FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

Premarket Submissions including Design Changes

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Outline

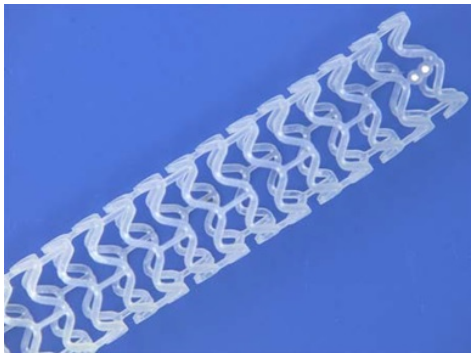
- Product definition
- Testing requirements
- Submission Types
- Early interactions with FDA
- Pre-Submissions
- IDEs and changes during an IDE
- Premarket submission content
- What to expect during FDA review
- Design and Other Changes after Clearance/Approval

Product Definition

- Product Definition can include:
  - Device Design
  - Indications for Use
  - Claims

Product Definition

- Device Design
  - What is it?
  - How is it made?
  - Primary mechanism of action?



Product Definition

Indications for Use

- Target patient population?
  - Young, old, or ….
- Extent of disease state?
  - Occasional, permanent, or ….
- How it is used
  - Surgical, transcatheter, or ….
- Clinical benefit to the patient?
  - Reduction, elimination, or …..

Product Definition

Claims

- Talk to your marketing department!
- Do you want to say it is better?
- Do you want to say it is safer?
- Do you need a particular claim to support reimbursement?

Testing Requirements

- Comprehensive risk assessment / FMEA
- Risk mitigation plan
- Device evaluation
  - Bench testing
  - Pre-clinical testing
  - Clinical testing

Submission Types for your Device

- 510(k): Substantial Equivalence
- PMA: Reasonable assurance of safety and effectiveness
  - Original
  - Modular
  - PMA Supplement
  - DeNovo: general and special controls provide a reasonable assurance of safety and effectiveness
  - Humanitarian Device Exemption: Safety and probable benefit for <8,000 subject per year
  - Other Considerations: “Breakthrough” Candidate?
    - Breakthrough Devices Program Guidance issued Dec 2018 (https://www.fda.gov/media/108135/download)

Early Interactions with FDA are Encouraged

- BEFORE PRE-MARKET STUDIES ARE CONDUCTED:
- Tell us about your device and your general strategy and get our thoughts
- Ask for a classification determination (513(g))
- Discuss complex pre-clinical testing: MR evaluation, drug testing, chronic performance
- Review a test protocol before testing; Very helpful for animal study work where it is critical to get it right the first time.
- Not a pre-review of the submission!

"Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program" Guidance issued May 2019 (https://www.fda.gov/media/114034/download)

Early Interactions With FDA Can Also Support An IDE

- TO SUPPORT AN IDE SUBMISSION:
- Device and target indication
- Study design / Sample size
- Endpoints / Definitions

Tips for Preparing your Pre-Submission

Do

- Conduct relevant research
- Think about whether initial interactions with FDA would be helpful
- Include only relevant information in your package

Don't

- Have broad questions
- Have too many questions
- Expect a pre-review

Tips for the Pre-Submission Meeting

Do

- Use written feedback to refine your agenda
- Use the meeting time wisely
- Ensure the right people are at the meeting

Don't

- Feel obligated to hold meeting if written feedback meets needs
- Don't provide significant new information after written feedback is sent

Post Pre-Submission Meeting Tips

Do

- Do submit meeting minutes within 15 days
- Check in if significant time has elapsed since receiving feedback
- Include summary of Pre-Sub discussions in subsequent pre-market submissions and how you addressed feedback

Don't

- Include new discussion topics in the meeting minutes

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

The Importance of Managing Changes During An IDE

- During an IDE, you may have:
  - Changes to the device design
  - Changes to suppliers
  - Changes to manufacturing
  - Protocol changes

  - Changes or Modifications During the Conduct of a Clinical Investigation Guidance Document (May 2001):
  - https://www.fda.gov/media/72429/download

Content To Include In Premarket Submissions

- Table of Contents
- Page numbers
- Divide submission by review area
  - Admin, SE comparison, pre-clinical testing, clinical testing, etc.
- Pre-submission, IDE, & communication history
- Device, protocol change history
- IDE advisories; “considerations” from IDE letters
- Most recent versions of protocols
- Review “refuse to accept” guidance documents for minimum content requirements
- eCopy requirements outlined in guidance at:
  - https://www.fda.gov/media/83522/download

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; lead reviewer should be primary contact unless other arrangements are made with consulting reviewers
- Be responsive
  - Answer our questions when you say you will
  - If you don't understand a question, call/email and ask

Summary of MDUFA Performance Goals

Submission Type	Action	FDA Review Days	Percent of Submissions to Meet FDA Days				
			FY18	FY19	FY20	FY21	FY22
510(k)s	Substantive Interaction	60	95%	95%	95%	95%	95%
	Decision	90	95%	95%	95%	95%	95%
De Novos	Decision	150	50%	55%	60%	65%	70%
Original PMAs & Panel-Track Supplements	Substantive Interaction	90	95%	95%	95%	95%	95%
	Decision if No Panel	180	90%	90%	90%	90%	90%
	Decision With Panel	320	90%	90%	90%	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%	95%	95%	95%
	Decision	180	95%	95%	95%	95%	95%
Real-Time PMA Supplements	Decision	90	95%	95%	95%	95%	95%
Pre-Submissions	Written Feedback	70 or 5d prior to meeting	1,530 (65%)	1,645 (70%)	1,765 (75%)	1,880 (80%)	1,950 (83%)
CLIA Waiver by Applications	Substantive Interaction	90	90%	90%	90%	90%	90%
	Dual CLIA / 510(k)	180	90%	90%	90%	90%	90%
	Decision if No Panel	150	90%	90%	90%	90%	90%
	Decision With Panel	320	90%	90%	90%	90%	90%

During the Review, You Should:

- Be prepared
  - Have your team ready to answer questions; have copies of the submission and any previously submitted info (i.e., Q-Sub, IDE) available
  - Be ready for inspections (PMA)
- Plan for the possibility of submitting a submission issue request (SIR):
  - Obtain clarification on identified deficiencies
  - Are through the Q-Submission program

During the Review, You Should :

- Be ready to interact on labeling
  - Have your decision makers available for quick turnaround
  - Marketing: Don’t go to the printer with draft labeling the week after the submission is sent to FDA

Advice for a PMA Review

- Plan for the possibility of a Panel meeting
  - FDA will tell you as soon as we know – many times decision is driven by data in the PMA
- Be realistic when advising on timelines for ramp up of manufacturing facilities and distribution chains
- Work with the epidemiologist on post-approval study plans early – our goal is to approve protocol at time of PMA approval

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 Device is Cleared or Approved, Now I Need to Make a Change

- The path depends on the submission type:
  - For 510K Cleared Devices:
    - Deciding When to Submit a 510(k) for a Change to an Existing Device Guidance (Oct 2017):
      - https://www.fda.gov/media/99812/download
    - Deciding When to Submit a 510(k) for a Software Change to an Existing Device (Oct 2017):
      - https://www.fda.gov/media/99785/download
    - The Special 510(k) Program (Sept 2019):
      - https://www.fda.gov/media/116418/download
  - PMA Approved Devices require PMA Supplements

Guiding Principles of the 510(k) Modifications Guidance

- Modifications made with intent to significantly affect safety or effectiveness of a device
  - Per 21 CFR 807.81(a)(3)(i), a change that could significantly affect safety or effectiveness requires a 510(k)
  - Change that's intended to significantly affect safety or effectiveness (e.g., to address adverse events) requires a 510(k)
  - Changes not intended to significantly affect safety or effectiveness should still be evaluated through this guidance

Modifications to PMA Approved Devices require PMA Supplements

- Guidance: Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process (Dec 11, 2008):
  - https://www.fda.gov/media/73328/download
- Supplements (21 CFR 814.39)
  - Panel Track supplement
  - 180 Day supplement
  - "Real-time" Supplement
  - 30 Day Notice – 21 CFR 814.39(f)
  - Special Changes Being Effected – 21 CFR 814.39(d)
  - Site Change Supplement
- Annual Reports (21 CFR 814.84)

Panel Track Supplement

- Defined as:

  "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
- New SSED required
- May or may not go to panel

- 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:
  - Principle of operation
  - Control mechanism
  - Design specification
  - Performance
  - Labeling

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

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:
  - Device design; Software
  - instructions for use, warnings, or precautions or other labeling that does not affect the indications or contraindications
  - sterilization and packaging methods.
- Change should be:
  - validated according to scientific principles we have relied on in previous reviews and accepted test methods or procedures for devices of that type, wherever applicable, such as an FDA-recognized standard or guidance document
  - adequately supported by pre-clinical or animal testing, with no new clinical data
  - typically involving review within a single scientific discipline, rather than a multidisciplinary review
- Recommend that the applicant contact the Assistant Director of the Review Team prior to submitting
- Guidance: Real-Time PMA Supplements (Dec 2019):
  - https://www.fda.gov/media/73126/download

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

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:
  - Performance or Design specifications
  - Manufacturing / sterilization site of a finished device
  - Material specifications
  - Device operating software
  - In the cases above, request a Real-time or 180 Day Supplement
- Guidance: 30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75- Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes (Dec 16, 2019):
  - https://www.fda.gov/media/72663/download

1. 515(d)(6) of the FD&C Act or 21 US 360e(d)(6) and 21 CFR 814.39(f)
2. 737(5) of the FD&C Act or 21 US 379i(5)

"Special PMA Supplement – Changes Being Effected"

- 21 CFR 814.39(d)
- Labeling
  - changes that add or strengthen a contraindication, warning, precaution, or information about an adverse reaction
  - changes that add or strengthen an instruction that is intended to enhance the safe use of the device
  - changes that delete misleading, false, or unsupported indications
- Manufacturing
  - Adds a step to the quality control or manufacturing process to enhance safety but does not affect effectiveness
  - May include checks on purity, strength, reliability, etc.

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
- Guidance: Manufacturing Site Change Supplements: Content and Submission (Dec 17, 2018):
  - https://www.fda.gov/media/124387/download

1. 21 CFR 814.39(a)

PMA Annual Reports are also used to identify changes

- Per 21 CFR 814.84, reports must include:
  - A list of changes described in 21 CFR 814.39(a) and (b)
  - A summary and bibliography of the following information not previously submitted as part of the PMA:
    - Unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices and known to or that reasonably should be known to the applicant. 21 CFR 814.84(b)(2)(i)
    - Reports in the scientific literature concerning the device and known to or that reasonably should be known to the applicant. 21 CFR 814.84(b)(2)(ii)
  - Number of devices shipped or sold, and for implants, the number of devices implanted (if available)
    - 21 CFR 814.82(a)(9) used to support
  - Each Unique Device Identifier (UDI) in use for the device
    - 21 CFR 814.84(b)(4)

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:
  - description of the change made, including a comparison to the previously approved version;
  - rationale for making the change, including identification of event(s) related to the rationale/reason for the change (e.g., MDR number(s), recall number);
  - listing/grouping of associated changes that were made to address the same issue;
  - scientific and/or regulatory basis for concluding that the change had no impact on safety or effectiveness in order to allow FDA to understand how the applicant determined the change did not require a PMA Supplement or 30-Day Notice.

- Guidance: Annual Reports for Approved Premarket Approval Applications (PMA) (Dec 16, 2019):
  - https://www.fda.gov/media/73391/download

Contact Information

- Division of Consumer and Industry Education
  - https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance
  - DICE@fda.hhs.gov
  - 1 (800) 638-2041

- OPEQ / ORP / Division of Submission Support
  - (301) 796-5640

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