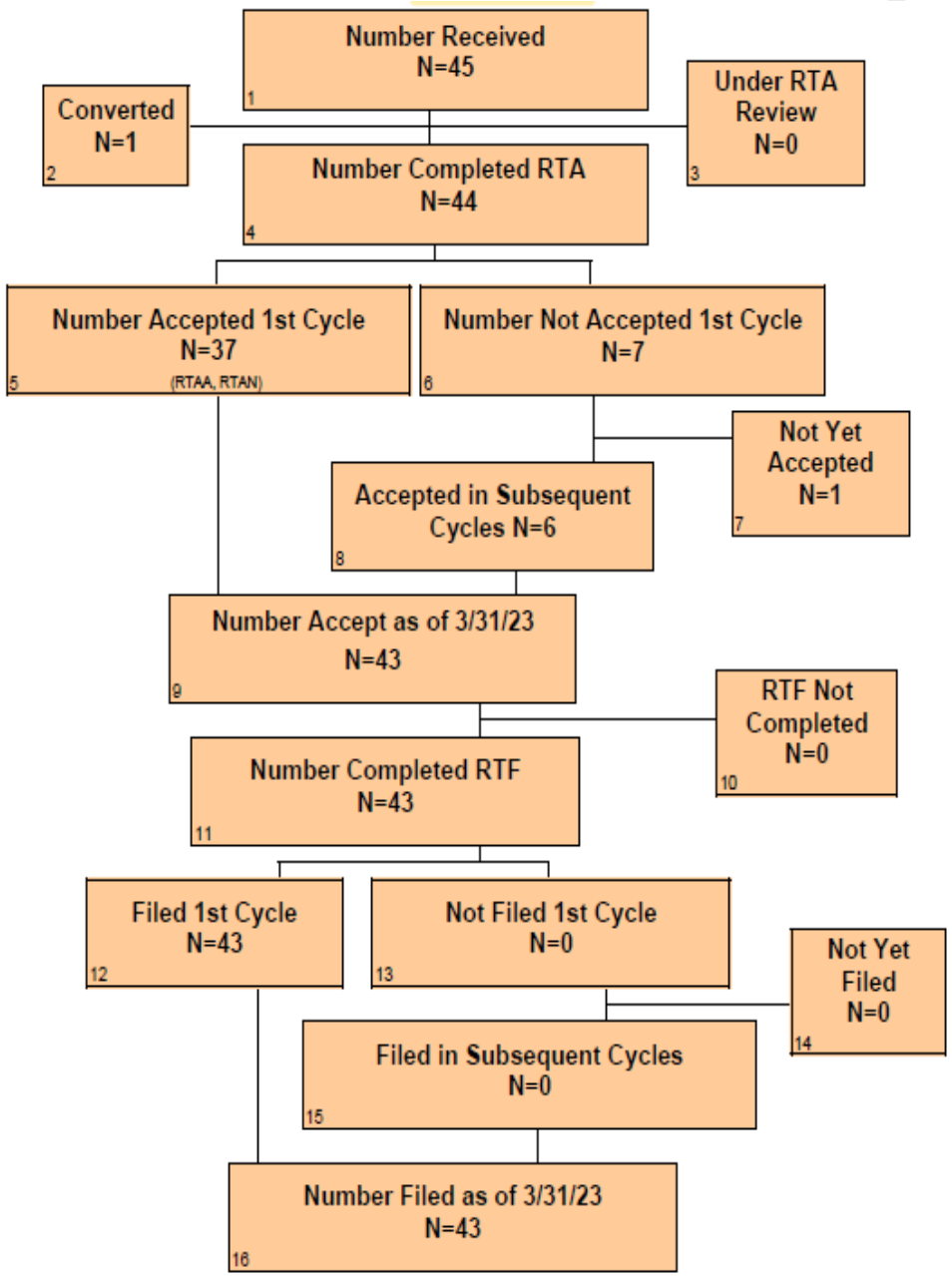
FDA Decision On PMA

- Approval with conditions (21CFR 814.44 (d))
- Approvable pending… (21CFR 814.44 (e))
  - QSR inspection
  - Agreement to approval conditions
  - …
- Not approvable (21CFR 814.44 (f))
  - major deficiencies
- Denial of approval (21CFR 814.45)

FDA Decisions On PMA

FY 2022 PMA Originals and Panel-track Supplements

(from MDUFA IV Performance Report dated Mar. 31, 2023)



FDA Decisions On PMA

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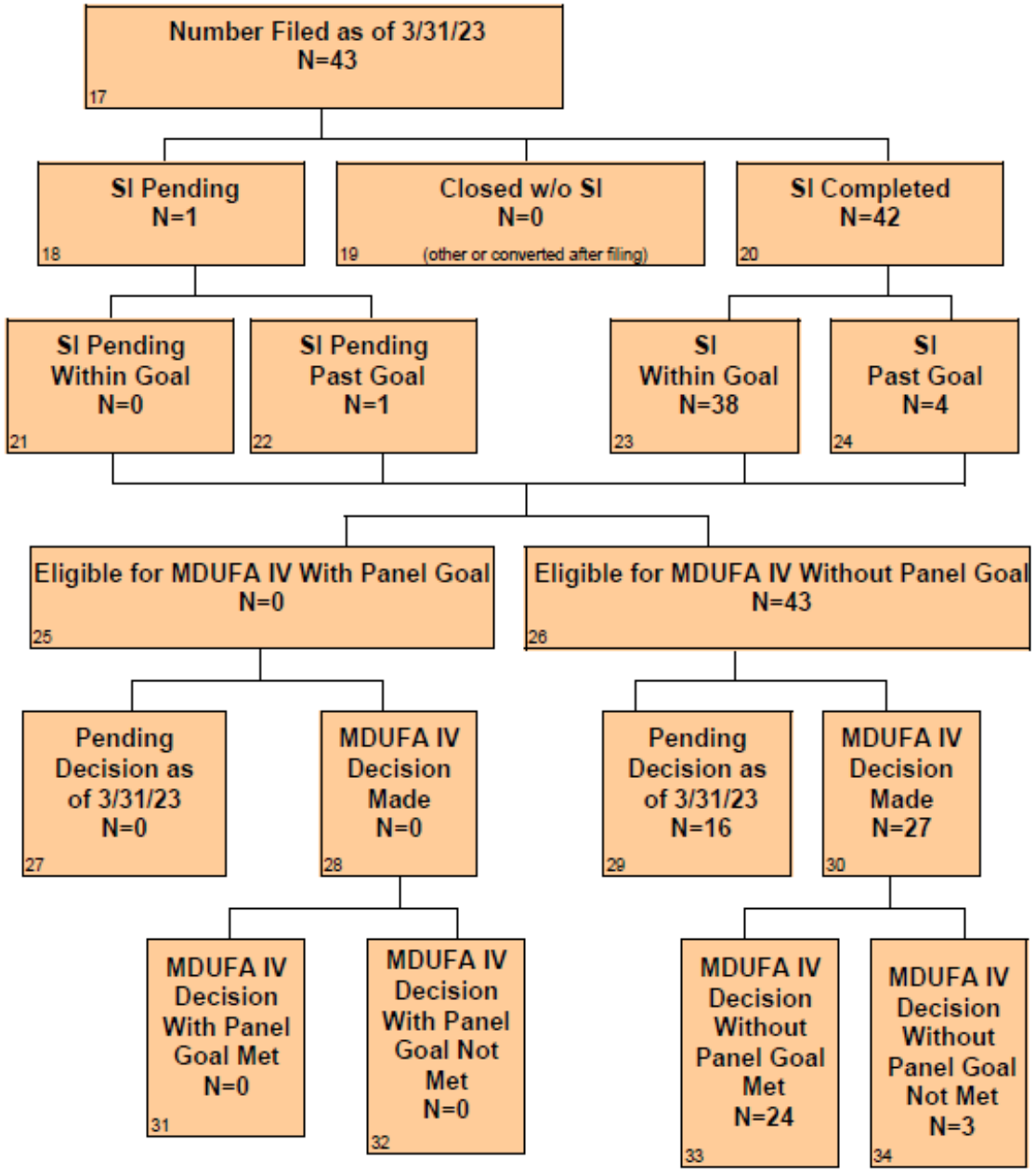


What submissions are required post-approval?

PMA Submissions Post-Approval
(FDCA 515(d)(6) and CFR814.39)

- Changes
  - Special supplement (certain labeling and manufacturing changes - 30 days)
  - 30-day notice (minor manufacturing change)
  - 135-day supplement (manufacturing change not qualified for 30-day notice)
  - Real time supplement (minor change - 90 days)
  - 180-day supplement (significant change(s))
  - Panel-Track supplement (new indication – same clock as an Original PMA)
- Annual reporting (regular and post-approval study)

Thanks!

Quynh Hoang
Senior Regulatory Consultant
FDA and Life Sciences

qhoang@kslaw.com
+1 202 626 2939

Development of a Premarket Approval (PMA) Submission Strategy

May 23, 2023

Stacy Monza
Biomedical Engineer
PMA, HDE, Q-Sub, and Device Lifecycle Tracking Team
Division of Submission Support | Office of Regulatory Programs
Office of Product Evaluation and Quality
CDRH | Food and Drug Administration
stacy.monza@fda.hhs.gov

Outline

- Class III devices
- PMA Review and Approval
- Product Definition
- Development of Testing Requirements and Strategy
- Early Interactions
- PMA Submission Content
- Original PMA Review
- 100 Day Meeting and Modular PMAs
- Planning for Product Iterations (Modifications to PMA Approved Devices)
- Types of PMA submissions
- PMA User Fees/MDUFA Goals
- Available Resources

PMAs Required for Class III Medical Devices

Class III devices (21 USC 360c(a)(1)(C)(ii)) are those that:

PMA Review and Approval

PMA **approval** is based on a determination by FDA that the PMA contains sufficient **valid scientific evidence** to assure that the device is **safe and effective** for its intended use[1]:

Product Definition

Device Design

Product Definition

Indications for Use

Product Definition

Claim(s)

Development of Testing Requirements and Strategy

- Comprehensive risk assessment / FMEA
- Risk mitigation plan
- Device evaluation

Before Pre-Market Studies are Conducted:

To Support an IDE Submission:

IDE to Marketing Application Issues can be Mitigated

- Make sure your requested sample size accounts for worst case attrition
- Audit sites frequently to minimize deviations or missed data
- Consider consenting patients for long-term follow-up (post-approval option)
- Be aware of “Future Concerns” and address them early

During an IDE, you may have:

Content To Be Included in a PMA Submission

Table of Contents, Page Numbers, Divide submission by review area

Summary in sufficient detail:

Helpful Guidance Documents

Complete description of:

- The device, each functional component, properties of the device relative to the indications, principles of operation, methods, facilities, and controls used for manufacture, processing, packaging, storage, and installation..

Technical sections in sufficient detail of non-clinical and clinical testing

Pre-submission, IDE, Breakthrough, & communication history

Device, protocol change history

Most recent versions of protocols and labeling

PMA Pediatric Information is Required

Original PMA Review - Summary of Review Timelines

Procedures for PMA review defined by 21 CFR 814.44

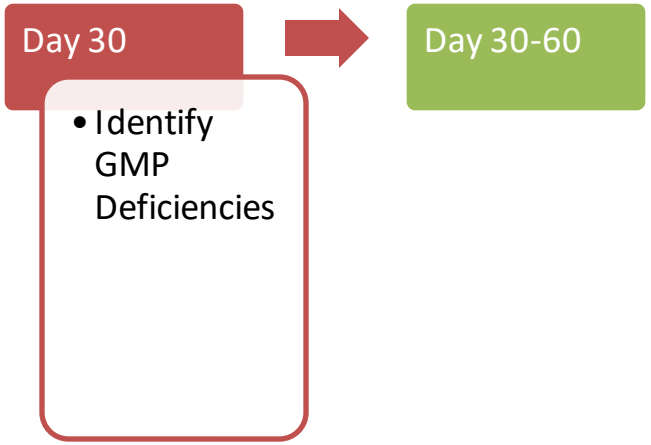
Review Timelines and Decision Points

Original PMA – GMP review

Sponsor must follow quality systems regulations (QSR) – 21 CFR 820

Desk review of GMP documentation

GMP Review Timeline Is Independent of Device Review



Original PMA – BIMO review

OCEA / Bioresearch monitoring (BIMO)

Original PMA – Amendments

Amendments may be submitted per 21 CFR 814.37

Unsolicited major amendments (UMAJ) add time to the FDA review clock

100 Day Meeting

Meeting with sponsor 100 days from filing date of PMA

- Request should come in no later than 70 days from filing

Meeting should include:

Modular PMAs

Sponsor and FDA agree upon a "shell" (logged in as MYYXXXX/M000)

Sections of PMA submitted sequentially

- 90 day review clock per module

Acceptance or Deficiency letter is issued

- Response to deficiency submitted as an amendment (90 day review clock)

Converted to original PMA (or HDE) when final module is received

Helpful Guidance Document

Important Premarket Submission Considerations

Review all relevant guidance documents (cross-cutting and device-specific)

Be upfront

- The submitted evidence is rarely perfect, clearly identify issues and present justifications for acceptability

Be in touch with the Lead Reviewer

- The lead reviewer should be primary contact unless other arrangements are made with consulting reviewers

Be responsive

During the PMA Review, You Should

- Be prepared

Advice for a PMA Review

Plan for the possibility of a Panel meeting

Work collaboratively with team to establish PAS protocol, enrollment milestones, and study completion timelines.

Some Common Pitfalls During Review

- Administrative Issues
- Product description insufficient or inconsistencies throughout document
- Supportive data insufficient or missing without rationale
- Inadequate responses to data requests
- Prior interactions / discussions not addressed
- Poor communication

My PMA is Approved, Now Can I Relax?

Unfortunately, the answer is no

There are annual reporting requirements

What to do with Post-Approval Product Iterations (Modifications)

Supplements (21 CFR 814.39)

Panel Track Supplement

Defined as[1]:

- "a supplement to an approved premarket application or premarket report under section 515 that requests a **significant** change in design or performance of the device, or a **new indication** for use of the device, and for which **substantial** clinical data are necessary to provide a reasonable assurance of safety and effectiveness."

Generally new indications for an existing device

Review process almost identical to an original PMA

May or may not go to panel

180 day review clock, substantive interaction (SI) by day 90.

Acceptance and Filing Review is necessary.

1. 737(4)(B) of the FD&C Act or 21 US 379i(4)(B)

180 Day Supplement

Defined as[1]:

- "a supplement to an approved premarket application or premarket report under section 515 that is not a panel-track supplement and requests a significant change in components, materials, design, specification, software, color additives, or labeling."

Confirmatory clinical data only (e.g., limited number of patients, shorter study duration, and/or subset of endpoints)

Changes may include:

Real-Time Supplement

Defined as[1]:

- "a supplement to an approved premarket application or premarket report under section 515 that requests a minor change to the device, such as a minor change to the design of the device, software, sterilization, or labeling, and for which the applicant [PMA holder] has requested and the agency has granted a meeting or similar forum to jointly review and determine the status of the supplement."

Used for minor changes, including:

30 Day Notice

Authorized[1] and Defined[2]

Appropriate when changes, which could affect the safety or effectiveness of the devices, include changes to the manufacturing procedure or changes in the method of manufacture

Not appropriate when there are changes to:

“Special PMA Supplement – Changes Being Effected”

- 21 CFR 814.39(d)
- Labeling

Site Change Supplement

After approval of a PMA, an applicant shall submit a PMA supplement for review and approval by FDA before making a change that affects the safety or effectiveness of the device, including a change that uses a different facility or establishment to manufacture, process, or package the device[1]:

Are 180-day supplements

Includes those that require pre-approval inspection, as well as those that do not

No User Fee

Helpful Guidance Document

PMA Annual Reports are also used to identify changes

Per 21 CFR 814.84, reports must include:

PMA Annual Reports can include changes without a supplement

21 CFR 814.39(b) allows changes without a supplement

- "…if the change does not affect the device's safety or effectiveness and the change is reported to FDA in postapproval periodic reports required as a condition to approval of the device, e.g., an editorial change in labeling which does not affect the safety or effectiveness of the device.

Applicant should provide:

Post-Approval Study (PAS) Reports

Typically required every 6 months for first two years, annually thereafter

May include:

Post-Approval Supplements

Changes to Post-Approval Study Protocol

No User Fee

FY23 User Fees for PMA Submission Types

Application Type	Standard Fee	Small Business Fee†
510(k)	$19,870	$4,967
513(g)	$5,961	$2,980
PMA, PDP, PMR, BLA	$441,547	$110,387
De Novo Classification Request	$132,464	$33,116
Panel-track Supplement	$353,238	$88,309
180-Day Supplement	$66,232	$16,558
Real-Time Supplement	$30,908	$7,727
BLA Efficacy Supplement	$441,547	$110,387
30-Day Notice	$7,065	$3,532
Annual Fee for Periodic Reporting on a Class III device (PMAs,PDPs, and PMRs)	$15,454	$3,864

1st original PMA by qualifying small business granted one-time waiver of user fee

https://www.fda.gov/industry/fda-user-fee-programs/medical-device-user-fee-amendments-mdufa

Summary of PMA MDUFA IV & V Performance Goals

Submission Type	Action	FDA Review Days	Percent of Submissions to Meet FDA Days	
			MDUFA IV	MDUFA V (FY23-FY27)
Original PMAs & Panel-Track Supplements	Substantive Interaction	90	95%	95%
	Decision if No Panel	180	90%	90%
	Decision With Panel	320	90%	90%
	Decision Following Panel	60	As resources permit	
	Response to Approvable	60	As resources permit	
180-Day PMA Supplements	Substantive Interaction	90	95%	95%
	Decision	180	95%	95%
Real-Time PMA Supplements	Decision	90	95%	95%

Note, there are more MDUFA V goals than are listed here.

Some Important PMA Related Guidance Documents, but NOT all of them

Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device PMAs, De Novo Classifications, and HDEs (Aug 30, 2019)	• https://www.fda.gov/media/115672/download
Factors to Consider When Making Benefit-Risk Determinations in Medical Device PMA and De Novo Classifications Guidance (Aug 30, 2019)	• https://www.fda.gov/media/99769/download
Breakthrough Device Program Guidance (Dec 18, 2018)	• https://www.fda.gov/media/108135/download
Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process Guidance (Dec 11, 2008)	• https://www.fda.gov/media/73328/download
Guidance on PMA Interactive Procedures for Day-100 Meetings and Subsequent Deficiencies (Feb 19, 1998)	• https://www.fda.gov/media/72655/download
Medical Device Accessories – Describing Accessories and Classification Pathways (Dec 20, 2017)	• https://www.fda.gov/media/90647/download
eCopy Program for Medical Device Submissions Guidance (Apr 27, 2020)	• https://www.fda.gov/media/83522/download
Supplements for Approved PMA or HDE Submissions During COVID-19	• https://www.fda.gov/media/138265/download

Additional PMA Team Members

Contact Information

Division of Consumer and Industry Education

U.S. FOOD & DRUG ADMINISTRATION

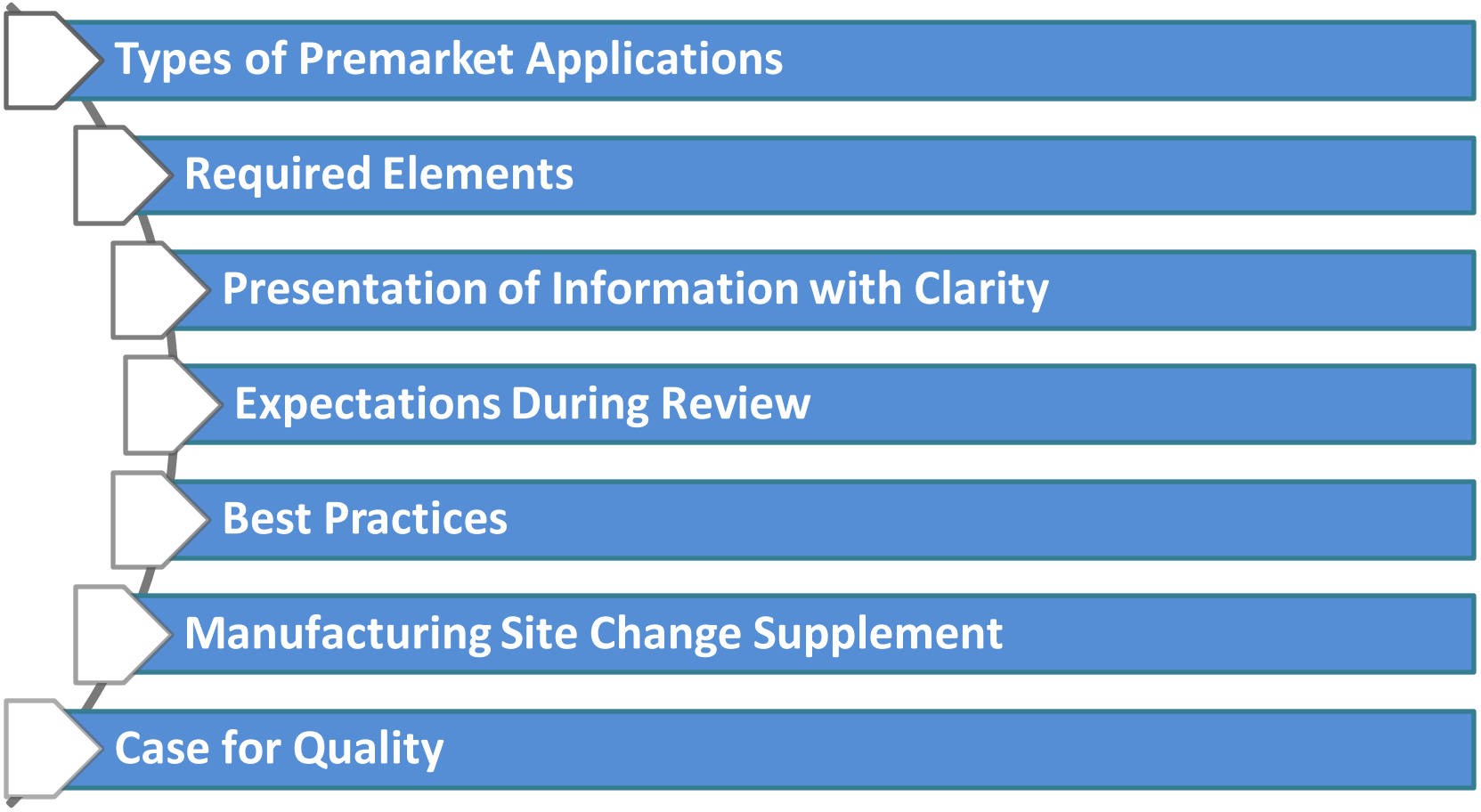
Mechanics of PMA Quality System Submission Development and Review

Jhumur D. Banik, M.S.
Policy Analyst, Biomedical Engineer

May 23, 2022

PMA, HDE, Q-Submission and Device Tracking Lifecycle Team
Division of Submission Support (DRP1)
Office or Regulatory Programs (ORP)
Office of Product Evaluation and Quality (OPEQ)
Center for Devices & Radiological Health (CDRH)

Objectives


Types of Premarket Applications
Required Elements
Presentation of Information with Clarity
Expectations During Review
Best Practices
Manufacturing Site Change Supplement
Case for Quality

Code of Federal Regulations & Federal Food, Drug, and Cosmetic Act

- Medical device premarket applications should be submitted in accordance with section 515(c)(1) of the FD&C Act.
- The regulation governing premarket approval is located in Title 21 Code of Federal Regulations (CFR) Part 814, Premarket Approval.
- A class III device that fails to meet PMA requirements is considered to be adulterated under section 501(f) of the FD&C Act.

Types of Premarket Applications

- Traditional Premarket Approval (PMA)
- Modular PMAs
- Humanitarian Device Exemptions (HDEs)

Types of Premarket Applications

- ***Traditional Premarket Approval (PMA)***
  - Complete PMA application is submitted to FDA for review all at once.
  - Generally used if the device has already undergone clinical testing and has been approved in a country with established medical device regulations.
- Modular PMAs
- Humanitarian Device Exemptions (HDEs)

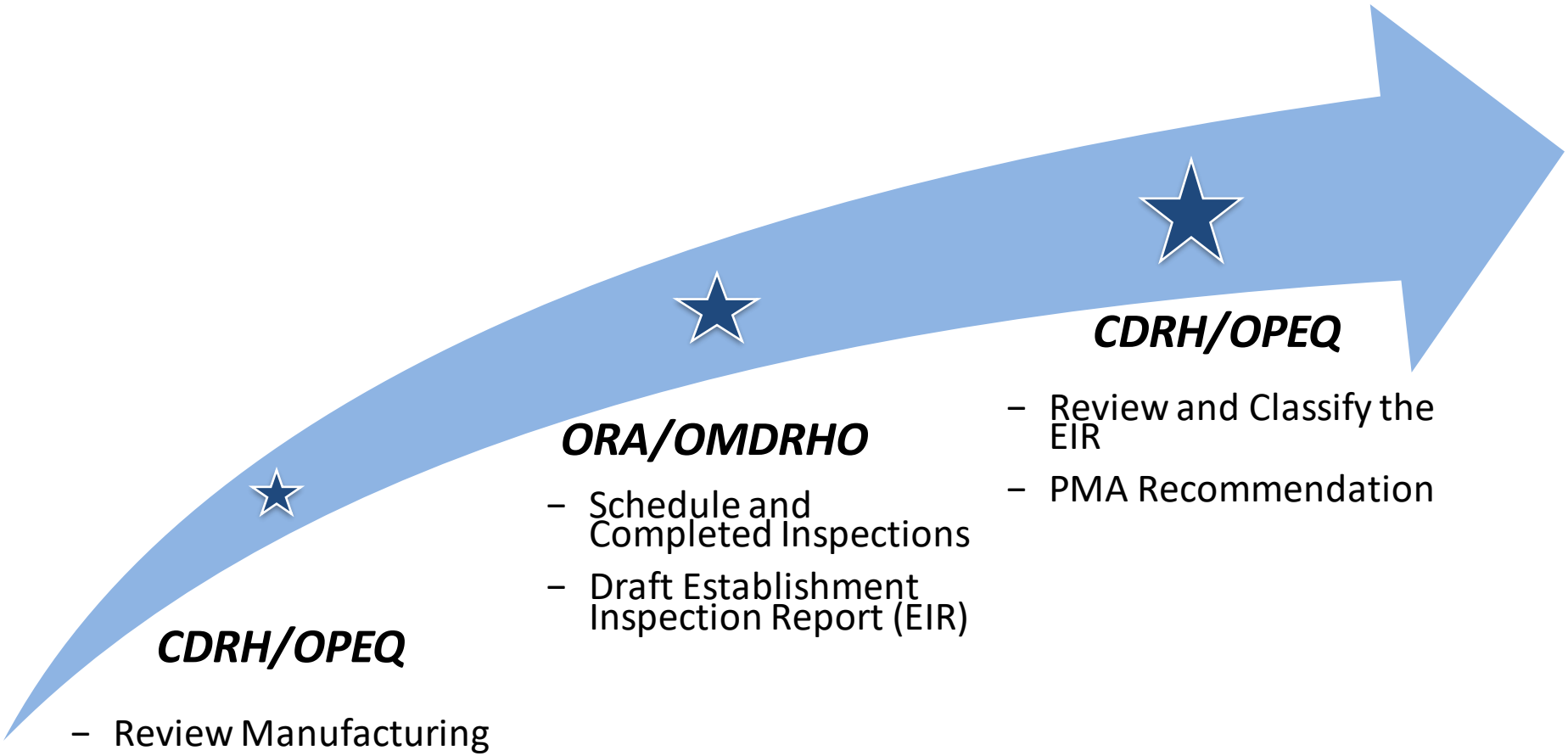
Types of Premarket Applications

- Traditional Premarket Approval (PMA)
- ***Modular PMAs***
  - Contents are broken down into well-delineated components (or modules) and each component is submitted to FDA for review as soon as the applicant has completed the module.
- Humanitarian Device Exemptions (HDEs)

Types of Premarket Applications

- Traditional Premarket Approval (PMA)
- Modular PMAs
- ***Humanitarian Device Exemptions (HDEs)***
  - An approved HDE authorizes marketing of the humanitarian use devices (HUD).
  - HUD is a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year
  - HDE application is similar in both form and content to a PMA application, but is exempt from the effectiveness requirements of a PMA.

Major Steps for PMA



CDRH/OPEQ

- Review Manufacturing Information
- Generated Inspection Requests

ORA/OMDRHO

- Schedule and Completed Inspections
- Draft Establishment Inspection Report (EIR)

CDRH/OPEQ

- Review and Classify the EIR
- PMA Recommendation

CDRH/OPEQ Review: Guidance Document

- Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff, February 3, 2003
- Consistent with QS regulation requirements (21 CFR 820) and is divided into sections:
  - Design Controls
  - Manufacturing Controls
- Ensures that the premarket submissions comply with the content requirements (21 CFR 814.20(b)(4)) .

CDRH/OPEQ Review: Guidance Document

- This guidance is aligned with the "systems approach" embraced by CDRH and the medical device industry, that is being used in the Quality System Inspection Technique (QSIT) implemented on January 1, 2000.

Guidance Document Format

- The information in this guidance is provided in a numbered and bulleted outline format and provides a recommended format for the submission.
  - Numbers – information to provide
  - Bullets – criteria against which the information is evaluated

Organizing Manufacturing Section

To Start

Organizing Manufacturing Section

- Two principal component sections
  - Design Control information
  - Information on other key procedures (mostly manufacturing)
- FDA guidance asks mostly for procedures.
- In addition to procedures, you can submit a narrative summary of the procedures.
- Identify location of attached procedures.
- Submit separate volumes for different manufacturing sites or vendors.

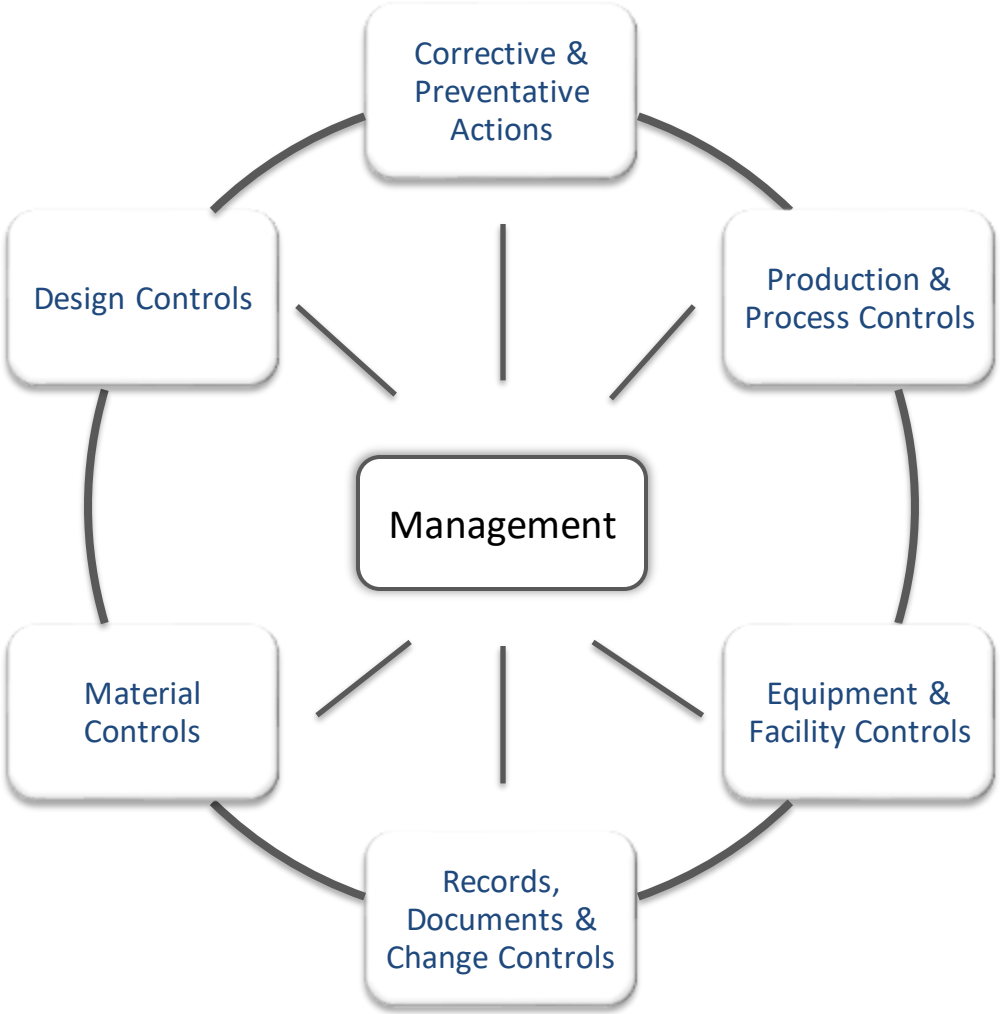
Important Information: Cover Letters

- Identification elements:
  - Full name and street address (no P.O. Box number),
  - Telephone number (with area code),
  - FDA Facility Establishment Identifier (FEI) or registration number, and
  - Relationship of (each) manufacturing facility to applicant.

Important Information: Cover Letters

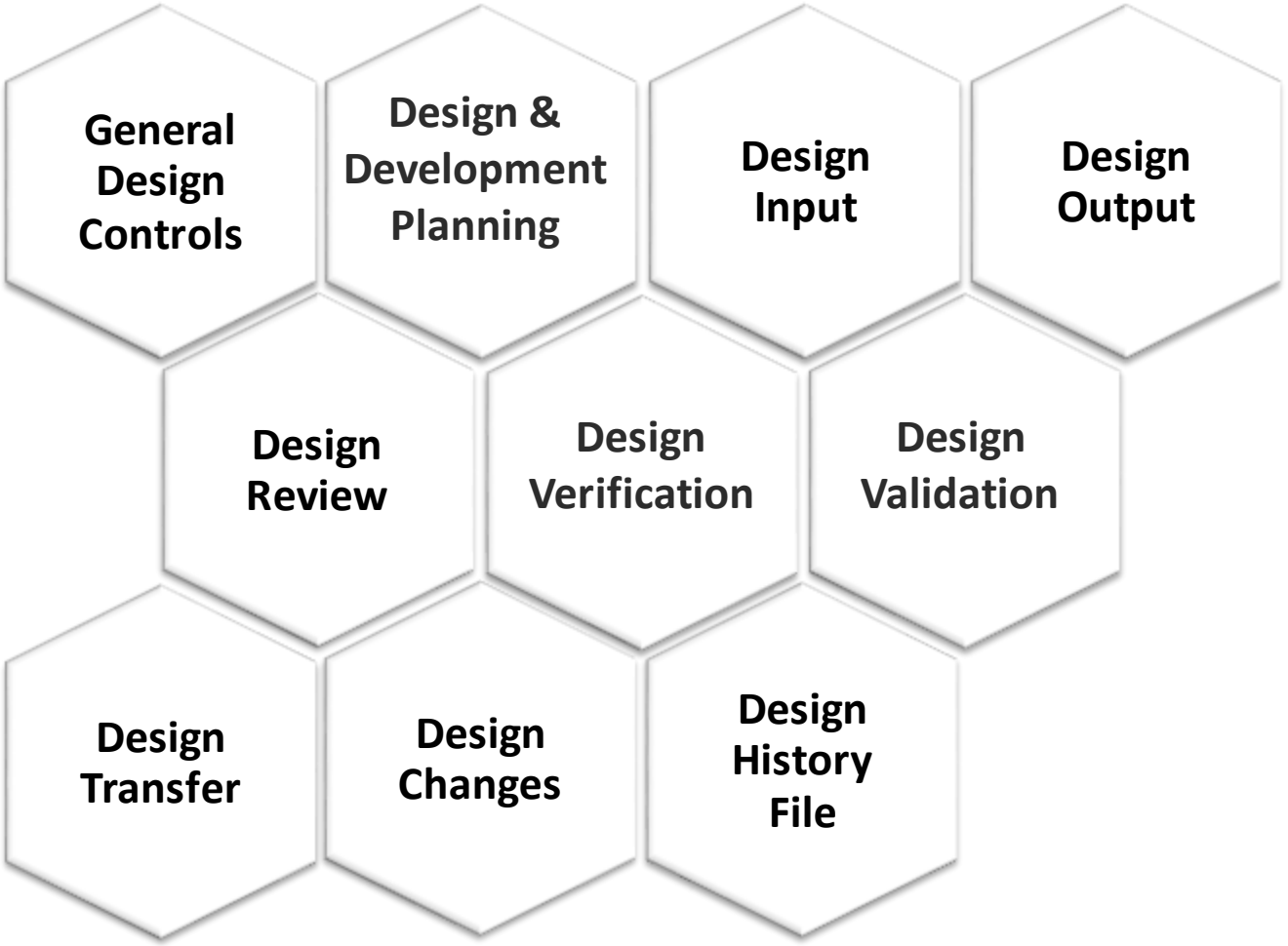
- Contact person (and alternates) and their telephone number(s).
- The date the site(s) will be ready for inspection.
  - The location and affiliation information will help CDRH determine the appropriate facilities to be inspected under the preapproval process.

7 Subsystems of the Quality System



Organizing the Manufacturing Section

Design Controls (21 CFR 820.30)



Example of Design Control Information

Design Output, 820.30(d)

- You should provide a copy of the procedure(s) used to define and document design output in terms that allow an adequate and measurable evaluation of conformance to design input requirements for the device under review.

- Provide a list of the design outputs you consider essential for the proper functioning of the device for the device under review.

Example of Design Control Information

Design Output, 820.30(d)

- Your procedure(s) should contain or refer to design output acceptance criteria.

- Your procedure(s) should explain the mechanism used to ensure that you identify those design outputs that are essential for the proper functioning of the device.
  - Your identification of essential design outputs will help us determine the adequacy of your design verification and design validation.

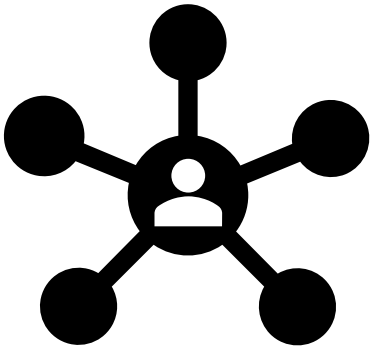
Example of Design Output Deficiency

Your firm provided corporate work instruction and procedure, WI Corporate Design Outputs, XXXXXX, and Corporate SOP Change Request Approval Matrix, XXXXXX. These documents are high level procedures for design output activities and review and approval of design outputs. However, these documents do not list design outputs that are considered essential for the proper functioning of the device under review and do not contain or refer to design output acceptance criteria specific to the device. Please include these elements in your response.

Organizing Manufacturing Section

- Quality System Manual (§820.20)
  - Management Review (§820.20[c])
  - Quality Audits (§820.22)
- Purchasing controls (§820.50)
- Production and Process Controls (§820.70)
- Inspection, Measurement and Test Equipment (§820.72)
- Process Validation (§820.75)
- Receiving Acceptance Activities (§820.80)
- Final Acceptance Activities (§820.80(d))
- Non-conforming Product (§820.90)
- Corrective and preventive action (CAPA) (§820.100)
- Complaint files (§820.198)
- Servicing (§820.200)
- Production Flow Diagram

Example of Manufacturing Information



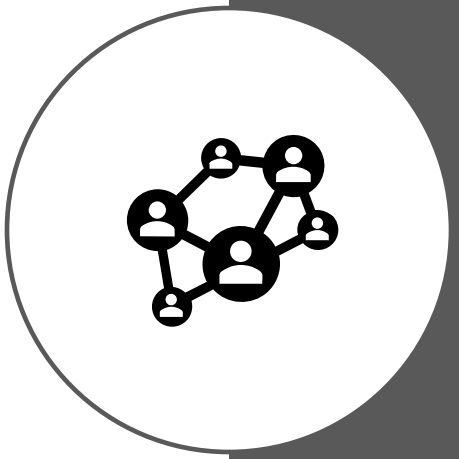
Purchasing Controls, 21 CFR 820.50

- You should provide a copy of the procedure(s) for purchasing controls. This is especially important if you use a contract design service or contract manufacturer(s) for the device under review. The controls applicable to these suppliers should be specified.

Example of Manufacturing Information

Purchasing Controls, 21 CFR 820.50

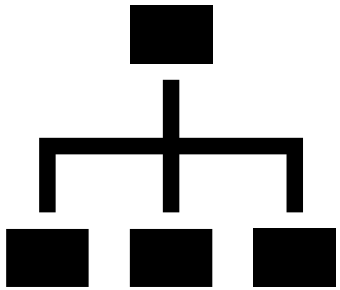
- Your procedure(s) should describe your supplier evaluation process and describe how you will determine type of and extent of control you will exercise over suppliers.
- Your procedure(s) should define how you maintain records of acceptable suppliers and how you address the purchasing data approval process.
- Your procedure(s) should explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.



Example of Manufacturing Information

Process Validation, 21 CFR 820.75

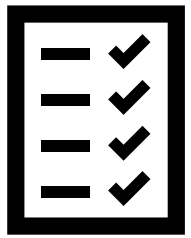
- You should submit a Validation Master Plan for validation of the device under review and the device's manufacturing site(s).
  - Should include validation of software;
  - Identify processes that haven't been validated in the past
  - Identify processes that will be verified by inspection and test.



Example of Manufacturing Information

Process Validation, 21 CFR 820.75(a)

- You should provide a copy of the validation procedure(s) or individual validation plan(s) for each process that will be validated for the device under review. When available, you should provide a copy of any completed validation reports.



Example of Manufacturing Information

Process Validation, 21 CFR 820.75(a)

Example of Manufacturing Information

Process Validation, 21 CFR 820.75(a)

Example of Process Validation Deficiency

Your firm provided Master Validation Matrix and the Master Validation Plan/Report, DOCXXXX. However, your firm did not submit validation procedures of individual validation plans for each process that will be validated for the “device”. If available, please submit any completed validation reports. The validation procedures or plans should contain or refer to objective and measurable acceptance criteria, describe how appropriate statistical methods for data collection and analysis are used, and should define the criteria for re-validation. Please address these elements to meet the requirements of 21 CFR 820.75(a).

PMA Manufacturing Section When Using a Contract Manufacturer

Volume 1: PMA Sponsor

- *PMA Sponsor Cover Letter*
- *Overview: Manufacturing Section*
- *Device Description*
- *Facility Overview*
- *Summary of Design Control Procedures*
- *Summary of Manufacturing Procedures*

Attachment: Quality Manual

Attachment: Procedures

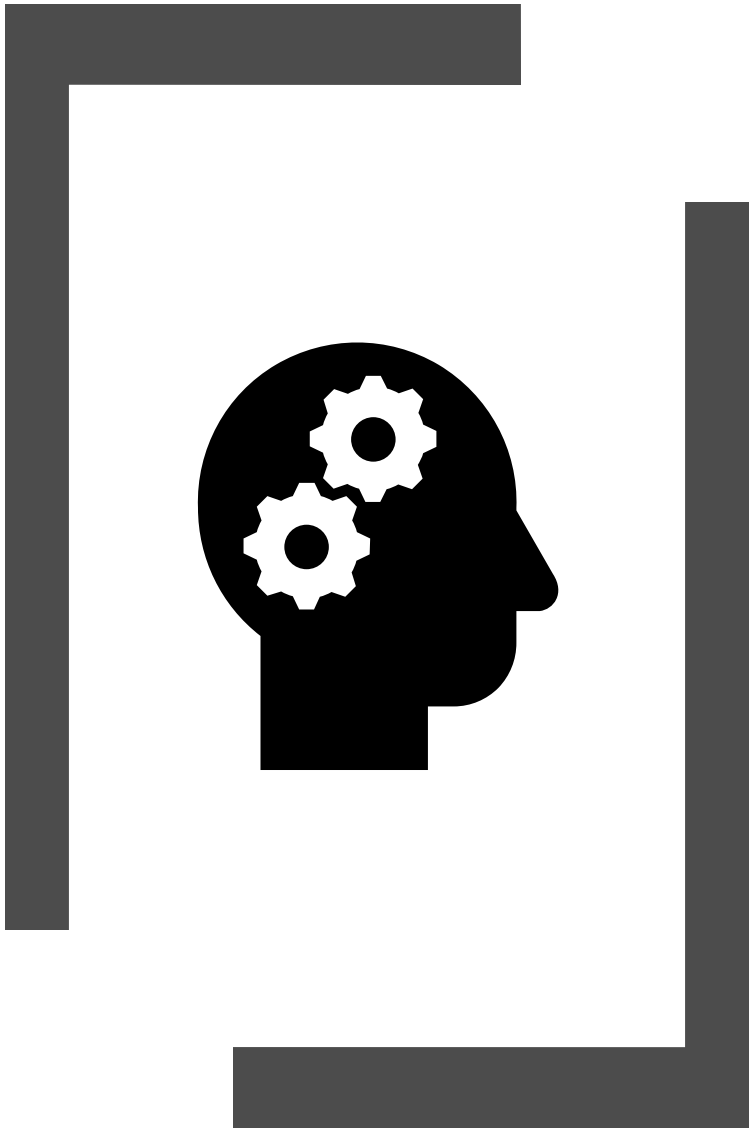
Volume 2: Contract Manufacturer

- *PMA Sponsor Cover Letter*
- *Overview: Contract Manufacturer*
- *Contract Mfr. Facility Overview*
- *Device Description*
- *Summary of Manufacturing Procedures* (discuss only those procedures contracted)

Attachment: Contract Manufacturer's Quality Manual

Attachment: Contract Manufacturer's Procedures

→ **Key: arrow indicates that the sponsors volume will make reference to the vendors volume**



Process – OPEQ Manufacturing Review

- CDRH/OPEQ will review the manufacturing section of the submission according to the guidance document.
- CDRH/OPEQ will communicate their assessment to the applicant if there are deficiencies identified in the Quality System information included in the submission.

Communication of Deficiencies

- Communication may take the form of:
  - Formal Letter
  - Email
  - Telephone Call

Additional Information

- Under the PMA amendment and supplement programs, applicants should submit Quality System information that differs from that previously submitted in the original application; or the information that is directly involved with the reason for the amendment or supplement.

PMA Amendment

- Information an applicant submits to FDA to modify a pending PMA or a pending PMA supplement [21 CFR 814.3(f)].
  - This submission typically occurs in response to deficiencies.

- PMA amendment includes all additional submissions to a PMA or PMA supplement before approval of the PMA or PMA Supplement

- Additional correspondence after PMA or PMA supplement approval is also considered a PMA amendment.

PMA Supplements

- A supplemental application to an approved PMA for approval of a change or modification in a class III medical device, including all information submitted with or incorporated by reference.

- Manufacturing site change supplements are 180-day supplements (21 CFR 814.39(c) and 814.40)
  - No User Fee
  - Reviewed by CDRH's Office of Product Evaluation and Quality (CDRH/OPEQ).
  - They may require a preapproval inspection.

Final Guidance

Manufacturing Site Change Supplements: Content and Submission. Guidance for Industry and FDA Staff. Issued on December 17, 2018.

Guidance only applies to a manufacturer of a medical device with an approved PMA, or a humanitarian device exemption (HDE).

Guidance Document

- Legal Disclaimer
  - FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.
  - The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

Manufacturing Site Change Supplement Guidance Document

- Explains:
  - A. What constitutes a manufacturing site change
  - B. What documentation should be included in a site change supplement
  - C. The general factors FDA intends to consider when determining whether to conduct an establishment inspection prior to approval of a PMA supplement for a site change.

Definitions

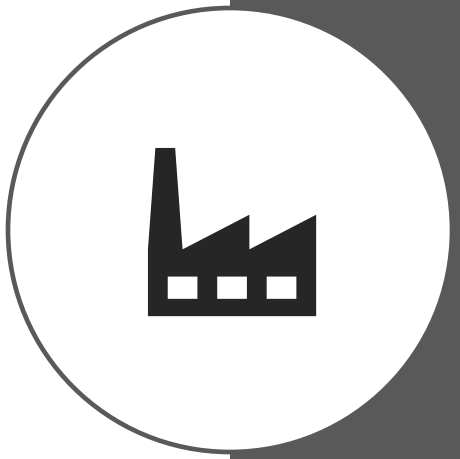
- ***Site Change Supplement***:
  - A 180-day, no-fee PMA supplement that relates to the use of a different facility or establishment to manufacture, process, or package the device

- ***30 Day Notice***:
  - A submission to FDA for changes deemed to be a modification in a manufacturing procedure or method of manufacturing of a PMA approved device that could affect safety and effectiveness.

Site Change Supplement

What constitutes a new manufacturing site?

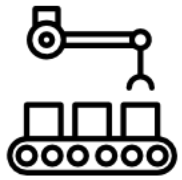
1. A site not approved as part of the original PMA or a PMA supplement;
2. The site(s) was approved as part of the original PMA or PMA supplement, but only for the performance of different manufacturing activities.



30 Day Notice

- An applicant should submit a 30-day notice, under 21 CFR 814.39(f), for use of a new supplier of those components that are critical to the finished device's function, operation, or specifications.

- Firms that manufacture components that do not also manufacture finished devices are not subject to the QS regulation requirements.
  - The finished device manufacturer ensures compliance with QS requirements through the application of purchasing controls and acceptance criteria for all components purchased or otherwise received.

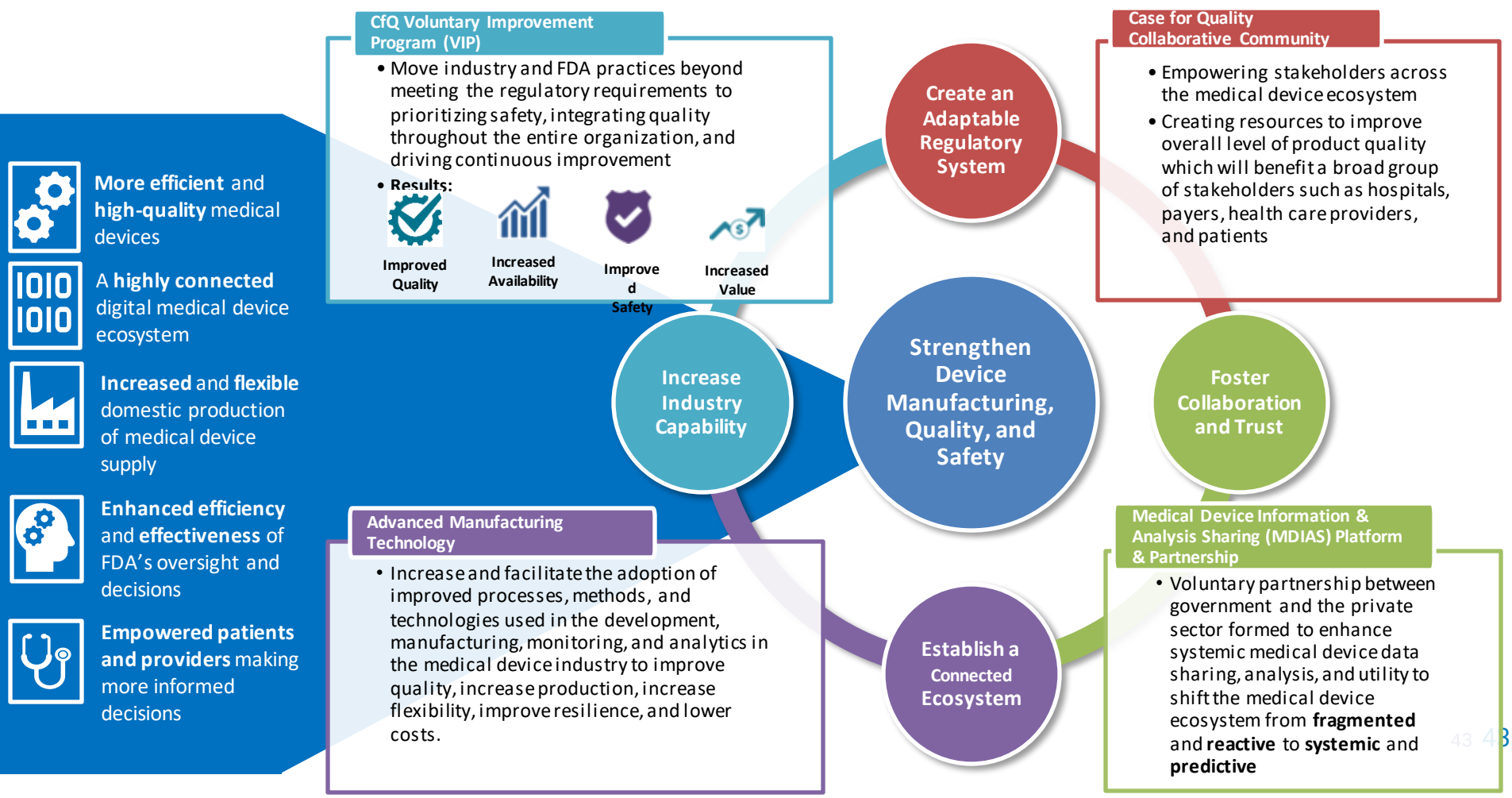


Site Change vs. 30 Day Notice

Typical Scenarios:

1. Moving the site in which manufacturing activities take place
2. Expanding an existing site,
3. Building a new facility or establishment,
4. Moving equipment within a facility
5. Changing the manufacturing, processing, or packaging activities within a site

THE CDRH CASE FOR QUALITY: SHIFTING THE REGULATORY MINDSET FROM COMPLIANCE TO QUALITY


More efficient and high-quality medical devices
A highly connected digital medical device ecosystem
Increased and flexible domestic production of medical device supply
Enhanced efficiency and effectiveness of FDA's oversight and decisions
Empowered patients and providers making more informed decisions
CfQ Voluntary Improvement Program (VIP)
• Move industry and FDA practices beyond meeting the regulatory requirements to prioritizing safety, integrating quality throughout the entire organization, and driving continuous improvement
• Results:
Improved Quality
Increased Availability
Improved Safety
Increased Value
Create an Adaptable Regulatory System
Case for Quality Collaborative Community
• Empowering stakeholders across the medical device ecosystem
• Creating resources to improve overall level of product quality which will benefit a broad group of stakeholders such as hospitals, payers, health care providers, and patients
Increase Industry Capability
Strengthen Device Manufacturing, Quality, and Safety
Foster Collaboration and Trust
Advanced Manufacturing Technology
• Increase and facilitate the adoption of improved processes, methods, and technologies used in the development, manufacturing, monitoring, and analytics in the medical device industry to improve quality, increase production, increase flexibility, improve resilience, and lower costs.
Establish a Connected Ecosystem
Medical Device Information & Analysis Sharing (MDIAS) Platform & Partnership
• Voluntary partnership between government and the private sector formed to enhance systemic medical device data sharing, analysis, and utility to shift the medical device ecosystem from fragmented and reactive to systemic and predictive

Moving Beyond Compliance To A Proactive Learning System Focused on Quality Outcomes for Patients

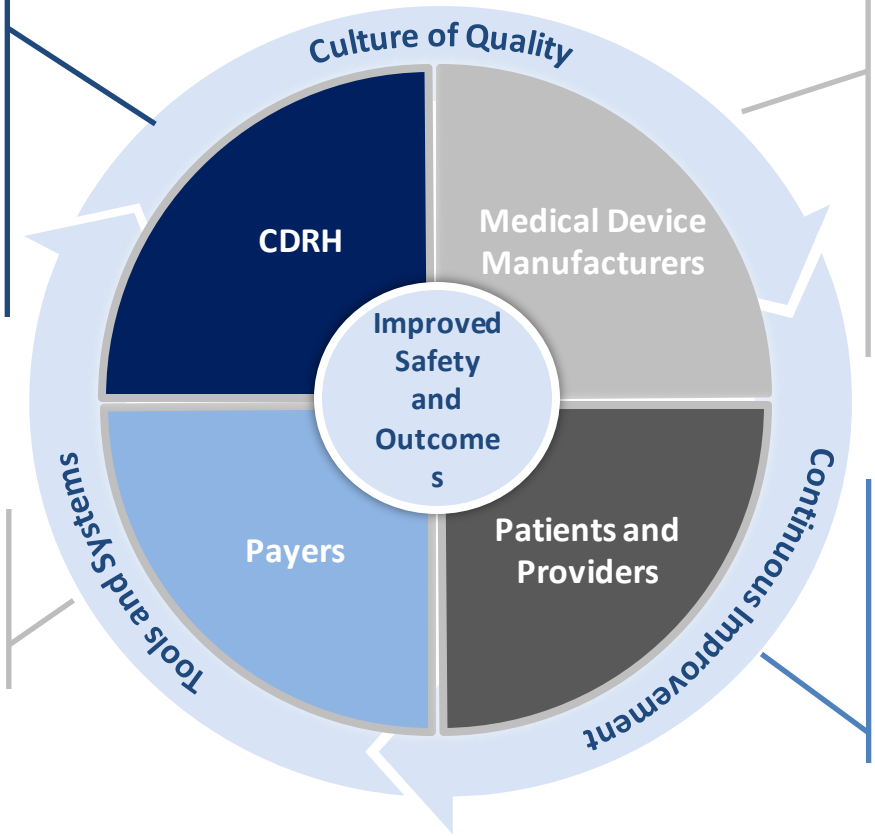
New tools for oversight

Patient and provider input throughout the lifecycle

Improved data from all stakeholders throughout the lifecycle

Engage earlier in design

Promote advanced technologies and digital capabilities



Advanced technology in design and production

Proactive safety improvements

Collaboration to address safety issues

Improved data for safety and innovation

Rapid response to issues and disruptions

Fully compliant

Quality and performance data informs purchasing decisions

Engaged in design and development activities

Access to information and resources on device quality

Collaborate when issues occur

Inform regulatory outcomes throughout the product lifecycle

Improved data sharing

Current CfQ Activities

- Medical Device Information & Analysis Sharing
- Advanced Manufacturing Efforts
- Voluntary Improvement Program (VIP)
- CAPA Improvement Pilot
- Accelerate Sustainable Capability (ASC) Pilot

Voluntary Improvement Program (VIP)

Case for Quality

Voluntary Improvement Program (VIP)

What

Collaboratively developed voluntary third-party quality maturity appraisal program

Why

Move industry and FDA practices and behavior away from just focusing on meeting the regulatory requirements to continuous improvement

Results

- ✓Improved product quality & availability
- ✓Increased manufacturing performance & value
- ✓Best practice sharing and investment in improvement
- ✓Identified broad improvement opportunities

FDA Supporting Activities

FDA Activities Accelerating Changes and Continuous Improvement:

- Appraisal data included in risk-based inspection planning, FDA may forgo certain inspections (such as surveillance, post-approval, risk-based inspections, preapproval)

- Modified submission formats and review timeframes
  - Manufacturing change notice submissions
  - Manufacturing site changes
  - Original PMA manufacturing, streamlined, waiver of preapproval inspection

Case for Quality Resources

Resource	URL
FDA Case for Quality Site	https://www.fda.gov/medical-devices/quality-and-compliance-medical-devices/case-quality
MDIC Case for Quality Site	https://mdic.org/program/case-for-quality/
makeCAPACool Whitepaper	https://mdic.org/news/mdic-releases-case-for-quality-capa-process-improvement-whitepaper/
Enrollment in the accelerating sustainable capability pilot	https://mdic.org/project/case-for-quality-accelerate-sustainable-capability-pilot/
Case for Quality Mailbox	CaseForQuality@fda.hhs.gov

Relevant Guidance

- **21 CFR Part 814 – Premarket Approval of Medical Devices**
  - https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=814
- **21 CFR Part 820 – Quality System Regulation**
  - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=820
- **Preamble to the QS Regulation Final Rule**
  - https://www.fda.gov/medical-devices/quality-system-qs-regulationmedical-device-good-manufacturing-practices/medical-devices-current-good-manufacturing-practice-cgmp-final-rule-quality-system-regulation

Relevant Guidance

- **Quality System Information for Certain Premarket Application Reviews: Guidance for Industry and FDA Staff; February 2003**
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quality-system-information-certain-premarket-application-reviews

- **The Review and Inspection of Premarket Approval Application Manufacturing Information and Operations; January 2008**
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/review-and-inspection-premarket-approval-application-manufacturing-information-and-operations

Relevant Guidance

- **Guidance for Industry and FDA Staff – 30-Day Notices, 135-Day PMA Supplements and 75-Day HDE Supplements for Manufacturing Method or Process Changes; December 2019**
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/30-day-notices-135-day-premarket-approval-pma-supplements-and-75-day-humanitarian-device-exemption

- **Manufacturing Site Change Supplements: Content and Submission. Guidance for Industry and FDA Staff; December 2018**
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/manufacturing-site-change-supplements-content-and-submission-0

Future Changes

- FR Notice for Proposed Rule to amend current Part 820 to harmonize with ISO 13845:2016
  - FR released February 23, 2022: link
- Virtual FDA Advisory Committee Meeting
  - March 2, 2022 (9am-6pm): link

Contact Information

OPEQ / ORP/ Division of Submission Support
OPEQSubmissionSupport@fda.hhs.gov

- Joshua Nipper, Director - Division of Submission Support
  301-796-5640
  Joshua.Nipper@fda.hhs.gov

- Jhumur Banik, Acting Assistant Director (Policy Analyst) – PHQ Team – Division of Submission Support
  Jhumur.Banik@fda.hhs.gov

Additional Team Members

PMA/HDE/Q-Sub (PHQ) Team:

- Jhumur Banik (Acting Assistant Director)
- Susannah Gilbert (Team Lead)
- Lalit Jalota
- Stacy Monza
- Wanda Sawyer-Major
- Senora Smallwood
- Ka Nam To
- Edward Webman
- Farid Yaghouby

Thank You!

Questions?


FDA
U.S. FOOD & DRUG
ADMINISTRATION

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During Submission Review

AdvaMed PMA Workshop, 23 May 2023

Jennifer Bolton, Boston Scientific Corporation

Overview

- Interactions with FDA
- When/How to Expect Questions
- Types of FDA Letters
- Timelines
- Day 100 Meetings
- Labeling Review

Interactions with FDA

Interactions with FDA

- Pre-PMA Meeting
- Submit PMA Shell – if modular
- Submit PMA
- Acceptance/Filing reviews
- Substantive Interaction
- Day 100 Meeting w/FDA
- Respond to Deficiencies
- Preapproval Inspections
- FDA Advisory Committee (Panel) meeting – if needed
- Post-panel Questions
- Negotiate final labeling and Post-Approval Study (PAS)
- FDA Decision

When/How to Expect Questions

When/How to Expect Questions

- If Modular
  - Expect questions about 90 days after each modular submission
- During filing reviews
  - Use PMA checklist and include references to where the information is contained in PMA to reduce chance of questions
- End of Substantive Interaction – 90 days after filing PMA
  - Questions in form of Major Deficiency Letter or Interactive Review (IR)
  - Once in Interactive Review, questions can continue coming at any time
  - Build good relationship with reviewer and discuss how review is going, if/when to anticipate further questions after responding to deficiencies or IR questions
- After Advisory Committee (Panel) Meeting
  - Panel feedback may trigger additional FDA questions
- Final Labeling
  - After technical and clinical questions answered to FDA's satisfaction

Types of Letters

Types of FDA Letters

- Major Deficiency Letter
  - Due 90 days after PMA filing
- Approvable Letter
  - Substantially meets requirements, and FDA believes approvable if additional info are submitted or specific conditions agreed to, e.g., awaiting inspection of international site
- Not Approvable Letter
  - Application may not be approved or FDA unable to reach decision due to lack of significant information
- Denial of Approval
  - If applicant fails to follow requirements, false statement of material fact, applicant does not permit FDA to inspect facilities, clinical study not in compliance with IRB and Informed Consent regulations, etc.
- Approval Letter
  - Includes approval, plus any Conditions of Approval (CoA)

Timelines

Timeline: Interactions with FDA

Topic	Timeline
Pre-PMA Meeting	Planning stage, shortly before submitting modular shell (if modular)
Submit PMA Shell (if modular)	FDA response usually within 2 weeks
Submit PMA (or modules)	MDUFA Goals (Performance Metrics) FDA's objective: 90-day review/module
Acceptance review	15 days of receipt of PMA (final module)
Filing review	45 days of receipt (of accepted PMA)
Substantive Interaction – major deficiency letter or email moving to Interactive Review, includes statement if panel meeting is needed	90 calendar days of PMA filing date

Timeline: Interactions with FDA

Topic	Timeline
Day 100 Meeting w/FDA	Scheduled ~100 days after submission
Respond to Deficiencies	-
FDA Advisory Committee Panel meeting (if needed)	-
Post-panel Questions	-
Negotiate final labeling and Post-Approval Study (PAS)	-
Preapproval Inspections (design/mfg site QSR and/or site(s)/sponsor BIMO)	Concurrent to review, common for QSR to not schedule until after filing review, BIMO audits could be anytime during study or during PMA review
FDA decision	Within 180 FDA days of filing (or 320 if panel)

Timeline: PMA Amendments

Sponsor can submit:

- Unsolicited Major Amendment
  - Substantial new data
  - Review clock is extended by number of days equal to 75% of difference between filing date and date FDA receives amendment
- Solicited Major Amendment
  - Submitted at FDA's request via a major deficiency letter or not approvable letter
  - Clock stops at receipt of letter and restarts with complete response (not with a partial response)
- Minor Amendment
  - Clarification of previously submitted data or additional information of minor nature
  - No effect on review clock
- Withdrawal of Application
  - Stops the review clock
  - Withdrawal treated as final FDA action that satisfies decision goal

Substantive Interaction: MDUFA IV Goal

Boston Scientific

Table 1.3 CDRH - PMA Original and Panel-Track Supplements Substantive Interaction Performance Goal

Substantive Interaction (SI) Goal	FY 2018 95% SI Within 90 FDA Days	FY 2019 95% SI Within 90 FDA Days	FY 2020 95% SI Within 90 FDA Days	FY 2021 95% SI Within 90 FDA Days	FY 2022 95% SI Within 90 FDA Days
Eligible for SI	71	55	73	72	43
SI Goal Met	69	54	70	56	38
SI Goal Not Met	2	1	3	15	4
SI Pending Within Goal	0	0	0	0	0
SI Pending Past Goal	0	0	0	0	1
Closed Without SI	0	0	0	1	0
Current SI Performance Percent Goal Met	97.18%	98.18%	95.89%	78.87%	88.37%

Note: 2023 YTD data presented in MDUFA V Quarterly Performance Report, Goal Met: 100%

MDUFA Quarterly Performance Report, May 10, 2023, MDUFA Reports | FDA

PMA Decision: MDUFA IV Goal

Table 1.5 CDRH - PMA Original and Panel-Track Supplements (Without Panel Review) MDUFA IV Decision Performance Goal

Performance Metric	FY 2018 90% Within 180 FDA Days	FY 2019 90% Within 180 FDA Days	FY 2020 90% Within 180 FDA Days	FY 2021 90% Within 180 FDA Days	FY 2022 90% Within 180 FDA Days
Number of PMAs Filed	66	53	69	70	43
Non-MDUFA IV Decision	0	0	0	1	0
MDUFA IV Decision	66	53	66	63	27
MDUFA IV Decision Goal Met	65	48	61	50	24
PMAs Pending MDUFA IV Decision	0	0	3	6	16
PMAs Pending MDUFA IV Decision Past Goal	0	0	0	5	1
Current Performance Percent Goal Met	98.48%	90.57%	92.42%	73.53%	85.71%

Note: 2023 YTD data presented in MDUFA V Quarterly Performance Report, Goal Met: N/A

MDUFA Quarterly Performance Report, May 10, 2023, MDUFA Reports | FDA

PMA Decision: MDUFA IV Goal

Table 1.6 CDRH - PMA Original and Panel-Track Supplements (with Panel Review) MDUFA IV Decision Performance Goal

Performance Metric	FY 2018 90% Within 320 FDA Days	FY 2019 90% Within 320 FDA Days	FY 2020 90% Within 320 FDA Days	FY 2021 90% Within 320 FDA Days	FY 2022 90% Within 320 FDA Days
Number of PMAs Filed	5	2	4	2	0
Non-MDUFA IV Decision	0	0	0	0	0
MDUFA IV Decision	5	2	4	1	0
MDUFA IV Decision Goal Met	5	1	4	1	0
PMAs Pending MDUFA IV Decision	0	0	0	1	0
PMAs Pending MDUFA IV Decision Past Goal	0	0	0	0	0
Current Performance Percent Goal Met	100.00%	50.00%	100.00%	100.00%	N/A

Note: 2023 YTD data presented in MDUFA V Quarterly Performance Report, Goal Met: N/A

MDUFA Quarterly Performance Report, May 10, 2023, MDUFA Reports | FDA

Day 100 Meetings

Day 100 Meeting

- Applicant may request a Day 100 Meeting
  - Intention: Review status of application with reviewer(s), Team management and Division/Office level management
  - Submit request with PMA or as PMA/A ≤70 days of filing
  - Specify face-to-face, video conference, list of attendees, potential dates
  - Meeting minutes prepared and submitted similar to other FDA/Industry meetings
- Recommendations
  - Always submit request with PMA application
  - Schedule Day 100 meeting if any issues during review or poor interaction with FDA reviewer/management
  - If review is going well, consider asking for a conference call to clarify any deficiencies or IR Qs instead:
    - Allows for more informal meeting without need to include Division/Office level management
    - Typically get same information vs. Formal Day 100 Meeting

Labeling Review

Labeling Review

- Technical portions of labeling conducted alongside test data, e.g., MRI labeling
- Rest of labeling review not typically conducted until all technical and clinical questions have been resolved
- Most time often spent on clinical study summaries and any patient information brochures
- Expect to work interactively with FDA Lead Reviewer, Team Lead, Assistant Director, and Medical Officer
  - Can require multiple rounds of review with FDA
- Approval based on condition that Applicant files final Labeling Amendment shortly after PMA approval

Patient Labeling

- Patient labeling has two main purposes:
  - To help counsel patients on risks and benefits associated with use of device, explaining why device is being used in their diagnosis or treatment
  - To guide patients or lay users when they are expected to operate or use device
- Must be understandable to patients
- Must be made readily available to patients
  - Printed copies for physicians to distribute to patients
  - Best Practice: also provide online so patients can find information if they lose printed copy of patient information guide
- Labeling review and revisions can require multiple interactions with FDA

SSED Review

- Summary of Safety and Effectiveness Data
- FDA document, although Applicant provides initial draft
- Will be posted publicly on FDA website with Approval Letter and final labeling
- Includes:
  - Indications for Use
  - Device Description
  - Summary of Preclinical Studies
  - Summary of Clinical Studies
- Can require multiple rounds of review with FDA

Useful FDA Documents

- *PMA Review Process (webpage)* https://www.fda.gov/medical-devices/premarket-approval-pma/pma-review-process
- *Premarket Approval Application Modular Review* (November 2003) https://www.fda.gov/media/73513/download
- *PMA: Effect on FDA Review Clock and Goals* (October 2022) https://www.fda.gov/media/73504/download
- *Acceptance and Filing Reviews for PMAs* (December 2019) https://www.fda.gov/media/83408/download
- *PMA Interactive Procedures for Day-100 Meetings and Subsequent Deficiencies* (February 1998) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-pma-interactive-procedures-day-100-meetings-and-subsequent-deficiencies-use-cdrh-and

Useful FDA Documents

- *PMA Labeling (webpage)* https://www.fda.gov/medical-devices/premarket-approval-pma/pma-labeling
- *Device Labeling (webpage)* https://www.fda.gov/medical-devices/overview-device-regulation/device-labeling
- *Unique Device Identification – UDI (webpage)* https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/unique-device-identification-udi-system
- *Use of Symbols in Labeling (webpage)* https://www.fda.gov/medical-devices/device-labeling/use-symbols-labeling
- *Medical Device Patient Labeling* (April 2001) https://www.fda.gov/media/71030/download
- *MDUFA Reports* (Annual Reports and Quarterly Performance Reports) https://www.fda.gov/industry/medical-device-user-fee-amendments-mdufa/mdufa-reports

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Conditions of Approval Studies

AdvaMed PMA Workshop, 23 May 2023

Jennifer Bolton, Boston Scientific Corporation

Overview

- Criteria and Objectives
- Early Collaboration with FDA
- Reaching Agreement
- Reporting Outcomes
- 522 Studies

Criteria and Objectives

Post-Approval Studies (PAS)

- Typically required for Class III devices under 21 CFR 814.82(a)(2)
  - "Continuing evaluation and periodic reporting on the safety, effectiveness, and reliability of the device for its intended use. FDA will state in the PMA approval order the reason or purpose for such requirement and the number of patients to be evaluated and the reports required to be submitted."
  - Longer term / continued follow-up of pivotal study – often to 5 or 10 years depending upon device, indication, patient population, etc.
  - Depending upon design, could be referred to as a "Surveillance" instead of a "Study"
- Oversight by same office/team as PMA approval
  - Provides continuity

Why Post-Approval Studies?

- “Real World” – how is the device really being used?
  - Indicated
  - Off-label
- Gather long-term data on device, including subgroups
- Balance premarket burden
- Show effectiveness of training programs
- May detect signals
- Gather data to expand indications / other labeling updates

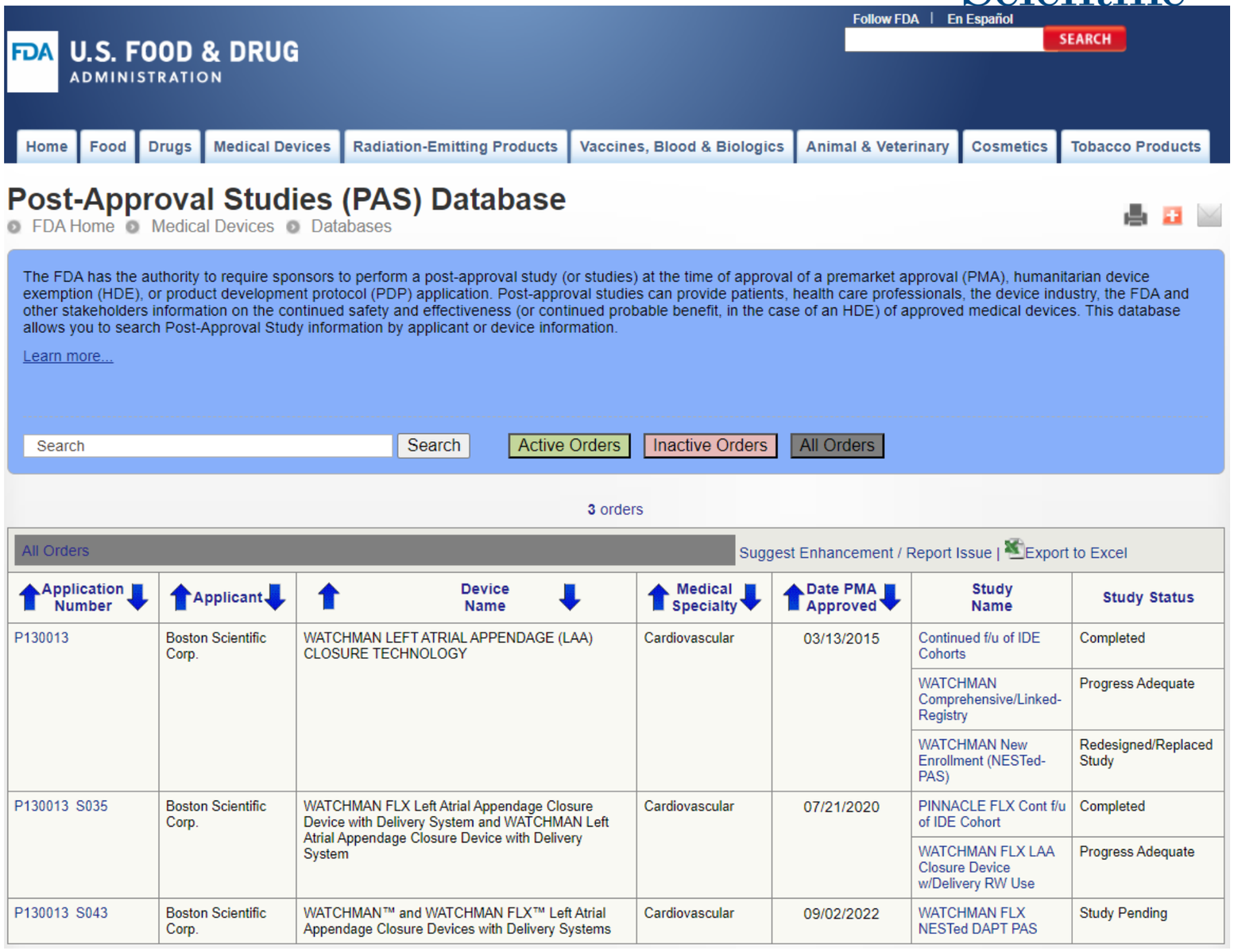
Pre- and Post-Market Balance

- Least Burdensome
- Reasonable assurance of safety and effectiveness must be demonstrated premarket
- FDA recognizes that some questions may not be fully resolved by the time of approval (i.e., long-term safety issues)
- Benefit-Risk – FDA may approve a device when there is uncertainty regarding certain benefits or risks if this uncertainty is sufficiently balanced by other factors, including the overall benefit/risk profile and the extent of post-market controls
  - Examples from FDA's 2015 Guidance on pre/postmarket balance include mature technology, urgent public health need, assay migration studies for IVDs, long-term performance, and rare adverse events, among others

Balancing Premarket and Postmarket Data Collection for Devices Subject to PMA (April 2015)
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/balancing-premarket-and-postmarket-data-collection-devices-subject-premarket-approval

Comprehensive/Linked/Registry Based Surveillance

- Registry-based comprehensive surveillance leverages national and international registry infrastructure linked with other data sources (e.g., claims data) for longitudinal assessment of device performance
- Surveillance relies on data collection within existing health care delivery systems
- **Generally, involves** shared responsibilities amongst multiple stakeholders, including professional societies running the registries, FDA epidemiologists performing the surveillance analysis, payers assisting with linking to administrative data, and industry supporting the registries



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Post-Approval Studies (PAS) Database

FDA Home › Medical Devices › Databases

The FDA has the authority to require sponsors to perform a post-approval study (or studies) at the time of approval of a premarket approval (PMA), humanitarian device exemption (HDE), or product development protocol (PDP) application. Post-approval studies can provide patients, health care professionals, the device industry, the FDA and other stakeholders information on the continued safety and effectiveness (or continued probable benefit, in the case of an HDE) of approved medical devices. This database allows you to search Post-Approval Study information by applicant or device information.

Learn more...

Search | Search | Active Orders | Inactive Orders | All Orders

3 orders

All Orders | Suggest Enhancement / Report Issue | Export to Excel

Application Number	Applicant	Device Name	Medical Specialty	Date PMA Approved	Study Name	Study Status
P130013	Boston Scientific Corp.	WATCHMAN LEFT ATRIAL APPENDAGE (LAA) CLOSURE TECHNOLOGY	Cardiovascular	03/13/2015	Continued f/u of IDE Cohorts	Completed
					WATCHMAN Comprehensive/Linked-Registry	Progress Adequate
					WATCHMAN New Enrollment (NESTed-PAS)	Redesigned/Replaced Study
P130013 S035	Boston Scientific Corp.	WATCHMAN FLX Left Atrial Appendage Closure Device with Delivery System and WATCHMAN Left Atrial Appendage Closure Device with Delivery System	Cardiovascular	07/21/2020	PINNACLE FLX Cont f/u of IDE Cohort	Completed
					WATCHMAN FLX LAA Closure Device w/Delivery RW Use	Progress Adequate
P130013 S043	Boston Scientific Corp.	WATCHMAN™ and WATCHMAN FLX™ Left Atrial Appendage Closure Devices with Delivery Systems	Cardiovascular	09/02/2022	WATCHMAN FLX NESTed DAPT PAS	Study Pending

How FDA Tracks Post-Approval Study Status

Boston Scientific

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Learn more...

Search | Search | Active Orders | Inactive Orders | All Orders

240 orders

Active Orders | Suggest Enhancement / Report Issue | Export to Excel

Application Number	Applicant	Device Name	Medical Specialty	Date PMA Approved	Study Name	Study Status
P160017 S091	MEDTRONIC MINIMED, INC.	MiniMed 780G System	Clinical Chemistry	04/21/2023	MiniMed 780G New Enrollment Study	Protocol Pending
P130008 S089	INSPIRE MEDICAL SYSTEMS	Inspire Upper Airway Stimulation	Anesthesiology	03/20/2023	Inspire UAS New Enrollment PAS	Protocol Pending
P200045 S002	Bolton Medical, Inc.	RelayPro Thoracic Stent-Graft System	Cardiovascular	03/07/2023	Registry Data Collection for Dissection	Protocol Pending
					Cont f/u Dissection Study Subjects	Study Pending
					Cont f/u Transection Study Subjects	Study Pending
P190023 S002	Abbott Medical	Navitor Transcatheter Aortic Valve Implantation System; Navitor Transcatheter Aortic Heart Valve; FlexNav Delivery System; Navitor Loading System	Cardiovascular	01/13/2023	Registry-Based Real-World Use Surveillance Study	Ongoing
					Continued F/U of the IDE Portico NG Study	Study Pending
P110016 S080	Abbott Medical	FlexAbility™ Ablation Catheter, Sensor Enabled™	Cardiovascular	12/14/2022	LESS VT Continued F/u of IDE	Study Pending
					LESS VT NICM Post-Approval Study	Study Pending

Cont f/u Transection Study Subjects

Suggest Enhancement / Report Issue | Export to Excel

General	
Study Status	**Study Pending**
Application Number / Requirement Number	P200045 S002/ PAS002
Date Original Protocol Accepted	03/07/2023
Date Current Protocol Accepted	
Study Name	Cont f/u Transection Study Subjects
Device Name	RelayPro Thoracic Stent-Graft System
General Study Protocol Parameters	

Cont f/u Transection Study Subjects Reporting Schedule

Reporting Schedule	Report Date Due	FDA Receipt Date	Applicant's Reporting Status
1 year report	03/06/2024		
2 year report	03/06/2025		
3 year report	03/06/2026		
4 year report	03/06/2027		

Early Collaboration with FDA

PAS Protocol Review

- Include Post-market section in PMA Submission
  - Can include protocol synopsis or full protocol
- Study Protocol vs. Surveillance Plan?
  - Surveillance Plan: if nested within a source of RWD like a national registry AND if all data needed is gathered by registry, additional consent not needed
  - Study Protocol: if stand-alone study, or if nested within a RWD source but collecting additional data
- Discuss interactively with FDA
- FDA's goal is to finalize PAS protocol prior to or at time of PMA approval
  - Often finalized after PMA approval via PMA/S

Study Protocol / Surveillance Plan Contents

- Essentially same as Premarket clinical protocols
  - Primary and secondary endpoints
  - Inclusion/exclusion criteria where applicable
  - Follow-up schedule and assessments
  - Statistical methods, including success criteria and hypotheses

- Provide expected milestone dates to FDA
  - Initiation
  - Enrollment completion
  - Follow-up completion

Reaching Agreement

Agreement with FDA

- CDRH and Sponsor agree on protocol for post-approval study/surveillance
  - If final agreement isn't reached prior to PMA approval, Sponsor should submit the protocol as a PMA supplement within 30 days of PMA approval
  - FDA intends to complete the review of a PMA supplement and respond within 60 calendar days
- FDA requests that sponsor sign an agreement to conduct PAS prior to issuance of PMA approval letter
  - Typically, a few days before approval letter
- PMA approval letter outlines basic elements of PAS protocol(s)
  - Specifies Study or Surveillance
  - Endpoints, sample size, follow-up schedule and assessments
- Changes to approved PAS protocols can be submitted as PMA supplements

Reporting Outcomes

Status Reports

- Reporting frequency included in PMA approval letter
- Typically: submit PMA/R every 6 months for the first 2 years and annually thereafter from the date of the PMA approval letter
  - Report timelines based from the date of the PMA approval letter, not from the date the protocol is approved
- Submissions continue until the Sponsor has submitted the Final Post-Approval Study Report and FDA advises that the commitment has been fulfilled
- FDA's website has content requirements for interim and final reports
  - Generally includes: device and Sponsor information and high-level results
  - Very similar to premarket study reports
- Results from PAS should be included in the labeling as data become available
  - Any updated labeling must be submitted to FDA in the form of a 180-day PMA/S

FDA Categorization of Study Status

- **Protocol Overdue**: Study protocol not approved, ≥6 months since issuance of order
- **Protocol Pending**: Study protocol not approved, <6 months since issuance of order
- **Study Pending**: Period between protocol approval and review of first report
- **Progress Adequate**: Study has begun, and study progress is consistent with protocol
- **Progress Inadequate**: Study has begun, but study progress is inconsistent with the protocol
- **Completed**: Sponsor has fulfilled CoA, and FDA closed the study – *Final study status*
- **Terminated**: Sponsor has not fulfilled or cannot fulfill the condition of approval, appropriate efforts to fulfill the CoA have been exhausted, FDA has terminated the study – *Final study status*
- **Revised/Replaced**: Sponsor has not fulfilled or cannot fulfill the condition of approval, appropriate efforts to fulfill the condition of approval have been exhausted, FDA has revised and or replaced the original study design
- **Other**: Used when study status does not fit another category – *Interim study status*

Failure to Comply with PAS Requirements

- Possible results of failure to comply with post approval study requirements:
  - Post-market surveillance under §522 (21 CFR Part 822) (*to be discussed later)*
  - Withdraw approval of PMA under §515(e) (21 CFR 814.46(a))
  - Civil money penalties
    - A significant or knowing failure to report information about a post-approval study; or
    - Such failure constitutes a risk to public health
- May be instances when PAS cannot be completed
  - Voluntary withdrawal or recall
  - Study design or data inadequacies
- FDA may require that PAS be repeated if agency believes PAS objectives not achieved

522 Studies

Why 522 Studies?

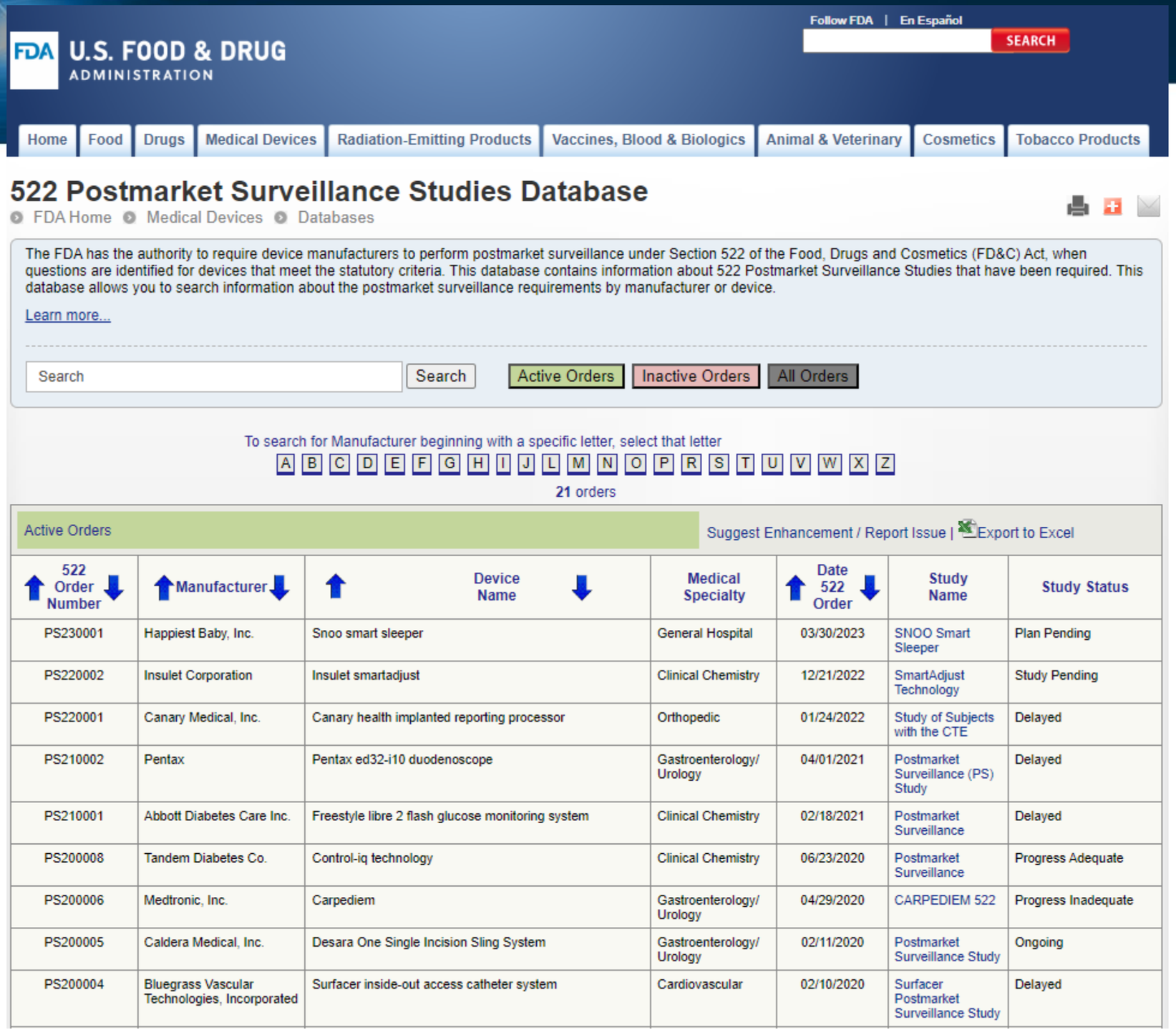
- Identification of device issues through a variety of sources
  - Analysis of Adverse Event reports
  - Recall or corrective action
  - Post-approval data
  - Review of premarket data
  - Reports from other government authorities
  - Review of scientific literature

- Issuance of 522 Order
  - Identify premarketing submission (510(k), PMA, PDP, HDE, or de novo)
  - Public health questions
  - Rationale for the 522 order
  - Post-market surveillance design recommendations

FDA 522 Database

- 21 orders
  - Metal-on-Metal Hips
  - TMJ Implant
  - Duodenoscopes
  - Permanent Birth Control

- Report status categories similar to PAS, plus:
  - **Noncompliant**: fails to comply with a requirement under section 522
  - **Consolidated**: multiple 522 orders consolidated under one order



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522 Postmarket Surveillance Studies Database

FDA Home › Medical Devices › Databases

The FDA has the authority to require device manufacturers to perform postmarket surveillance under Section 522 of the Food, Drugs and Cosmetics (FD&C) Act, when questions are identified for devices that meet the statutory criteria. This database contains information about 522 Postmarket Surveillance Studies that have been required. This database allows you to search information about the postmarket surveillance requirements by manufacturer or device.

Learn more...

Search | Search | Active Orders | Inactive Orders | All Orders

To search for Manufacturer beginning with a specific letter, select that letter

A B C D E F G H I J L M N O P R S T U V W X Z

21 orders

Active Orders | Suggest Enhancement / Report Issue | Export to Excel

522 Order Number	Manufacturer	Device Name	Medical Specialty	Date 522 Order	Study Name	Study Status
PS230001	Happiest Baby, Inc.	Snoo smart sleeper	General Hospital	03/30/2023	SNOO Smart Sleeper	Plan Pending
PS220002	Insulet Corporation	Insulet smartadjust	Clinical Chemistry	12/21/2022	SmartAdjust Technology	Study Pending
PS220001	Canary Medical, Inc.	Canary health implanted reporting processor	Orthopedic	01/24/2022	Study of Subjects with the CTE	Delayed
PS210002	Pentax	Pentax ed32-i10 duodenoscope	Gastroenterology/ Urology	04/01/2021	Postmarket Surveillance (PS) Study	Delayed
PS210001	Abbott Diabetes Care Inc.	Freestyle libre 2 flash glucose monitoring system	Clinical Chemistry	02/18/2021	Postmarket Surveillance	Delayed
PS200008	Tandem Diabetes Co.	Control-iq technology	Clinical Chemistry	06/23/2020	Postmarket Surveillance	Progress Adequate
PS200006	Medtronic, Inc.	Carpediem	Gastroenterology/ Urology	04/29/2020	CARPEDIEM 522	Progress Inadequate
PS200005	Caldera Medical, Inc.	Desara One Single Incision Sling System	Gastroenterology/ Urology	02/11/2020	Postmarket Surveillance Study	Ongoing
PS200004	Bluegrass Vascular Technologies, Incorporated	Surfacer inside-out access catheter system	Cardiovascular	02/10/2020	Surfacer Postmarket Surveillance Study	Delayed

522 Postmarket Surveillance Plan

- Protocol similar to PAS and premarket clinical protocols
- Work interactively with FDA on surveillance plan
- Reporting schedule similar to PAS
  - Often every 6 months for first 2 years followed by annually thereafter
  - Final report due within 3 months of study/surveillance completion
  - Content of 522 reports similar to PAS

Failure to Comply with 522 Order

Since 522 Orders are delivered due to a device issue:

- Failure to comply with a 522 order is a prohibited act and renders the device misbranded
- Can lead to a warning letter, seizure of device, civil money penalties or prosecution
- Situations where impossible or inappropriate to complete a 522 order:
  - If a surveillance plan will not answer or adequately address questions in a 522 order (e.g., design or data inadequacies or due to discontinuation in device marketing or manufacturing)
  - Request to terminate 522 study is less likely to be granted for long-term implants (per guidance document)
  - FDA recommends early communication for these problems

Useful FDA Documents

- *Procedures for Handling Post-Approval Studies Imposed By PMA Order* (October 2022) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/procedures-handling-post-approval-studies-imposed-pma-order
- *Balancing Premarket and Postmarket Data Collection for Devices Subject to PMA* (April 2015) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/balancing-premarket-and-postmarket-data-collection-devices-subject-premarket-approval
- *Postmarket Surveillance Under Section 522 of the Federal Food, Drug and Cosmetic Act* (October 2022) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarket-surveillance-under-section-522-federal-food-drug-and-cosmetic-act
- *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices* (August 2017) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices
- *National Evaluation System for Health Technology (NEST)* https://www.fda.gov/about-fda/cdrh-reports/national-evaluation-system-health-technology-nest
- *Post-Approval Studies (PAS) Database* https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm

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Preparation for Advisory Panels

Jessica Ringel
Partner, King & Spalding LLP
jringel@kslaw.com

Agenda

- Introduction to Advisory Committees
- The whys and whens of PMA Panel Meetings
- Preparing for a Panel Meeting
- What to expect during and after a Panel Meeting
- Best practices for a Panel Meeting

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Introduction to Advisory Committees

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What Is an Advisory Committee?

- A group of outside expert advisors, convened to provide advice and feedback to FDA
  - Scientific experts, e.g., physicians, researchers, statisticians
  - Members of the public, i.e., consumer rep, industry rep, patient rep
- Consists of standing members, including a Chair
  - And temporary voting members, as needed
- Meetings are convened by FDA, as needed

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What Does an Advisory Committee Do?

- **FDA Advisory Committees:** utilized to conduct public hearings on matters of importance that come before FDA, to review the issues involved, and to provide advice and recommendations to the Commissioner
  - 21 CFR 14.5(a)
- **Medical Devices Advisory Committee:** reviews and evaluates data on the safety and effectiveness of marketed and investigational devices and makes recommendations for their regulation
  - 21 CFR 14.100(d)(1)

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Medical Device Advisory Committee Panels

- Anesthesiology and Respiratory Therapy Devices
- Circulatory System Devices
- Clinical Chemistry and Clinical Toxicology Devices
- Dental Products
- Ear, Nose, and Throat Devices
- Gastroenterology and Urology Devices
- General and Plastic Surgery Devices
- General Hospital and Personal Use Devices
- Hematology and Pathology Devices
- Immunology Devices
- Microbiology Devices
- Molecular and Clinical Genetics
- Neurological Devices
- Obstetrics and Gynecology Devices
- Ophthalmic Devices
- Orthopaedic and Rehabilitation Devices
- Radiological Devices

Medical Devices Dispute Resolution Panel

Panel Meeting Participants

- Panel members
  - Practitioners
  - Biostatistician(s)
  - Technical expert(s)
  - Patient/consumer representative*
  - Industry representative*
- FDA Office Director and staff
- FDA Designated Officer (DFO)
- Sponsor
- Public speakers

* Does not vote

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Voting Members

- Clinical, medical, statistical experts
- Designated as Special Government Employees (SGEs)
- Subject to federal requirements for disclosure of financial relationships and appearance of conflicts of interest
  - FDA can grant waivers to permit participation with financial or other COI
    - Approved by the Commissioner's office
    - Disclosed at the opening of the panel

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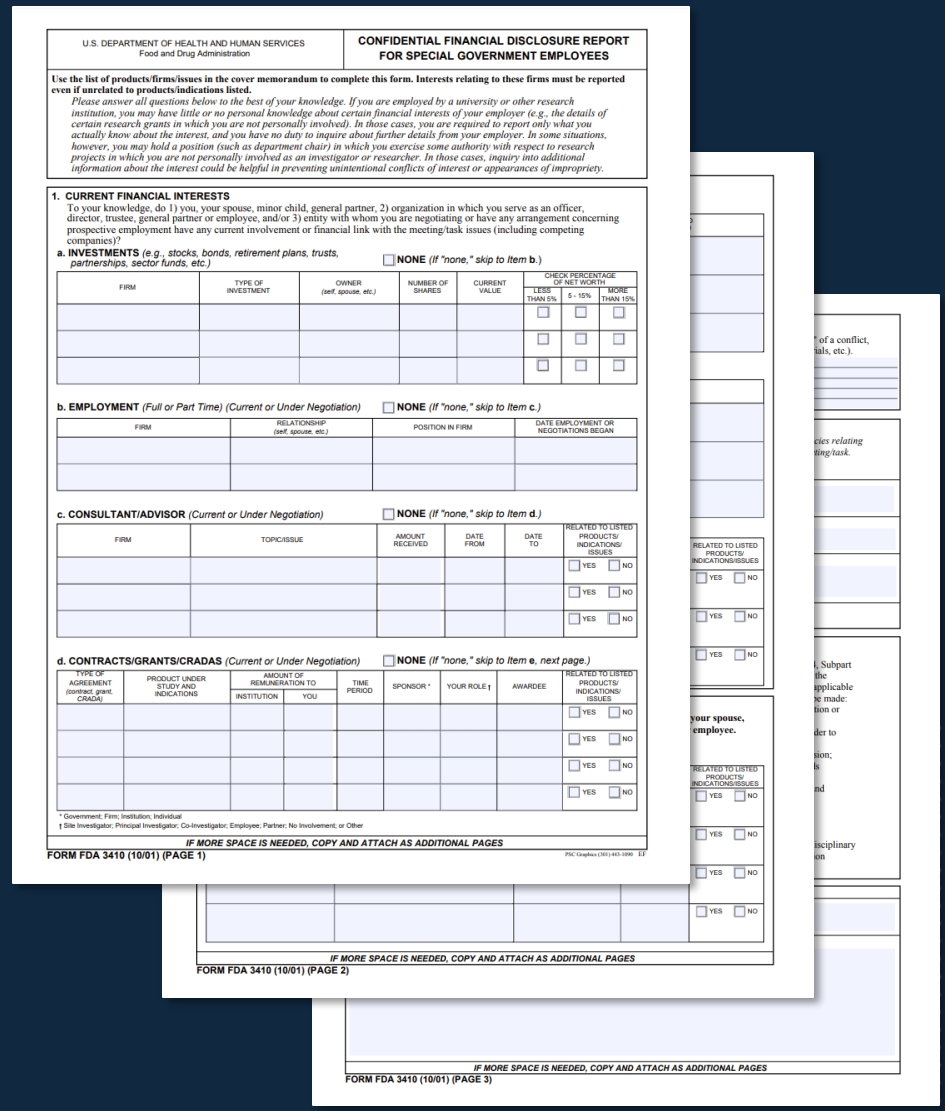
Financial Disclosure for SGEs (FDA-3410)

- SGEs cannot participate in a Panel Meeting that will have a "direct and predictable effect" on their financial interests
- Financial interest = anything that can financially impact the SGE or the interests of certain others
  - E.g., stocks, bonds, ownership stakes, patents, royalties, grants, employment, consulting arrangements, other contracts



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CONFIDENTIAL FINANCIAL DISCLOSURE REPORT FOR SPECIAL GOVERNMENT EMPLOYEES

Use the list of products/firms/issues in the cover memorandum to complete this form. Interests relating to these firms must be reported even if unrelated to products/indications listed.

Please answer all questions below to the best of your knowledge. If you are employed by a university or other research institution, you may have little or no personal knowledge about certain financial interests of your employer (e.g., the details of certain research grants in which you are not personally involved). In those cases, you are required to report only what you actually know about the interest, and you have no duty to inquire about further details from your employer. In some situations, however, you may hold a position (such as department chair) in which you exercise some authority with respect to research projects in which you are not personally involved as an investigator or researcher. In those cases, inquiry into additional information about the interest could be helpful in preventing unintentional conflicts of interest or appearances of impropriety.

1. CURRENT FINANCIAL INTERESTS

To your knowledge, do 1) you, your spouse, minor child, general partner, 2) organization in which you serve as an officer, director, trustee, general partner or employee, and/or 3) entity with whom you are negotiating or have any arrangement concerning prospective employment have any current involvement or financial link with the meeting/task issues (including competing companies)?

a. INVESTMENTS *(e.g., stocks, bonds, retirement plans, trusts, partnerships, sector funds, etc.)* ☐ **NONE** *(If "none," skip to Item b.)*

FIRM	TYPE OF INVESTMENT	OWNER *(self, spouse, etc.)*	NUMBER OF SHARES	CURRENT VALUE	CHECK PERCENTAGE OF NET WORTH: LESS THAN 5%	5 - 15%	MORE THAN 15%
					☐	☐	☐
					☐	☐	☐
					☐	☐	☐

b. EMPLOYMENT *(Full or Part Time) (Current or Under Negotiation)* ☐ **NONE** *(If "none," skip to Item c.)*

FIRM	RELATIONSHIP *(self, spouse, etc.)*	POSITION IN FIRM	DATE EMPLOYMENT OR NEGOTIATIONS BEGAN

c. CONSULTANT/ADVISOR *(Current or Under Negotiation)* ☐ **NONE** *(If "none," skip to Item d.)*

FIRM	TOPIC/ISSUE	AMOUNT RECEIVED	DATE FROM	DATE TO	RELATED TO LISTED PRODUCTS/ INDICATIONS/ ISSUES
					☐ YES ☐ NO
					☐ YES ☐ NO
					☐ YES ☐ NO

d. CONTRACTS/GRANTS/CRADAS *(Current or Under Negotiation)* ☐ **NONE** *(If "none," skip to Item e, next page.)*

TYPE OF AGREEMENT *(contract, grant, CRADA)*	PRODUCT UNDER STUDY AND INDICATIONS	AMOUNT OF REMUNERATION TO: INSTITUTION	AMOUNT OF REMUNERATION TO: YOU	TIME PERIOD	SPONSOR *	YOUR ROLE †	AWARDEE	RELATED TO LISTED PRODUCTS/ INDICATIONS/ ISSUES
								☐ YES ☐ NO
								☐ YES ☐ NO
								☐ YES ☐ NO
								☐ YES ☐ NO

* Government; Firm; Institution; Individual
† Site Investigator; Principal Investigator; Co-Investigator; Employee; Partner; No Involvement; or Other

IF MORE SPACE IS NEEDED, COPY AND ATTACH AS ADDITIONAL PAGES

FORM FDA 3410 (10/01) (PAGE 1)

IF MORE SPACE IS NEEDED, COPY AND ATTACH AS ADDITIONAL PAGES

FORM FDA 3410 (10/01) (PAGE 2)

IF MORE SPACE IS NEEDED, COPY AND ATTACH AS ADDITIONAL PAGES

FORM FDA 3410 (10/01) (PAGE 3)

The Whys and Whens of PMA Panel Meetings

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Why Does FDA Convene a PMA Panel Meeting?

- Novel device or novel technology
- Significant uncertainty whether benefits outweigh risks
- Significant questions about data integrity or data quality
- Significant public interest
- Additional or special expertise needed to assist CDRH decision-making
- At the request of PMA applicant

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When in the PMA Timeline Does FDA Notify the Sponsor?

- By Day 45, in the Filing Letter
- By Day 90, the Substantiative Interaction deadline

- At the applicant's request, after a Day 100 meeting

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How Often Does FDA Convene a PMA Panel Meeting?

- CY 2023: 0 (scheduled to date)
- CY 2022: 0
- CY 2021: 5
- CY 2020: 1
- CY 2019: 1
- CY 2018: 4
- CY 2017: 2

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Preparing for a Panel Meeting

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Panel Meeting Timing: Notice

- FDA notifies Sponsor of planned Panel Meeting approx. 55 business days before meeting
  - Date of meeting
  - The meeting's focus
  - Information the Sponsor may wish to include in briefing materials

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Panel Meeting Timing: Key Dates*

T-55 days	FDA notifies Sponsor of Panel Meeting date and topics
Within 7 days	Sponsor requests logistics call with FDA
T-42 days	Sponsor submits to FDA redacted and unredacted versions of briefing materials
T-42 to -22 days	Informal discussions between Sponsor and FDA regarding briefing materials and redactions
T-6 weeks to T-15 cal. days	FDA publishes Fed. Reg. notice
T-22 days	Sponsor submits final briefing materials
T-21 to -14 days	FDA sends Sponsor copy of FDA briefing materials
T-13 to -9 days	Sponsor reviews FDA materials and raises concerns about non- disclosable information
T-7 days	FDA response to Sponsor feedback on FDA materials
T-5 days	Sponsor and FDA exchange slides for review
T-2 days	FDA posts FDA and Sponsor materials to FDA website

* Business days, unless otherwise stated

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Briefing Materials Prepared by Sponsor

- Executive Summary
- Appropriate sections, including figures and tables, from PMA submission
- Proposed labeling
- Clinical trial details, safety and efficacy data
- Relevant publications/literature in the submission

Only data in the PMA submission should be included

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FDA Panel Pack

- Meeting agenda
- FDA's Executive Summary
  - May include regulatory history
  - FDA statistical analyses of both efficacy and safety data
- FDA's draft discussion questions
- FDA's voting questions
- Any additional information deemed appropriate by FDA (e.g., literature)

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Interactions with FDA

- Pre-meeting, Sponsor interacts with DFO on Panel Pack:
  - Provides requested redacted/unredacted materials such as Executive Summary, PMA application sections, IDE protocol, labeling, CRFs of certain subjects
  - Comments on FDA Executive Summary
  - Responds to FDA comments on Sponsor's Executive Summary
  - Comments on FDA questions for the panel

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What to Expect During and After

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Virtual or In-Person?

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Panel Meeting Process

- Applicant presentation
- FDA presentation
- Open public hearing
- Panel deliberations and FDA non-voting questions to the panel
- Panel Voting

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Typical Agenda

8:00 am	Call to Order by Chairperson; panel introductions; COI statements by DFO
8:15 – 9:15 am	Sponsor presentation
9:15 – 10:00 am	Panel questions to Sponsor
10:00 –10:15 am	Break
10:15 – 11:30 am	FDA presentation (regulatory/medical/statistician)
11:30 – 12:00 pm	Panel questions to FDA
12:00 – 1:00 pm	Lunch
1:00 – 2:00 pm	Open “Public Hearing”
2:00 – 2:45 pm	Panel deliberations
2:45 – 3:00 pm	Break
3:00 – 5:30 pm	FDA non-voting questions to the Panel; Panel discussion
5:30 – 5:40 pm	FDA and Sponsor summations
5:40 – 6:00 pm	Voting questions to the Panel; Panel statements for the record; adjourn

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Voting Questions Posed to the Panel for a PMA Device

1. Safety: Is there reasonable assurance that *Device* is safe for the proposed indication(s) for use?
2. Effectiveness: Is there reasonable assurance that *Device* is effective for the proposed indication(s) for use?
3. Benefit-Risk: Do the benefits of *Device* outweigh the risks for the proposed indication(s) for use?

- If you answered 'no' to any question, please state whether changes to the IFU, restrictions on use, or other controls, would make a difference in your answer

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Panel Voting Process

Recording Tools View Document1 - Word

Question 1

Yes – 13

No – 0

Abstain - 0

Question 2

Yes – 3

No – 7

Abstain - 3

Question 3

Yes – 3

No – 7

Abstain -3

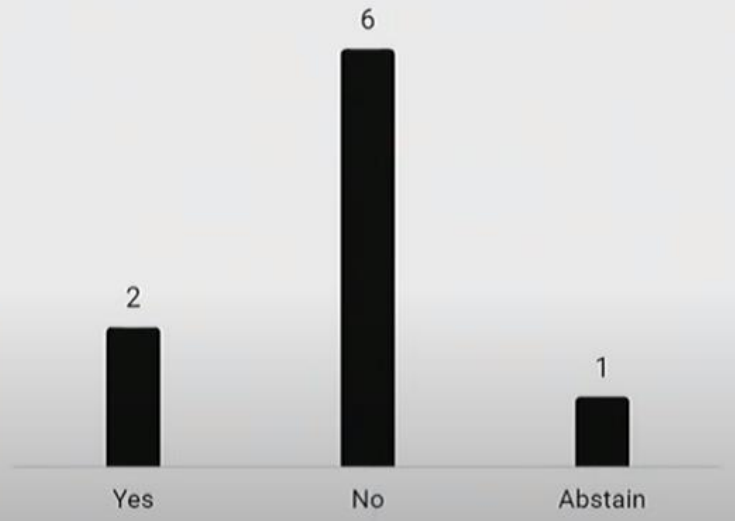
FDA U.S. FOOD & DRUG ADMINISTRATION Go to www.pigeonhole.at/3YXDZS to vote

You are viewing Program's screen View Options

Question 1 of 1

LIVE 1 participant | 9 votes

Do the probable benefits to health of the NUsurface Meniscus Implant outweigh the probable risks when used in patients in accordance with the proposed indications for use?



After the Meeting

- 24-Hour Summary
- Transcript (within 60 days)
- Resumption of FDA review of PMA
  - Interactive Review
  - Major Deficiency Letter

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Best Practices

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Best Practices

- Build the right team!
  - Sponsor personnel (Clinical, Regulatory, R&D), Investigators, other outside clinical experts, A/V firm, logistics coordinator
- Be prepared!
  - Anticipate questions from the Panel and prepare responses and slides
  - Identify roles and assign topics for the Q&A
- Practice, practice, practice!
  - Hold mock Panel meetings/dress rehearsals
- Treat your prep like a marathon and a sprint!

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Thank you

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U.S. FOOD & DRUG ADMINISTRATION

Preapproval Inspections

LCDR Jake Dyer

Senior Regulatory Officer

Medical Device Single Audit Program, Regulatory Inspections and Audits Team

Division of Establishment Support (DRP2)

Office of Regulatory Programs (ORP)

Office of Product Evaluation and Quality (OPEQ)

Center for Devices & Radiological Health (CDRH)

Overview

- Background on PMA Inspections
- Submission Types and FDA Review Milestones
- Preapproval Inspection Process
- FDA Review process
- Inspection preparation tips

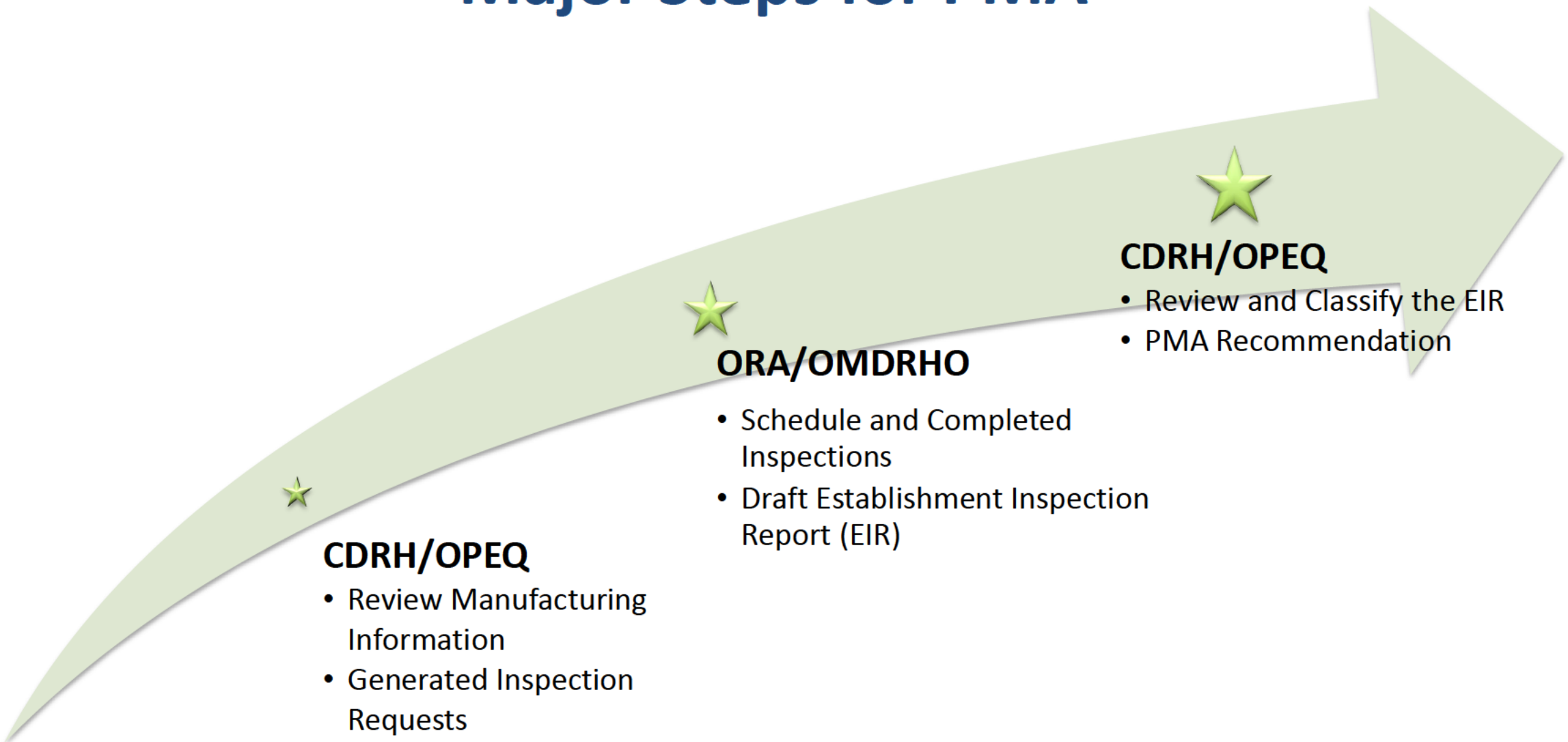
Background

- SEC. 515. [21 U.S.C. 360e] – Premarket Approval
- Title 21 Code of Federal Regulations (CFR) Part 814, Premarket Approval of Medical Devices.
  - Procedures for review of PMA
    - (e)(1)(iii) - An FDA inspection that finds the manufacturing facilities, methods, and controls in compliance with part 820 and, if applicable, that verifies records pertinent to the PMA
- 21 CFR 814.116 Procedures for review of an HDE
- Compliance Program Guidance Manual (CPGM), 7383.001, Medical Device PMA Preapproval and PMA Postmarket Inspections

Types of Submissions that Could Generate an Inspection Request

- Original Premarket Approval (PMA)
- Modules will be inspected after it has converted to a PMA
- Site Change Supplements
- Certain Humanitarian Device Exemptions (HDEs)
- Submissions for which a facility has a current Official Action Indicated (OAI) classification

Major Steps for PMA



CDRH/OPEQ

- Review Manufacturing Information
- Generated Inspection Requests

ORA/OMDRHO

- Schedule and Completed Inspections
- Draft Establishment Inspection Report (EIR)

CDRH/OPEQ

- Review and Classify the EIR
- PMA Recommendation

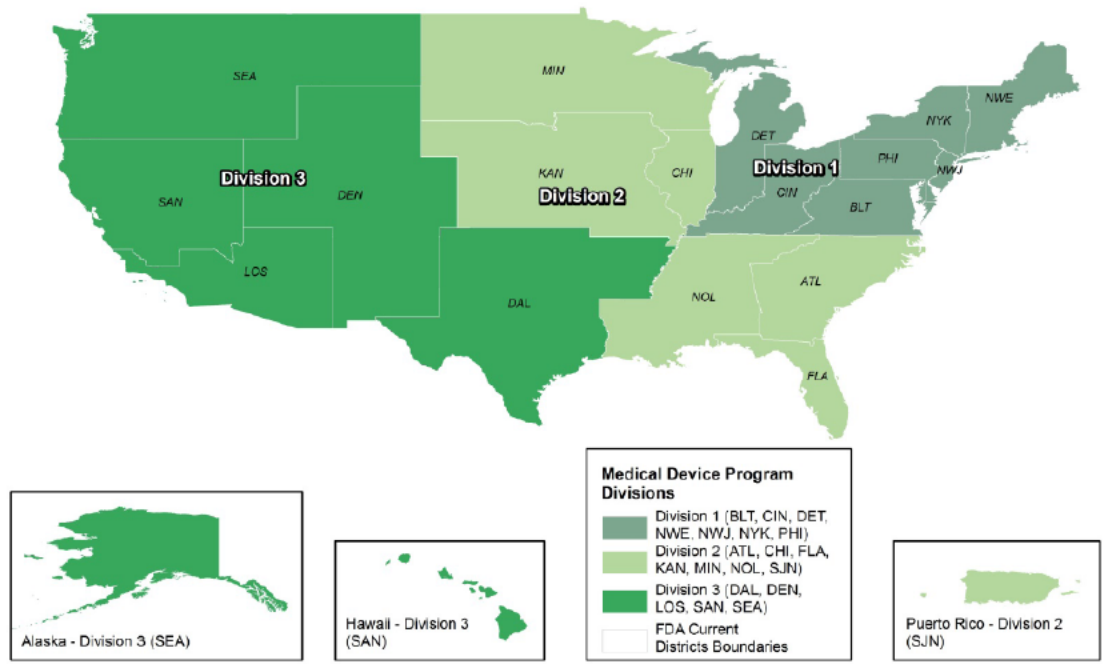
Preapproval Inspections

Ensure that you –

1. Identified all facilities that are used in the manufacture of the device in your submission
2. All sites are ready for inspection. This includes the completion of process validation activities.

Preapproval Inspections

- Domestic inspections are completed by the FDA ORA Divisions.
- Foreign inspections are completed by various FDA Investigators and CDRH is the “home” district.



Preapproval Inspections

The inspection should be completed within:

8 weeks domestic	10 weeks foreign

The Investigator then has an additional 30 days to complete the Establishment Inspection Report (EIR).

Preapproval Inspections

CDRH issues inspection assignments.

The FDA investigator who receives the assignment generally calls to pre-announce the inspection, usually no more than five days in advance of the planned visit.

The pre-announcement allows the site to ensure that the site staff and all required records will be available during the inspection.

Note: an inspection assignment will not be issued until the applicant has successfully addressed any manufacturing deficiencies in the submission.

Preapproval Inspections

QSIT approach

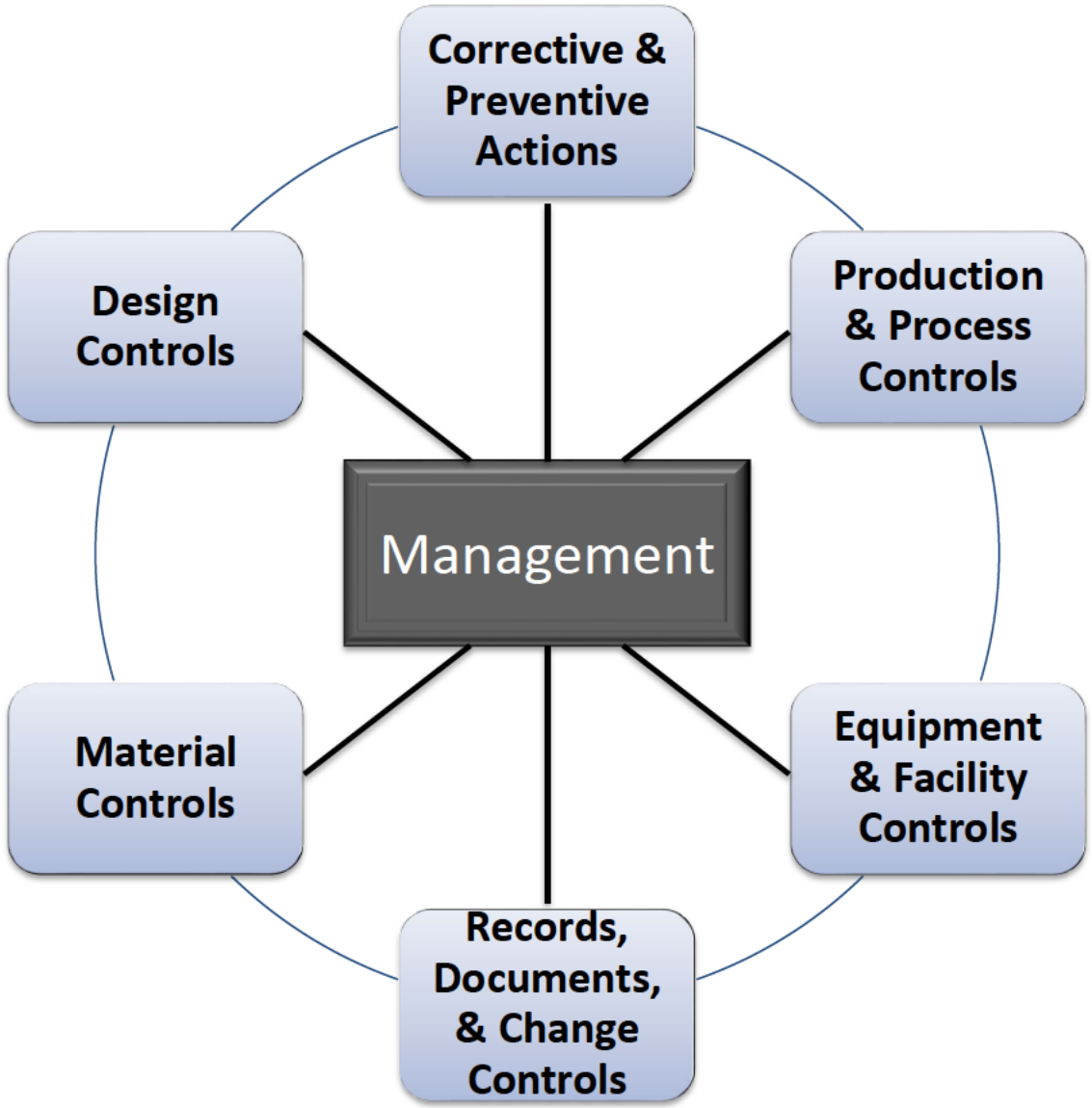
Level II baseline inspection

- Management Controls
- Design Controls
- CAPA
- Production and Process Controls

Investigator will determine:

- If procedures and systems have been adequately established and maintained
- If all process validations have been completed
- If processes are in control
- If manufacturing conditions are adequate

Preapproval Inspections 7 Subsystems of the Quality System



Preapproval Inspections

BE CORDIAL AND COOPERATIVE

MAKE A PHOTOCOPY MACHINE AVAILABLE

DOCUMENT THE INSPECTIONAL COVERAGE AND ANY ISSUES DISCUSSED BY THE FDA INVESTIGATOR

PROVIDE INFORMATION AND RECORDS THAT ARE CLEAR AND BE RESPONSIVE TO QUESTIONS FROM THE INVESTIGATOR, AS APPROPRIATE

DOCUMENT WHAT INFORMATION OR RECORDS WERE PROVIDED TO THE INVESTIGATOR

Points to Consider During a Preapproval Inspections

- Request to have a meeting at the end of each day to discuss inspection findings
- Based upon initial findings start to prepare corrections and response
- If corrections are already completed during the inspection, ask for the FDA 483 to be annotated.
- **Any questions/concerns that arise during the inspection should be raised to the investigator's ORA Divisions or CDRH.**

Preapproval Inspections

At the completion of the FDA inspection, the FDA investigator may issue a Form FDA 483 which lists significant inspection observations to the most responsible person at the site at the time of the closeout inspection.

Other observations may be discussed verbally with the site at the end of the inspection

The EIR, along with the Form FDA 483, if issued, and any supporting documentation or exhibits, is forwarded to CDRH for review and final inspection classification.

Inspection Classification

NAI – No Action Indicated

- No objectionable conditions or practices were found during the inspection (or the significance of the documented objectionable conditions does not justify further action)

VAI – Voluntary Action Indicated

- Objectionable conditions were found and documented, but they do not meet the threshold for regulatory action

OAI – Official Action Indicated

- Objectionable conditions were found and a regulatory action should be considered or recommended

Points to Consider – After an Inspection

If Form FDA 483 is issued at the conclusion of the inspection it is recommend you respond in writing to all the observations listed and the issues discussed verbally

- Your response may be evaluated before inspection classification
- Adequate responses may have a favorable impact on the final classification of the inspection

Within your written response include:

- An assessment of the root cause of the problem
- An evaluation of the extent of the problem
- Any corrections, corrective actions, and systemic corrective actions including a timeline for their implementation
- Supporting documentation

Points to Consider – After an Inspection

- Consider requesting a meeting with FDA when:
  - Inspection identified significant observations
  - There were communication concerns with the Investigator (i.e. major disagreements or misunderstandings)
  - There are complex product, process, or manufacturing issues

PMA Approval Process

CDRH/OPEQ will recommend PMA approval when:

- The manufacturing information has been reviewed and determined to be acceptable
- All inspections have been completed
- All EIRs have been reviewed and are classified as VAI or NAI

PMA approval is not recommended when:

- Inspection is classified OAI
- PMA OAI Letter typically will be issued
- Approvable pending GMPs

Post Approval Inspections

Post approval inspections are usually scheduled 8-12 months after approval.

This inspection will primarily focus on:

Any changes that may have been made to the design and/or manufacturing process	Compliance with the MDR regulations	Follow-up on prior observations

Premarket Approval Inspections

Preapproval Inspection	CY 2017	CY 2018	CY 2019	CY2020	CY2021	CY2022
Domestic Inspection	58	51	26	27	37	23
Foreign Inspection	23	29	33	7	0	29

Post Approval Inspection	CY 2017	CY 2018	CY 2019	CY2020	CY2021	CY2022
Domestic Inspection	64	27	12	10	20	13
Foreign Inspection	21	16	10	0	0	20

References

- 21 CFR Part 820
  - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=820

- Preamble to the QS Regulation Final Rule
  - https://www.fda.gov/medical-devices/quality-system-qs-regulationmedical-device-good-manufacturing-practices/medical-devices-current-good-manufacturing-practice-cgmp-final-rule-quality-system-regulation

- Compliance Program (7382.845) – *Inspection of Medical Device Manufacturers*
  - https://www.fda.gov/media/80195/download

References

- Quality System Inspection Technique (QSIT)
  - https://www.fda.gov/media/76038/download

- "Quality System Information for Certain Premarket Application Reviews: Guidance for Industry and FDA Staff" 2003
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quality-system-information-certain-premarket-application-reviews

- "The Review and Inspection of Premarket Approval Application Manufacturing Information and Operations" 2008
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/review-and-inspection-premarket-approval-application-manufacturing-information-and-operations

Contact Information

OPEQ/ORP/Division of Establishment Support/Regulatory Inspections and Audits Team

LCDR Jake Dyer

Jacob.Dyer@fda.hhs.gov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ADMINISTRATION

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Dealing with the Unexpected

PMA Submissions Workshop
May 23-25, 2023

Tony Blank
Tblank@AtriCure.com

The unexpected…

"To expect the unexpected shows a thoroughly modern intellect." (Oscar Wilde)

"No matter how much we think we understand the processes of nature, nature can always do something a little different, a little unexpected. It makes you realize how small we are." (David Vallee)

"Those who are easily shocked should be shocked more often." (Mae West)

Realities of Device Development

- Highly technical, complex field
  - Design
  - Manufacturing
- Limitations may exist in available methods
  - Laboratory models
  - Animal models
- Clinical studies are inherently a risky endeavor
  - Patient variability

Sources of the Unexpected

- Animal or laboratory testing
- Manufacturing testing/variability
- Clinical study outcomes
- Evolving scientific and regulatory expectations
- Adverse Advisory Panel Recommendation
- Post-market experience

Laboratory and Animal Studies

- Types of unexpected findings
  - Device failure in a laboratory test under stringent test conditions
  - Safety findings in an animal study
  - Manufacturing process validation
- Understanding the strengths and limitations of your test systems and methods
- Applicability of the findings to humans

Clinical Outcomes

- Examples of unexpected outcomes
  - May not meet primary study endpoint/hypothesis
  - May have a safety finding
  - May have device performance issues (malfunctions)
  - May have a differential effect in different patient subgroups
  - Study conduct issues
    - Subject discontinuations
    - Protocol violations and deviations
    - Missing data

Clinical Outcomes (con’t)

- Understand and investigate the finding
- Critically evaluate the finding and determine the impact on the study and resulting data
  - Additional research
  - Refinements in patient population
  - Conclusions about the device

Evolving Science

- Standard of medical care changes – control group
- Primary endpoint evolves
- Surrogate endpoint no longer qualified
- Expectations for effectiveness evolve over time
- Understanding of the disease changes over time

Panel Recommendation

- Panel may be critical of
  - Clinical study design
  - Data and its analysis
  - Implications of certain findings
  - Applicability of the study results to the “real world”
  - Post market issues (off-label use, training and skill of device users)

Post - Market Experience

- Trend in complaints or malfunctions
- Device failures
  - Long term patient follow-up
- Adverse events
  - Differences in patient populations and care

Scenario for Discussion

You're company has just completed follow-up for the clinical study of your new permanent implant and the results look great! The study met its primary endpoint and the Clinical Study Report has been completed.

One of the engineers in Process Development has determined that withing current setting of the mfg equipment, the material of the implant will have an increased susceptibility to fatigue failure. Risk analysis has determined this failure would be catastrophic to patients. The engineering team has developed a change to manufacturing that will eliminate the possibility of failure. A review of records reveals that nearly half of the devices implanted during the study are susceptible to this failure. To date, no failures have been observed, but engineering is certain it is only a matter of time before devices will begin to fail.

As the head of regulatory, you've been called into a meeting with the Board to discuss the situation. In particular, they would like your perspectives on (1) next steps and (2) impact on the PMA application.

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My Thoughts…

The first challenge in situations like those described in this Case Study is determining the appropriate manner to react. Typically folks will fall into one of two extremes – either (a) immediately presume the new analysis that 'one of the engineers' has completed is 100% accurate and predictive and the physicians, patients and FDA must be immediately notified or (b) immediately discount the analysis as an anomaly that cannot undo years of product development and no action is warranted. In my opinion the appropriate response of a company facing this scenario must be timely, purposeful and driven by science. If I were the Regulatory person meeting with senior management in this situation, I would advise the following steps be taken…

- Immediately identify a technical team to review the analysis, hypotheses and conclusions made by the engineer. This analysis should be done in conjunction with a review of the current risk analyses. The objective of this review should be to determine whether the conclusions drawn are reasonable.

- In parallel, a team should review the protocol-prescribed follow-up plan (including imaging and frequency) to assess the likelihood of failures (should they occur) being detected at the scheduled follow-up. If not – and the analysis confirms the engineer's conclusions – then appropriate members of the clinical team (as well as the clinical investigators and any necessary outside medical experts) should consider what additional follow-up or possible actions might be considered for patients with implanted devices to minimize their risk.

Fundamentally, the actions taken by the organization need to be focused on making timely, science based decisions to protect the patients with the implanted devices.

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My Thoughts…

With respect to communications…

- As described above, the company should engage the investigators in evaluate what – if any steps – should be taken to protect patients.
- If the analyses and hypotheses and confirmed by the team, clinical investigators will expect to be informed periodically on the status of patients in the trial. In particular, they will be interested to informed about about the frequency, severity and outcomes of fatigue failures in the clinical trial patients as this will assist them in the continuing care and follow-up of other patients in the trial. The organization would be well served to establish a formal process for regularly communicating defined information with all investigators in the trial.
- With respect to FDA, any new information that alters the risk/benefit conclusions upon which the clinical trial was initiated should be discussed with the Agency. My recommendation would be – presuming the analysis is verified – would be to contact FDA and arrange a meeting to review the analysis and action plan (in particular – any revisions to patient follow-up).
- With respect to Patients, this will be driven by the analysis and engagement with the Investigators and FDA. Clearly if the analysis determines that patients should have more frequent, longer term, or more intensive follow-up visits, then patients will need to be informed and likely will need to give further consent.

With regard to the likelihood and/or timing of PMA Approval – my advice to senior management would be to come back to that after the teams have completed their analyses and initiated actions necessary to protect the patients. In general, if there is fundamental flaw in the design and/or manufacture of the product, it's fair to say the timing and likelihood of Approval with the current iteration of the product is in jeopardy.

Final Points to Consider

- Determine the importance of the findings and when and how they should be communicated
  - Study subjects and investigators
  - Regulatory authorities
  - Market status worldwide

Final Points to Consider (con’t)

- Seek scientific and medical input to make the best, credible decisions
  - Resources within company
  - Resources outside the company
- Plan to address the findings
  - Premarket
  - Post-market
- Key risk management/mitigation plan

Thank you!

Questions?

Tblank@AtriCure.com

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THANK YOU!

Tblank@AtriCure.com

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NAMSA®

The Care and Feeding of Approved PMAs

Presented by: Monica Montanez, Principal Strategy Consultant

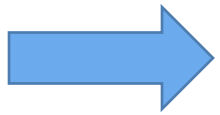
Date: May 24, 2023

Current Environment

- FDA's view of changes is very conservative; few changes qualify for annual reporting
  - There are several working groups and forums where Industry and FDA have been meeting to discuss appropriate reporting criteria
- FDA has been driving consistency:
  - Same type of change treated the same way across Industry
  - Trying to assure equity in the form of user fee costs
- Note that change submissions have become a significant revenue stream for FDA (ex: ~$7,065 user fee for a 30-Day Notice, $30,908 for a Real Time Review)

PMAs

- Class III, Highest Risk Devices
  - Supports 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 reasonably assure safety and effectiveness

➢ Increased risk of device  Increased regulatory controls

Post-Approval Controls

- Mandatory Conditions
  - PMA Supplement for certain changes
  - Periodic (annual) reports
  - MDR reporting
- Other postmarket controls
  - Post-approval studies (PAS)
  - Device tracking
  - Postmarket surveillance

Post-Approval Studies (PAS)

- Maybe required at time of approval, as a condition of approval
- The PMA approval order will state the reason or purpose for such requirement, the number of patients to be evaluated, and the reports required to be submitted

> Be advised that failure to comply with any post-approval requirement constitutes grounds for FDA withdrawal of approval of the PMA in accordance with 21 CFR 814.82(c) and 814.46(a)(2).
>
> In addition to the Annual Report requirements, you must provide the following data in post-approval study (PAS) reports for each PAS listed below.
>
> **1. OrganOx *metra*® WP01 Long-Term Follow-Up PAS (Protocol Version 1, dated November 2021)**

- PAS is distinct from postmarket surveillance/522 studies, which maybe required any time after PMA approval

Postmarket Surveillance Studies

- FDA has authority to require postmarket surveillance of a class II or class III device that meets any of these criteria:
  - Failure would be reasonably likely to have serious adverse health consequences
  - Expected to have significant use in pediatric populations
  - Intended to be implanted in the body for more than a year
  - Intended to be a life-sustaining or life-supporting device used outside a device user facility
- Examples:
  - TMJ devices
  - Implantable pacemakers
  - Metal on metal hips

Device Tracking

- FDA can require manufacturers to track certain devices from manufacture through the distribution chain
- Purpose of device tracking – to ensure manufacturers of certain devices establish tracking systems that will enable them to promptly locate devices in commercial distribution
- Tracking information may be used to facilitate notifications and recalls in the case of serious risks to health presented by the device
- Examples:
  - Defibrillators, pacemakers, pulse generators
  - Ventilators
  - AAA endovascular grafts

Medical Device Reporting Requirements

- Medical Device Reporting (“MDR”)
- Required within 30 day (or 5 days) of when manufacturer becomes aware of information that reasonably suggest that the device:
  - May have caused or contributed to a death or serious injury or
  - Has malfunctioned and such or a similar device marketed by the manufacturer would be likely to cause a death or serious injury if the malfunction were to recur

PMA Amendments

- Time-sensitive updates that do not affect safety and effectiveness
- Examples:
  - Release of labeling after PMA approval
  - Change in ownership
  - Change in contact information (e.g., company name, official correspondent, address)
  - Voluntary market withdrawal (cease marketing)
  - Modifying a pending PMA or a pending PMA supplement

Periodic (Annual) Reports

Also known as PMA “Annual Reports” (21 CFR 814.84)

Key Requirements:

- Submitted each year on the PMA’s approval anniversary.

  Continued approval of the PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. This report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84.

- Contents include:
  - Number of devices shipped or sold; number implanted
  - Changes previously submitted as PMA supplements
  - Other changes, not previously submitted
  - Summary and bibliography of published and unpublished reports

Current Environment

- FDA also has the option to retrospectively require PMAs for changes filed as Annual Reportable (AR)
  - When reviewing your annual report FDA may identify changes that "should have had" a prior approval submission and request that those be filed immediately
  - Sponsor has option to provide additional justification or submit supplement; generally, you get one chance to make your case
  - FDA is not enforcing suspension of manufacturing and usually no recall/ withdrawal in these scenarios, but they have the ability to do so

➢ Take-away: Your change description you provide in AR is critical

Annual (Periodic) Reports

- Includes a description of any changes not previously reported or made by the company (meaning changes that do not affect safety or effectiveness)
  - Examples:
    - Qualification of alternative supplier of a non-critical material, service, or component (with specifications left unchanged)
    - Increase in sample size for quality control testing or number of products sampled for release testing
    - Tightening of a manufacturing process parameter

Annual (Periodic) Report

- The number and type of changes reported are dependent on the company's business risk views (more aggressive = more changes in the annual report)
- If FDA disagrees with company's (i.e., non-reportable) decision, the company will receive an FDA letter requiring a new supplement be submitted to FDA (retrospective submission)
  - FDA continues to practice "enforcement discretion" although technically they could classify your device as adulterated under a strict interpretation of that statue; result = cease distribution until the change is approved

PMA Supplemental Submissions

PMA Supplement- When Required

- PMA Supplements are required:
  - When a proposed change to a PMA approved device ***affects the safety or effectiveness*** of the approved device.
  - Changes to a 510(k) cleared devices require submission of a new 510(k) notice only if the change could significantly affect the safety or effectiveness of the cleared device
  - In contrast, any change that affects the safety and effectiveness of a PMA device (positively or negatively) triggers a PMA supplement of some type
- Changes made to a PMA device that do not affect safety or effectiveness are generally reported in Annual Reports

Types of Changes that May Require a PMA Supplement

- New Indication for use
- Labeling changes
- Use of a different manufacturing or sterilization facility
- Changes in manufacturing methods, or quality control procedures
- Changes in sterilization procedures
- Changes in packaging
- Changes in performance or design specifications, circuits, components, ingredients, principal of operation, or physical layout of the device
- Extension of the expiration date of the device (no approved protocol)

Changes Affecting S & E

- All changes must meet the requirements of the Quality System Regulation under 21 CFR Part 820 include the design control requirement under §820.30. Design changes, including a risk analysis, validation (or where appropriate, verification) of the changes to design or manufacturing process. Refer to *FDA Guidance: Modifications to Devices Subject to Premarket Approval (PMA) –The PMA Supplement Decision-Making Process"* for additional information
  - Recommend incorporating the FDA guidance into an SOP linked to your change order process to ensure the changes are properly assess and captured in your QS documentation.

PMA Supplements – Review Times

Application Type	FDA Review
Panel-track supplement	320 days
180-day supplement	180 days
Manufacturing change supplement	180 days
Real-time supplement	90 days
Special changes being effected	May be implemented prior to FDA approval

PMA Supplements – User Fees (FY 2023)

Application Type	Standard Fee	Small Business Fee
PMA*	$441,547	$110,387
Panel-track Supplement	$353,238	$88,309
180-Day Supplement	$66,232	$16,558
Real-Time Supplement	$30,908	$7,727
30-Day Notice	$7,065	$3,532
Annual Fee for Periodic Reporting	$15,454	$3,864

*Small businesses with an approved small business designation with gross receipts or sales of $30 million or less are eligible to have the fee waived on their first PMA.

PMA Supplement Strategy

- FDA has created several different submission types to address the wide spectrum of possible changes
- Each has its own unique content requirements and process/timeline
- Some are clear, others may require a pre-submission dialog with the Branch: in particular:
  - 180 Day Supplement vs. Real-time Supplement
  - Special Supplement, Changes Being Effective (CBE)

PMA Supplements: Special Changes Being Effected

- Available in limited circumstances when the modification enhances the safety of a device or its use
- Narrow exception to the general rule of prior FDA approval of changes to a PMA
- No design changes
- Can only be utilized when:
  - There is newly acquired safety information;
  - The information was not previously submitted to FDA; and
  - This information:
    - Involves labeling changes that add or strengthen a contraindication, warning or precaution; or
    - Concerns an adverse reaction for which there is reasonable evidence of a causal association

PMA Supplements: Special Changes Being Effected

- Most appropriate for labeling changes
- Can be used for manufacturing changes that enhance safety
  - Permitted when there are enhancements to the quality control or manufacturing process that add a new specification or test method, or otherwise provide additional assurance of purity, identity, strength, or reliability of the device that improve safety but do no impact effectiveness
- Design Changes are *not* appropriate for this submission type
  - May be placed into effect by the applicant prior to the receipt of a written FDA order approving the PMA supplement (upon FDA receipt of acknowledgement letter)
  - In practice, FDA *requests* that they agree before this type of supplement is filed
  - Sometimes used in conjunction with a field issue if the “correction” is labeling (ex. Off-label safety issue) rarely used!

PMA Supplements: Real-Time

- Minor changes supported by pre-clinical or animal testing, with no new clinical data
- Involve review within a single scientific discipline, rather than multidisciplinary review
- Prior to submitting, must obtain concurrence from FDA review team
- May include changes to:
  - Device Design
  - Software
  - Instructions for use, warnings or precautions or other labeling that does not affect the indication or contraindications
  - Sterilization and packaging procedures

PMA Supplements: Real-Time

- Appropriate where the following circumstances also exist:
  - The change is of a type expected for that device type;
  - The change has been validated according to scientific principles, accepted test methods for that type of device, or via an FDA-recognized standard or guidance document;
  - The change is adequately supported by preclinical or animal testing, without the need for clinical data; and
  - Typically involves review by only one scientific discipline, as opposed to multiple disciplines
- FDA generally expects to complete review of Real-Time Supplement within 90 days

➢ Key Consideration: Straightforward change with a well-established evaluation paradigm

PMA Supplements: 30-Day Notice

- PMA supplements are required for any change to an approved PMA device that affects safety or effectiveness, *unless* such change is a modification in a manufacturing procedure or method of manufacturing

- Changes which affect safety or effectiveness that may qualify for a 30-day notice include, changes in manufacturing procedures or methods of manufacturing

- When FDA finds a 30-day notice inadequate, a 135-day PMA supplement must be submitted (21CFR 814.39(f))
  - Key Consideration: Straightforward change with a well-established evaluation paradigm

PMA Supplements: 30-Day Notice/135-Day Supplement

- Examples that may qualify include changes to:
  - Purchasing controls
  - Sterilization type or process parameters within the same facility
  - Automating existing processes
  - “Joining” processes where the properties of the new adhesive are well known and not considered to be a potential problem; where a different solvent or energy source is used to join the parts
  - Cleaning methods used to remove manufacturing materials
  - Manufacturing materials
  - Environmental conditions of the manufacturing, storage or distribution facilities
  - Suppliers of components or materials where specifications are unchanged

PMA Supplements: 30-Day Notice/135-Day Supplement

- In practice, generally reserved for relatively minor manufacturing changes
- May wish to consider seeking informal agency guidance where the changes at issue are not clearly outlined in FDA's guidance documents

  - Key Consideration: It is critical to differentiate and align internally on manufacturing changes vs. "design" changes

PMA Supplements: Manufacturing Site Change

- A PMA Supplement is required for a change regarding the use of a different facility or establishment to manufacture, process, or package the device
- Site Change Supplements are considered 180-Day PMA Supplements
  - Review times can vary depending on the amount of information required and whether a successful inspection is necessary for approval
- Supplement must demonstrate compliance with QS regulation
- Preapproval inspection may be necessary

PMA Supplements: Manufacturing Site Change

- Certain site changes that may be candidates for 30-Day notices versus Site Change Supplements
- Examples:
  - Moving manufacturing, processing, or packaging activities for a finished device from one site to a relocation site, both of which were ***approved in the PMA*** for the device, ***if*** the moved activities are already conducted at the relocation site for the same or similar device
  - Moving manufacturing, processing, or packaging activities for a finished device from one facility to another with the ***same establishment that has the same FDA Establishment Identifier (FEI).***

PMA Supplements: 180-Day Supplements

- 180-Day Supplements appropriate for certain types of significant changes that affect the safety and effectiveness of the device
- Typically used when only new preclinical testing is necessary
- Generally considered appropriate when key clinical data from the original submission are still applicable
  - Additional limited clinical data may be necessary as bridging data

PMA Supplements: 180-Day Supplements

- Examples of changes that may be candidates for 180-Day Supplements:
- Principle of operation
- Control mechanism (e.g., changing device operation from manual to automatic)
- Device design or performance
- Labeling
- New testing requirements or acceptance criteria

PMA Supplements: Panel Track Supplement

- The difference between a Traditional PMA and a Panel-Track Supplement can be subtle
  - Considerable FDA discretion

- The real question is typically the data that will support the change, not the type of submission

➢ Key Considerations:

Major alteration in indications for use

The ability to leverage data from the original PMA submission

Strategies for PMA Supplements

Key concepts:

- FDA approval utilizing the quickest and most appropriate PMA approval approach
- A company does not have to distribute/commercialize product or product modification after FDA approval
  - The prior baseline remains ‘approved”, unless the change is driven by a field issue/recall where continued distribution of the unchanged baseline may be considered adulterated product

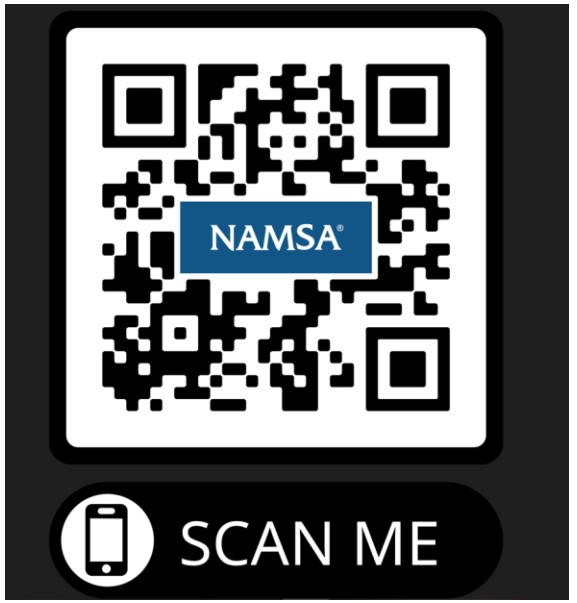
Strategies for PMA Supplements

Key concepts (cont.):

- If possible, submit all “changes” as “alternative” option
- May be able to “split” a larger change into smaller pieces, each “sub-change” with its own specific (different) regulatory strategy
  - Ex. Company wants to simultaneously change a manufacturing process and update their labeling
    - Combined into one submission this is 180 PMA/S
    - Alternate path: submit manufacturing change via 30-Day Notice and labeling change via Real-Time Supplement; both approvals complete within 90 days vs 180

FDA Draft: Predetermined Change Control Plan for AI/ML-Enabled Device Software Functions

- PMA Class III devices are in scope of this guidance
- PCCP Requirements:
  - Establishing a PCCP as part of the marketing application
    - Standalone section
    - TOC “Predetermined Change Control Plan”
    - Device Description, labeling and/or relevant sections
    - Described in the Summary of Safety and Effectiveness document (SSED) and approval order



Summary

- Class III medical devices are subject to substantial regulatory controls after approval
- Changes to PMA introduces various types of post-approval submissions:
  - Post approval periodic reporting (annual reports)
  - Post-approval studies (PAS) and reports
  - Amendments
  - 30-Day Notices
  - PMA Supplements – Real-time, Special Changes Being Effected, 180-Day Supplements, Panel Track Supplements
- Each submission type addresses different aspects of post-approval activity related to the device
- Predetermined Change Control Plan draft guidance-Submit your feedback by July 3rd.

NAMSA®

Thank You

CDRH Ombudsman Program: Roles, Responsibilities, and the Appeals Process

AdvaMed Workshop

Ken Skodacek
CDRH Deputy Ombudsman
May 24, 2023

Background & Experience

20 years - Industry

10 years - CDRH

5 years - Ombuds

* Other Activities

Why did I join FDA?

What is an ombuds?

om·buds·man

/ˈämbədzmən/

noun

an official appointed to investigate individuals' complaints against maladministration, especially that of public authorities.

Ombuds Standards of Practice

Confidential

Independent

Impartial

CDRH Ombudsman Program

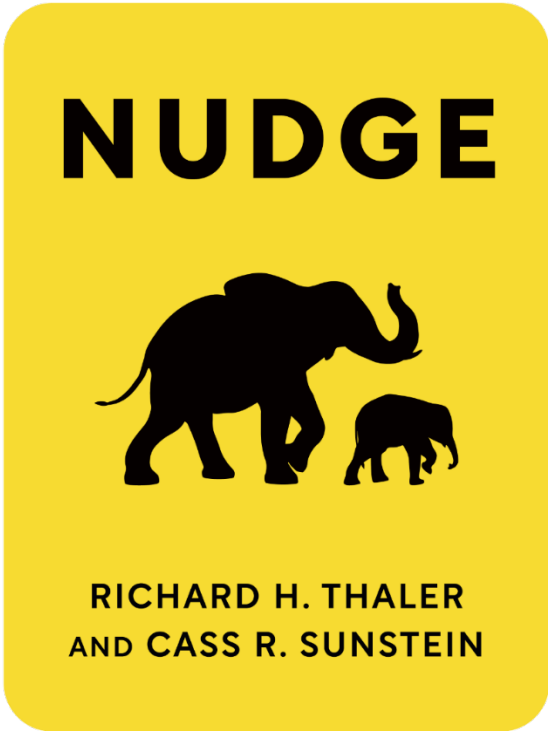
- Voluntary resource to manufacturers, consumers, & CDRH
- Direct, unrestricted access to CDRH staff at all levels
- High level of organizational, personnel, & regulatory awareness
- Encourages clear, candid, & constructive communication
- Focused on resolving differences in regulatory and/or scientific opinions, both external & internal
- Helps to resolve misunderstandings
- Ensures fairness in processes, including appeals

What is our role?

No, not this

More like this

Or this



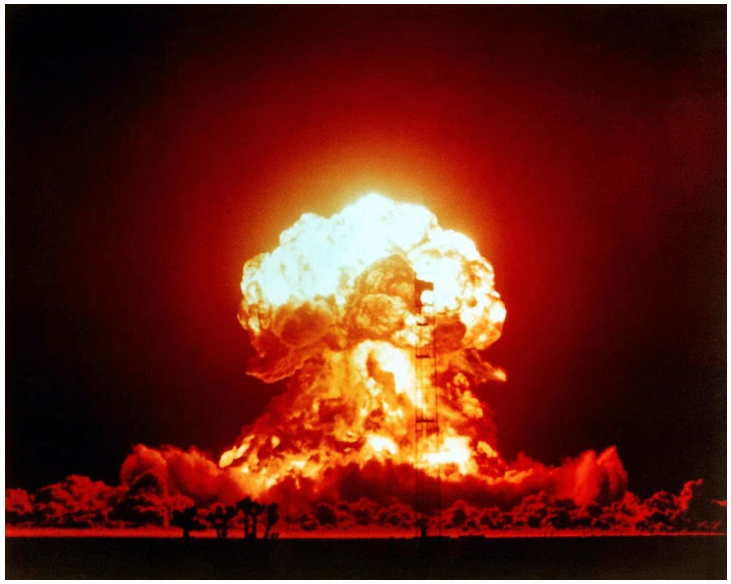
What is the “ombuds process”?

- Confidential conversation(s)
- Review of options
- Provide advice as requested

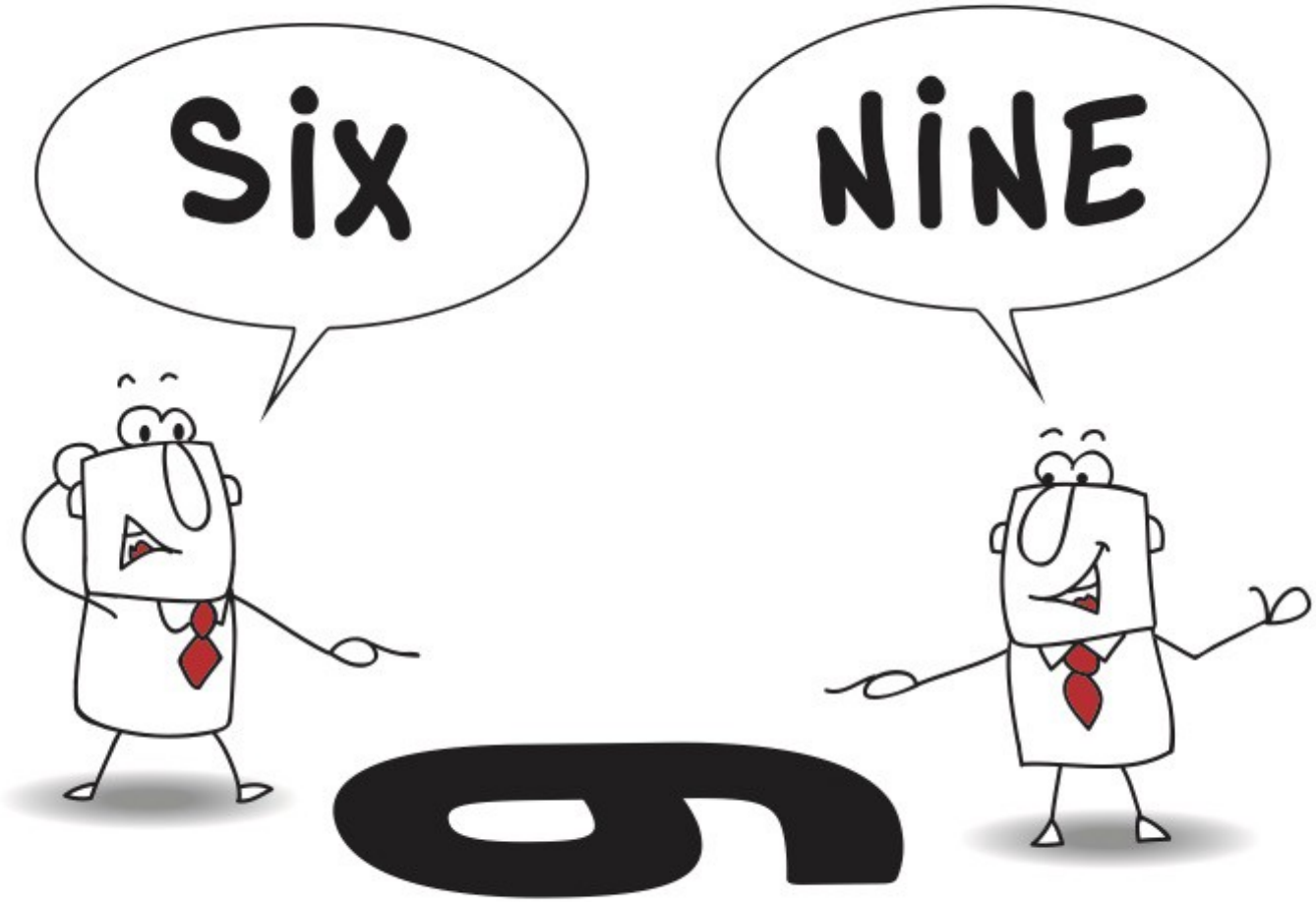
- Contact FDA staff and/or leadership
- Join internal meeting(s)
- Join external meeting(s)
- Additional follow-up conversations

CDRH Ombudsman Program is not

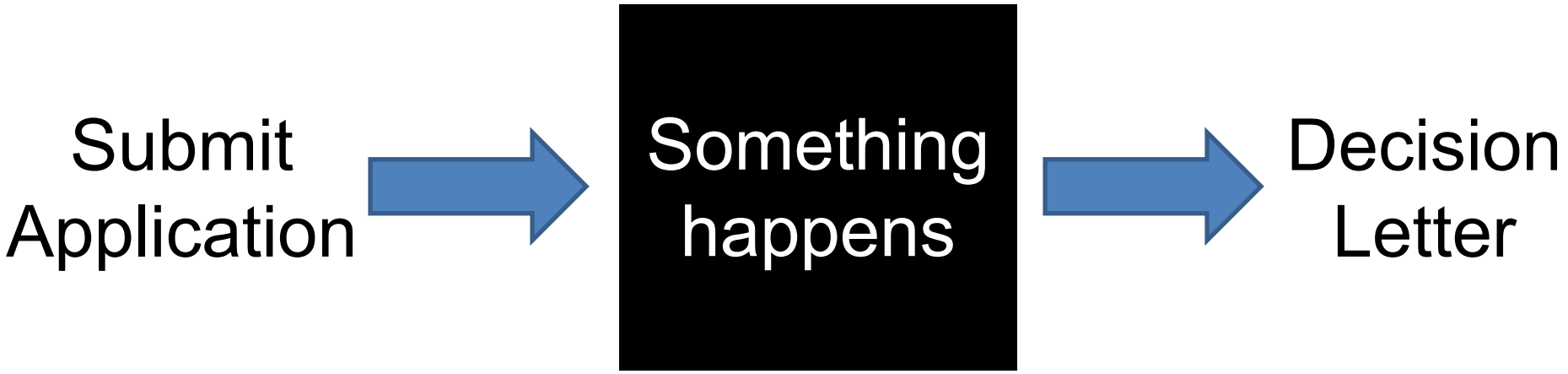
- 1st Option
- Only Option
- Nuclear Option



Expect Disagreements



Manufacturers View of the FDA Process



Unfulfilled Expectations

Beliefs vs. Supporting Data

In God we trust;

all others must bring data.

FDA Commissioner Robert Califf

…and analyze and present it as clearly and concisely as possible.

Manufacturer & FDA

Manufacturer

More experience with specific device

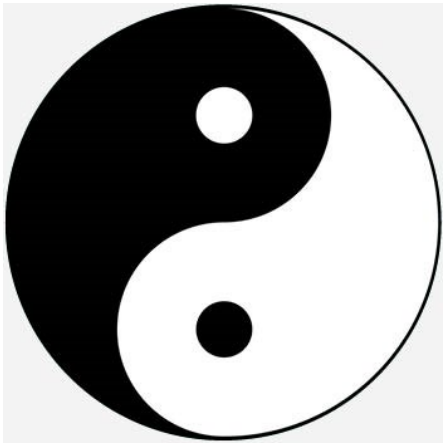
Familiarity with history

May have expert consultants (or not)

Focused on specific device

Perspective naturally influenced

Limited finances ($ in bank)



FDA

Experience with other devices

Limited perspective from submission

Specialized expertise as an organization

Juggling submissions

Small review team with fresh perspective

Limited time (statutory or MDUFA goals)

Considering contacting us?

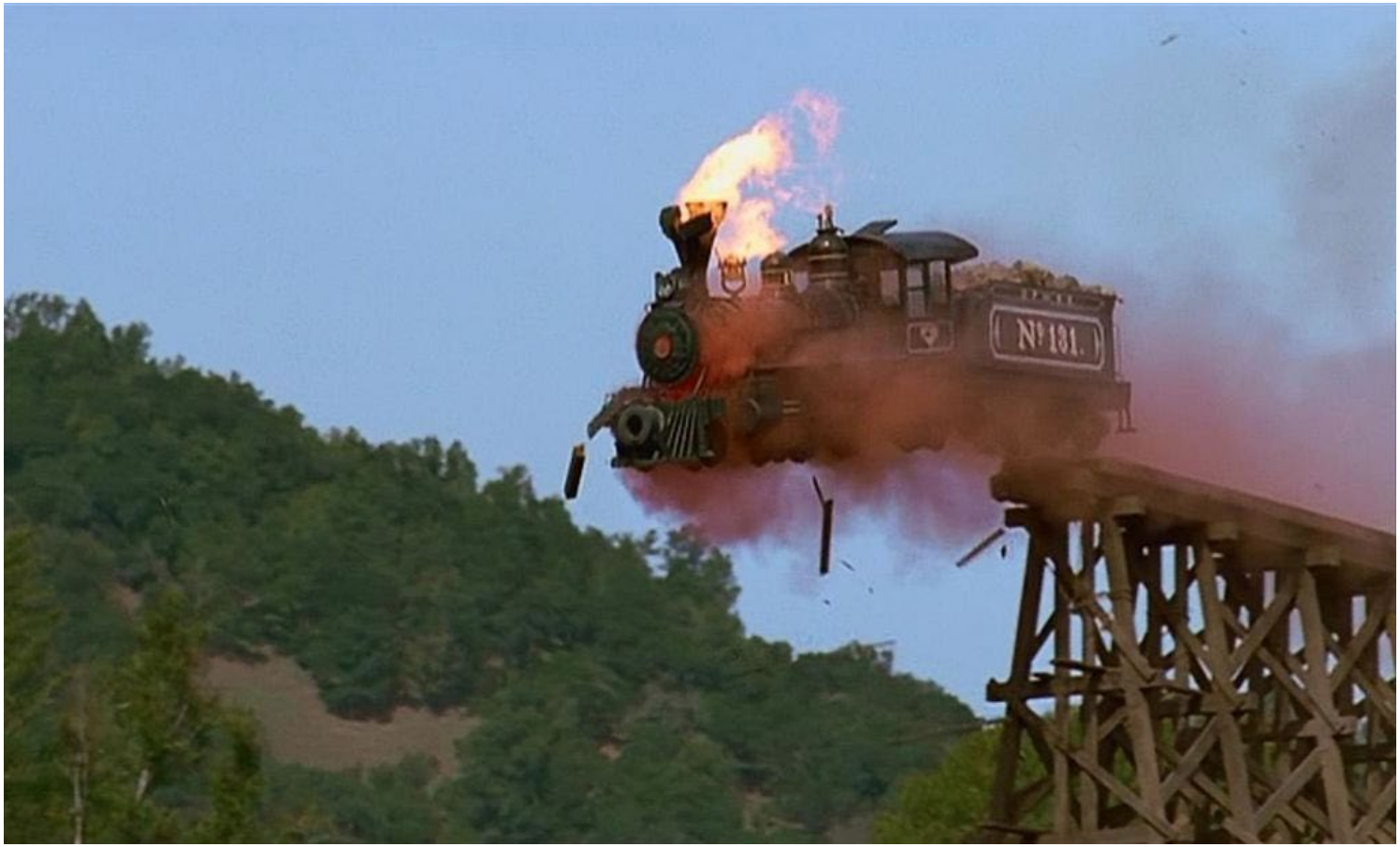
If / When

Considering Your Many Options

Does something seem “off”?

When should I contact you?

Figure 1: This is too late.



Hard Line for Regulatory Decisions

Before Final Decision	After Final Decision
Many Options	One Option

21 CFR Part 10.75 & 800.75

CDRH

FDA

"Request for Supervisory Review" – AKA "appeal"

Internal Agency Review of Decisions

- Decision of an FDA employee is subject to review by the employee's supervisor
- Review made by consultation between the employee and the supervisor or by review of the administrative file
- Interested person outside the agency may request internal agency review of a decision
- Internal agency review of a decision must be based on the information in the administrative file

Primary Appeal Resources

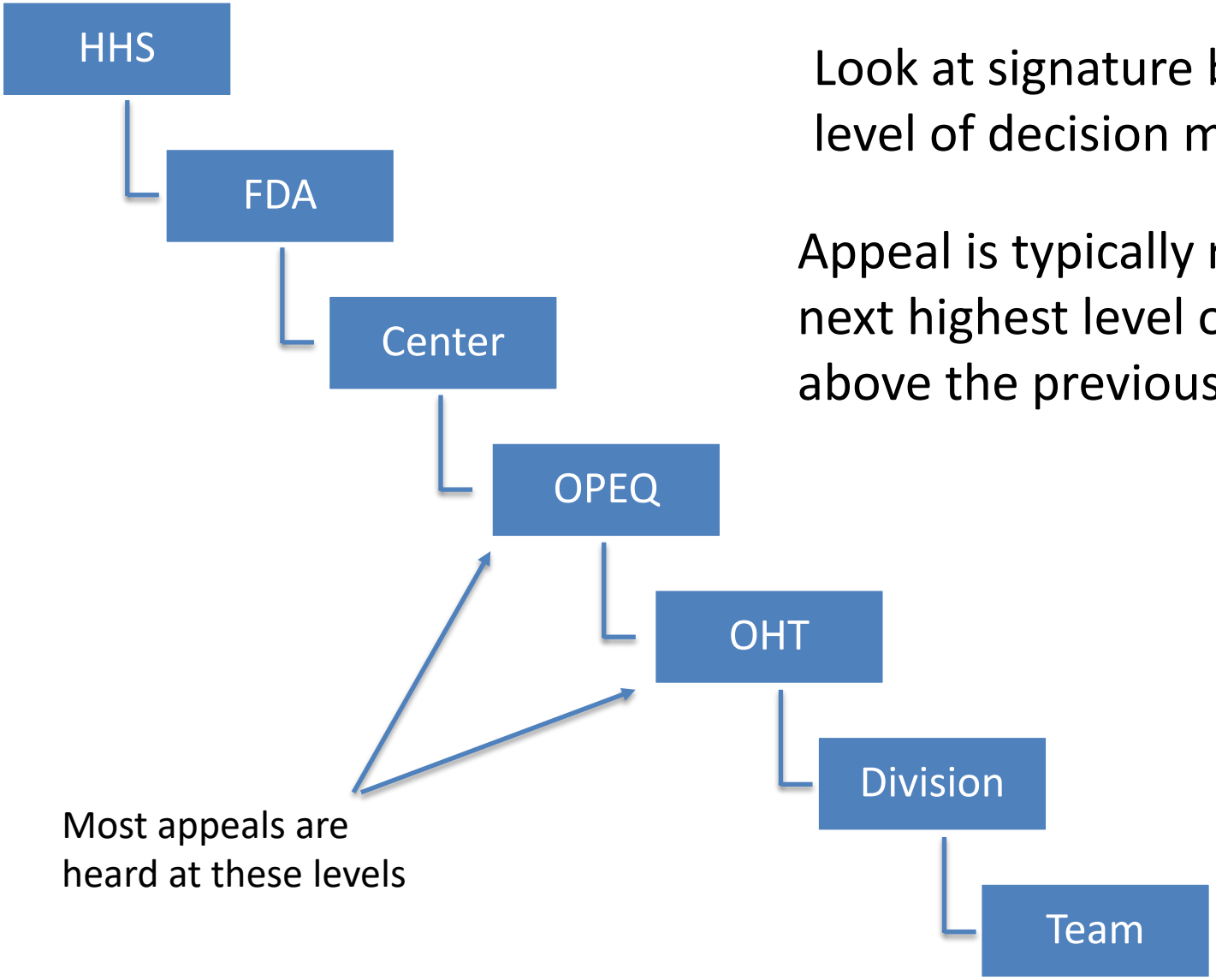
[21 CFR 10.75 Internal Agency Review (FDA)]

[21 CFR 800.75 Request for Supervisory Review (CDRH)]

[CDRH Appeals Processes]

[CDRH Appeals Processes - Questions and Answers about 517A]

Level of Appeal



Look at signature block for level of decision maker.

Appeal is typically reviewed at the next highest level of authority above the previous decision.

517A (Significant) Decisions

- 510(k): Not Substantially Equivalent; Substantially Equivalent
- PMA/HDE: Not Approvable; Approvable; Approval; Denial
- Breakthrough Devices Designation: Granted; Denied
- IDE: Disapproval; Approval; Approval with Conditions

Also refer to 21 CFR 800.75

Examples of Other Decisions

- 510(k) Requests for Additional Information
- PMA Major Deficiency Letter
- De Novo Final Decisions
- De Novo Requests for Additional Information
- HDE Requests for Additional Information
- 510(k) and PMA Refuse to Accept Letters
- 510(k) Deletions
- Postmarket Surveillance Orders (Section 522)
- CLIA Waiver Decisions
- Warning Letters
- Import Certificates
- 513(g) Letter
- PMA Refuse to File (see 814.42(d)(2))*

Requesting Substantive Summary

- Defined in 517A and guidance
- Scientific and regulatory rationale for decision
- Controversies and differences of opinion
- Consideration and application of least burdensome requirements

Potentially Insightful

We recommend that you make your request as quickly as possible as an amendment to the file, in preparation for submitting an appeal. You may also request copies of the associated review memos via FOIA as a first party, though you probably won't receive the information quickly enough to support your preparation for an appeal.

Submitting an Appeal

- Submit appeal to CDRH (e.g. to Doc Control Center as an amendment for premarket submissions)
- Opening statement: request for supervisory review per 10.75 (appeal)
- Preferred venue: meeting (telecon or in-person) or no meeting
- Summary of situation and basis for appeal
- Closing statement with specific requests
- Attachments with supporting documentation*

Appeal Timelines

You

30 days to appeal for 517A decisions

"Appeals received by the Center later than 30 days after the date of a significant decision are not eligible for review under section 10.75. FDA recommends that a 10.75 appeal of any decision be submitted within 30 days of the decision, but we will generally permit greater flexibility with respect to the timeframe of appeals of actions that are not significant decisions. Generally, appeals of other decisions received after 60 days would be untimely."

FDA

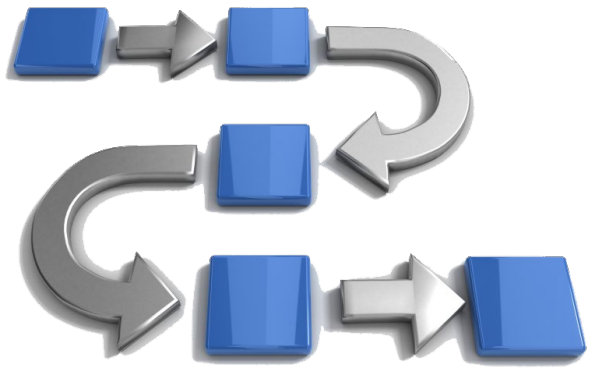
30 days to schedule meeting
+ 30 days to issue decision

OR

45 days to issue decision without a meeting

Appeal Process for CDRH

1. Receive and review request for appeal
   Accept or deny request
2. Assignment to and briefing of appeal authority
   Schedule meeting date and time
3. Preparatory meeting (internal to CDRH)
4. Meeting with applicant
5. Post-meeting discussion (internal to CDRH)
6. Preparation and review of decision letter
7. Decision letter issued by email



Appeal Meeting

- Review Authority

Focus

- Ombudsman Program
- Regulatory Advisor(s)
- Team Staff
- Team Management
- Program Staff
- Program Management

Be prepared for questions during the 1-hour meeting and be prepared to provide additional clarifying information after the meeting.

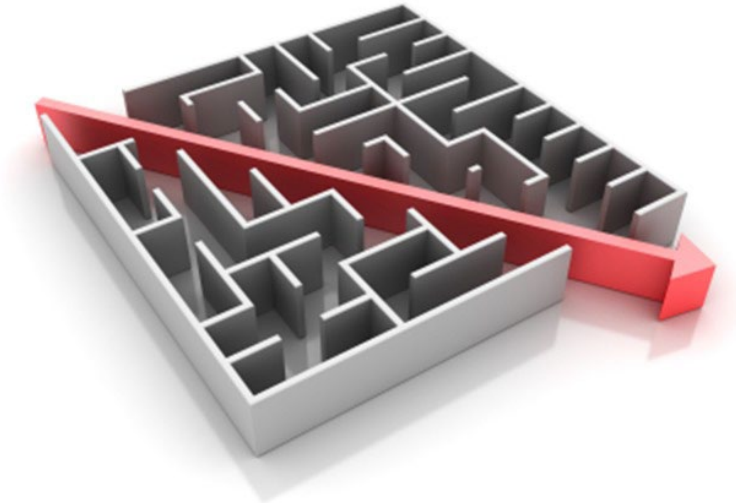
Outcomes of Appeals

A Decision Fully Overturned

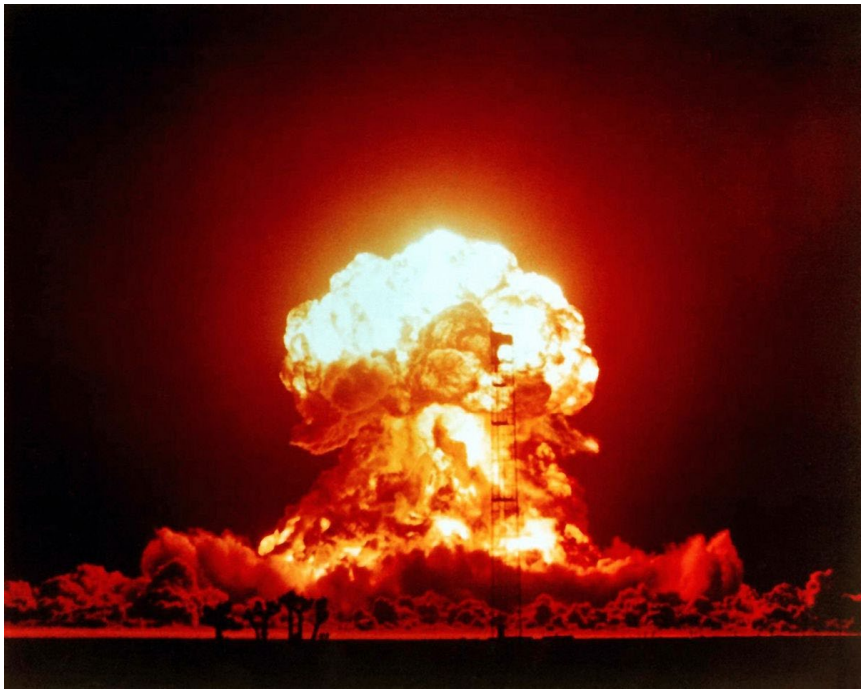
B Decision Partially Overturned

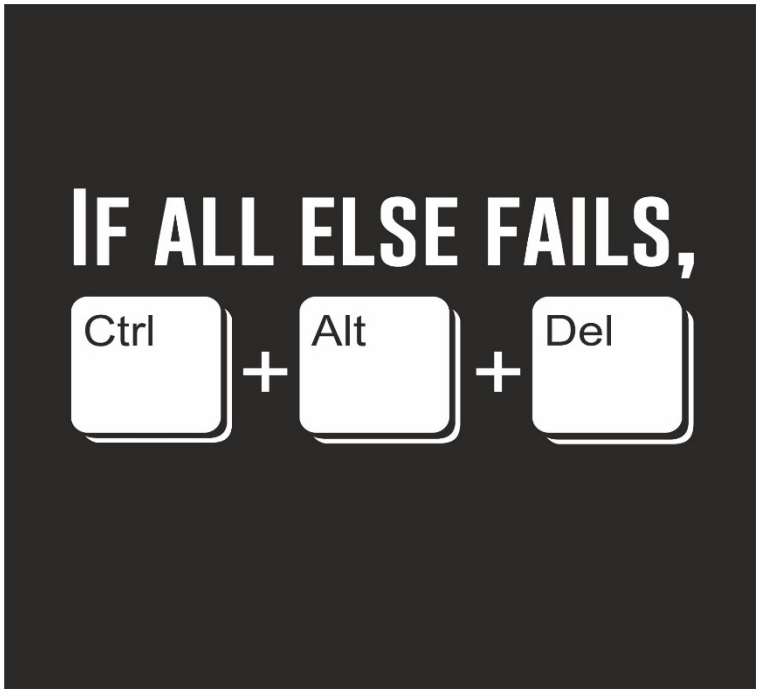
C Decision Fully Upheld

Clarity in rationale & potential paths forward



Are you considering AN APPEAL?





Non-Retaliation & Fairness

"Without question, companies are free to vigorously challenge agency positions and requirements, and to freely voice their views to the agency, the press, the public, and the Congress."

"The Center is strongly committed to ensuring that interactions with entities doing business with the Center are free from bias or retaliation at every stage, including the filing of an appeal of a Center action."

https://www.fda.gov/about-fda/office-chief-scientist/non-retaliation-policy

Insight: Other Options

<u>ANOTHER OPTION</u>

Informal Discussion about ***<u>Next Steps</u>***

Insight: Least Burdensome

Least Burdensome Provisions - Concept and Principles

Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions

Insight: Benefit/Risk

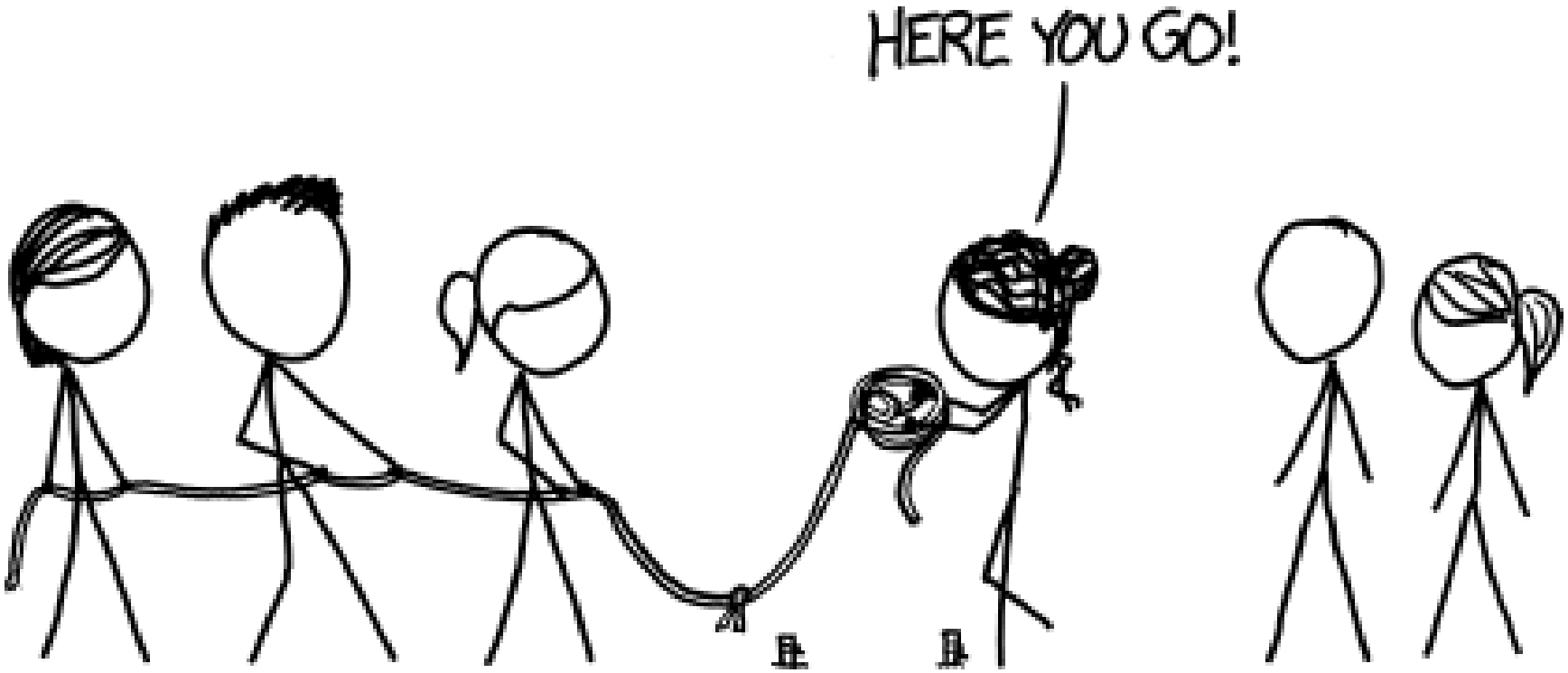
Benefit-Risk Factors to Consider When Determining Substantial Equivalence in **Premarket Notifications (510(k))** with Different Technological Characteristics

Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device **Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions**

Factors to Consider When Making Benefit-Risk Determinations for Medical Device **Investigational Device Exemptions**

Factors to Consider Regarding Benefit-Risk in Medical Device **Product Availability, Compliance, and Enforcement Decisions**

Insight: Shared Goals



This is not a competition with FDA.

Insight: Support

Insight: Non-Decisions

Can I appeal feedback from a Q-Submission?

Can I appeal IDE Study Design Considerations?

Can I appeal a withdrawn submission?

Can I appeal observations from a Form 483?


TIME FOR QUESTIONS

Ken.Skodacek@fda.hhs.gov
301-796-6364
CDRH Deputy Ombudsman

Abiy.Desta@fda.hhs.gov
301-796-0293
CDRH Ombudsman

CDRHOmbudsman@fda.hhs.gov

For ORA-related matters (inspections, importation, etc.),
you can also contact Erica Katherine, ORAOmbudsman@fda.hhs.gov.

De Novo or PMA Pathway Recap

1. NO Existing PMA Device.

2. NO Predicate, per criteria below:
   a. Same intended use? [Yes: go to 2b; No: NO predicate]
   b. Same technological characteristics? [Yes: predicate exists; No: go to 2c]
   c. Different technological characteristics that do not raise a new question of safety or effectiveness? [Yes: predicate exists; No: NO predicate]

3. De Novo if both criteria below are met.
   a. The technological characteristics for the proposed intended use are well understood such that bench/animal/clinical testing can be defined to assure device safety and effectiveness (i.e., special controls can be defined); and,
   b. Clinical testing (if needed) demonstrates benefits outweigh risks and reasonable effectiveness.

4. PMA if either 3a or 3b is not met.

AdvaMed
Advanced Medical Technology Association

PMA Case Studies

Case Study #1

AdvaMed
Advanced Medical Technology Association

Disclaimer

The views expressed here are solely mine and not of my firm or any of its clients.

De Novo or PMA Case Studies

De Novo or PMA Case Studies - Background

Company A's device is cleared with the indication, "*for the ablation of cardiac tissue*."

- *Physical State*: Tip (shown below) delivers focused energy to ablate the target tissue. Tip is placed around the beating heart during open chest surgery.
- *Technical Method:* Device delivers high frequency focused ultrasound (HIFU) to heat and create lesion at the target tissue volume.

Hindawi.com

De Novo or PMA Case Studies – Scenario #1

PROco would like to market a similar technology for the indication, "*for the ablation of prostate tissue*."

- *Physical State*: Tip (shown below) delivers focused energy to ablate the target tissue. Tip is introduced rectally to cradle the prostate.
- *Technical Method:* Device delivers high frequency focused ultrasound (HIFU) to heat and create lesion in the target tissue volume.

Question:

Should PROco plan to submit a

(a) De Novo, or

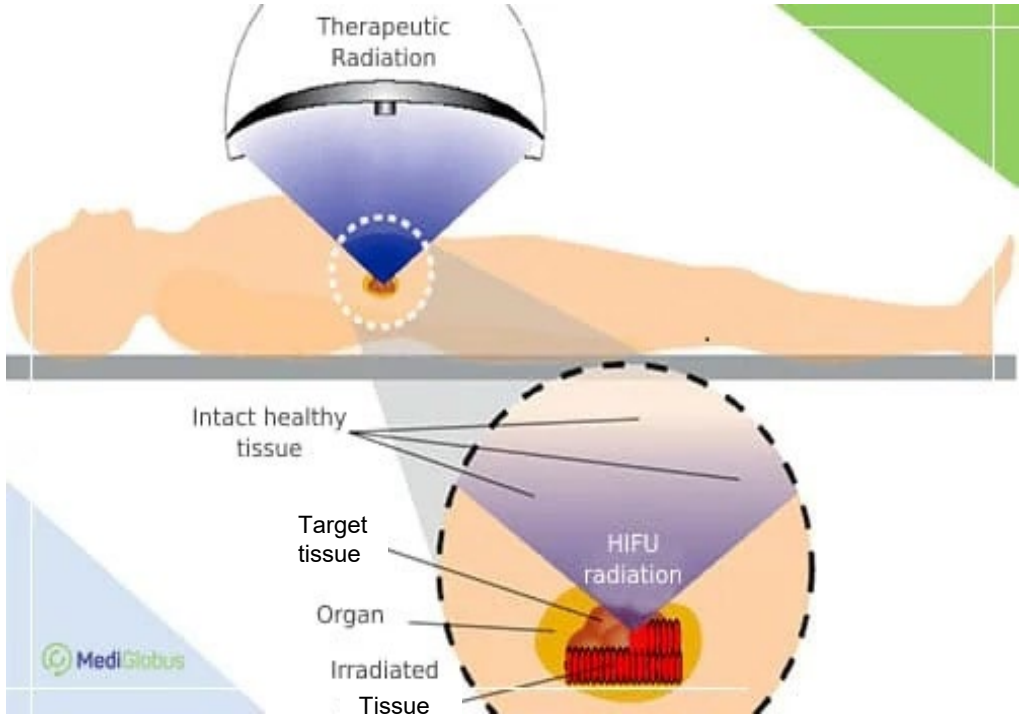
(b) PMA?

medicaldesignandoutsourcing.com

De Novo or PMA Case Studies – Scenario #2

- **PANco would like to market a similar technology for the indication, "for the ablation of pancreatic tissue."**

- *Physical State*: Tip delivers focused energy to ablate the target tissue. Tip is directed at a distance from the target tissue volume.
- *Technical Method:*
  - Device delivers high frequency focused ultrasound (HIFU) to heat and create lesion at the target tissue.
  - MRI imaging is used to plan the procedure and thermal mapping is used to monitor the ultrasound ablation during the procedure.



MediGlobus.com

Question:

Should PANco plan to submit a

(a) De Novo, or

(b) PMA?

Case Study #2

AdvaMed
Advanced Medical Technology Association

Disclaimer

The views expressed here are solely mine and do not represent BSC

Handling Difficult Data - Background

- You have drafted the PMA clinical section with everything except the actual data summaries.
- The clinical group has just provided you the first revision of the clinical study report for the pivotal clinical trial.
- During your review of the report, you note an asterisk next to the number in the column for “Percent successfully implanted” which list 100%. You see a footnote (in 10-point font) that states “*All procedures ultimately successful; 20% of procedures required modification of the delivery device during placement of the implant. See Attachment J in the Clinical Study Report.”
- You realize that Attachment J has not been provided in the first revision; you contact your clinical colleague and request a copy, who indicates they’ll get back to you.
- A few days later you receive an email from your contact’s manager indicating they have not determined whether Attachment J will go into the final report and ask you to weigh in.

Handling Difficult Data – Background (continued)

- You now receive a draft of Attachment J which contains the following information:
  - In one in five cases, it was noted in the case notes that the retraction wire for the outer sheath became caught on the pusher rod; attempts to free the wire were not successful
  - Access to the sheath retraction wire was subsequently obtained by separating the distal bond on the cartridge
  - The sheath was then manually grasped with a hemostat and retraction continued without further incident
  - This process was highly repeatable, and field clinical personnel standardized to this technique as it was a fairly obvious and straightforward fix
  - Design Engineering is in the process of validating the technique and also assessing root cause for design changes
- You go back to your copy of the clinical study report and find the following:
  - Implantation success is not an endpoint of the trial
  - The protocol does not account for any device modification
  - Tables of other information such as Adverse Events and Deviations, as well as IDE Progress Reports, do not appear to account for these cases

Discussion

- What is your proposed mitigation strategy?
  - Be sure to address both your existing IDE and planned PMA
  - What additional data may be helpful or possibly required to achieve PMA approval?
  - Recommendations regarding communicating the information – who will you communicate this information to? (both internal and external to your company)
- PMA plans
  - How would you summarize the information in the PMA?
  - Where in the PMA would you put that information?