Premarket Approval Application (PMA); Humanitarian Device Exemption (HDE); Breakthrough Devices Introduction to Medical Device Law and Regulation

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Agenda

- Premarket Approval Overview
- PMA Submission
- PMA Review and Approval Process
- PMA Amendments
- PMA Supplements
- PMA Meetings
- Advisory Panels
- Humanitarian Device Exemption
- Breakthrough Devices

Premarket Approval Overview

Premarket Approval (21 CFR 814)

- Premarket Approval (PMA) is required to commercially distribute Class III devices (highest risk) in the United States.
- Because of risk, general and special controls alone are insufficient to ensure safety and effectiveness.
- In contrast to a 510(k) clearance, which is based on a determination of "substantial equivalence", PMA approval is based on reasonable assurance of safety and effectiveness for the device's intended use (860.7(c)).
  - Safety and effectiveness based on "valid scientific evidence" (860.7(c)(2))
- A Class III device marketed without PMA approval is "adulterated."

Definitions and Determination of Safety and Effectiveness

- Safety (860.7(d))
  - "The **probable benefits** to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, **outweigh any probable risks.**"
  - "The **absence of unreasonable risk** of illness or injury associated with the use of the device for its intended uses and conditions of use."
  - Determination based on bench, animal, and clinical studies.
- Effectiveness (860.7(e))
  - "In a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide **clinically significant results**."
  - Determination based on "well-controlled investigations."

PMA Submission

Content of PMA Application

- Device description & principle of operation
- Non-clinical study test protocols and reports
- Clinical study information and data
- Bibliography of all known information
- Manufacturing and Quality System information
- Professional and patient labeling
- Environmental assessment
- Declaration of conformity with standards
- Financial disclosure by study investigators
- Certification form for clinicaltrials.gov
- Summary of Safety and Effectiveness Data (SSED) – made public on FDA website; “mini-PMA”

Clinical Studies

- Information from clinical studies is a required element of PMA submissions.
  - Constitutes valid scientific data
  - Supports reasonable assurance of safety and effectiveness
- Typical Types of Data
  - Clinical data collected from an Investigational Device Exemption (IDE) study – approval required to ship investigational devices (devices for evaluation in human subjects) in interstate commerce.
  - Outside the US (OUS) Studies (next slide)
  - Real World Evidence (RWE) (discussed later)

OUS Clinical Studies

- Sponsors often use OUS data in support of submissions (cost savings, minimize regulatory hurdles).
- FDA is open to utilizing this data as valid scientific evidence.
  - Applicability to US patient population
  - Comparisons to standard of care in US
  - Study design
    - Safety and performance versus safety and effectiveness
  - Compliance with Good Clinical Practice (GCP)
    - Independent ethics committee (analogous to Institutional Review Board (IRB)) review
    - Informed consent

Real World Evidence (RWE)

- Definitions
  - Real-World Data (RWD): "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources." Sources of RWD include electronic health records (EHRs), registries, home-use.
  - Real-World Evidence (RWE): "clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD."
- RWD and RWE may be used:
  - during review and decision-making for a PMA;
  - to address post-PMA approval study requirements; or
  - to expand indications for use for a PMA product.

Real World Evidence (RWE)

- Benefits of utilizing RWD and RWE
  - Use of RWD and RWE may speed up time to market for new products and reduce cost for PMA applicants.
  - Address limitations/challenges with traditional clinical studies
- Limitations of RWD
  - If data is incomplete or not at the patient level
  - Data sources may be biased
- Considerations for use of RWD
  - Reliability – how were data collected and analyzed?
  - Relevance – is the data appropriate to address the performance attribute?
- Utilize Q-sub program if wish to utilize RWE

Manufacturing/QS Information

- Manufacturing/QS information is a required and substantial element of PMA submissions (in contrast to 510(k) submissions).
- Utilize FDA Guidance "Quality System Information for Certain Premarket Application Reviews" (February 3, 2003) to prepare this part of PMA submission.
  - Quality System procedures (e.g. design controls, purchasing controls, complaint handling, etc.)
  - Device-specific design and manufacturing documentation (process validation, manufacturing procedures, design specifications, etc.)
- FDA review and resolution of open issues is a precursor to pre-approval inspection.

Device Master File (DMAF)

- Device Master File (DMAF) – a compilation of confidential documents submitted to FDA for the purpose of utilizing this information by reference in support of a pre-market submission, such as a PMA.
  - Pre-clinical/clinical data
  - Materials information
  - Manufacturing process procedures
- "Holder" submits DMAF to Center for Devices and Radiological Health (CDRH).
- DMAF is not reviewed outside the scope of a PMA.
- "Right of Reference" letter provided to PMA applicant
  - Allows PMA applicant to utilize DMAF in support of PMA without disclosing the DMAF's information to the PMA applicant.
- Information in the DMAF can be referenced in multiple submissions (e.g. different types of medical devices with same materials).

Types of PMAs

- Traditional
  - Required contents are submitted together in a single submission and reviewed concurrently by FDA staff.
- Modular
  - Required contents are submitted in modules and reviewed separately.

    - Typically 4 modules - animal, bench, manufacturing/Quality Systems, clinical
  - Submission of PMA shell is required prior to submission of 1st module.

    - Planned contents of each module and submission timeline
  - Modular approach allows PMA applicant to respond to deficiencies for a particular module while another module is under review.

PMA Review and Approval Process

PMA Review Process

- Administrative and Filing Review (45 days, first 15 days for RTA review)
  - FDA Guidance "Acceptance and Filing Reviews for Premarket Approval Applications (PMAs)"
- Substantive review (180 days from date of PMA filing)
  - Scientific/technical information review
  - Quality Systems/manufacturing information review
- "Hold" letters issued, SIR meetings, sponsor responses (amendments)/FDA response review
- Inspections (next slide)
- FDA Decision
  1) approval order
  2) "approvable" letter
  3) "not approvable" letter
  4) order denying approval

Inspections

- Prior to PMA approval
  - Bioresearch Monitoring (BIMO)
    - FDA conducts inspection of clinical study records against Good Clinical Practice (GCP) requirements.
  - Quality System
    - FDA conducts inspection after review of QS information (including device-specific manufacturing information) in the PMA and resolution of all open issues.
      - Inspection will include an onsite assessment of the firm's ability to design and manufacture the device.
- Post-approval

Approval Order

- Specifies device and indications for use for product to be distributed under the PMA
- Labeling restrictions (e.g. prescription use)
- Expiration dating
- Requirement to submit final labeling prior to commercialization
- Conditions of Approval
  - PMA Supplements (21 CFR 814.108)
  - Periodic reports (21 CFR 814.84)
  - Adverse Reaction and Device Defect Reporting (21 CFR 814.82(a)(9))
  - Medical Device Reporting (MDR) (21 CFR 806)
  - Post-market Surveillance Studies (PMS)
  - Other specific conditions that might be required based on the device type

PMA Amendments (21 CFR 814.37)

Definition of a PMA Amendment

- Type of submission prior to
  - Original PMA approval
  - PMA supplement approval
- Add or change information in original PMA/PMA supplement
- Submitted under the following circumstances:
  - PMA applicant decides to submit additional information (“unsolicited”)
  - FDA requests information from the application (e.g. as part of a deficiency letter) (“solicited”)

Types of PMA Amendments

- Major amendment
  - For significant amount of new or updated data
  - Affects PMA review clock
    - For unsolicited
      - Before “substantive interaction” (90 days following filing) – review extended by number of days between receipt of the original PMA and amendment.
      - Following SI – review extended by 75% of the number of days between original PMA filing and amendment receipt.
    - For solicited (“hold” letter) – review clock resumes
- Minor amendment
  - For minor information or clarification
  - Does not affect PMA review clock

PMA Supplements (21 CFR 814.39)

Definition of PMA Supplement

- Type of submission following original PMA approval
- Threshold for submission is a change that affects the safety and effectiveness of the device such as:
  - Indications for use
  - Labeling
  - Manufacturing, processing, or packaging facilities
  - Sterilization procedures
  - Packaging
  - Performance or design specifications
  - Shelf life

Types of PMA Supplements

- 180-day supplement
- Panel-track supplement
- Real-time supplement
- 30-day notice
- 135-day supplement
- Manufacturing site change
- Special “Changes Being Affected” supplement
- Annual report

Differentiating Factors of PMA Supplements

- Type of change
- Reason for change
- Impact of change on safety and effectiveness
- Data required to support change
  - Pre-clinical
  - Clinical
- FDA review timeframe (30 days, 180 days, etc.)
- Timing of implementation and FDA approval required
  - Implement, then notify FDA
  - Notify FDA, wait for approval, then implement

PMA Supplements

Supplement Type	Appropriate Type of Change	Supporting Data	FDA Approval Required?
180-day Supplement	Significant change in components, materials, design, specification, software, color additive, or labeling that affect the safety and effectiveness	New pre-clinical, may or may not need limited clinical to bridge gaps	Yes
Panel-track supplement	Significant change in design or performance of the device, or a new indication for use	New clinical, may or may not require new pre-clinical	Yes
Real-time supplement	Minor change to design, software, manufacturing, sterilization, or labeling, and for which meeting will occur	New pre-clinical only	Yes
30-day Notice	Manufacturing procedure or method affecting the safety and effectiveness (not manufacturing/sterilization site changes or to design or performance specifications)	To be determined based on change	No; can implement within 30 days, unless converted to a 135-day supplement or AI requested
135-day Supplement	Manufacturing procedure or method affecting the safety and effectiveness (not manufacturing/sterilization site changes or to design or performance specifications)	To be determined based on change	Yes
Manufacturing Site Change	Manufacturing site is changed for finished device	Contact FDA for supporting data requirements	Yes
Special "Changes Being Affected" Supplement	Labeling and manufacturing changes (not design changes) that enhance safety, but do not impact effectiveness	To be determined based on change	No, but change is temporary while under FDA review
Annual Report	Changes that do not impact safety and effectiveness	To be determined based on change	No

Determination of PMA Supplement Type

- Review and utilize 21 CFR 814.39 and FDA guidances:
  - "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" (December 11, 2008)
  - "Real-Time Premarket Approval Application (PMA) Supplements" (December 16, 2019)
  - "30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes" (December 16, 2019)
  - "Manufacturing Site Change Supplements: Content and Submission" (December 17, 2018)
- Discuss proposed supplement type with FDA (if needed)
- Document decision-making

What about changes that do not meet the criteria for PMA supplements?

- New PMA
  - Some changes are so significant, that a supplement is not appropriate and a new PMA is required.
    - Design change results in different intended use, mode of operation, technological basis of operation, patient population, or development of a “next gen” device.
- Memo to file
  - Periodic reports are typically used as a “catch all” for changes that do not impact safety and effectiveness.
  - Very minor changes that do not affect safety and effectiveness (e.g. translations, typo corrections, etc.) should be documented in sponsor’s QS (document-to-file), not in annual report.

Poll Question

- Your company is making a change to its device, which is an approved coronary artery stent. The change consists of a manufacturing procedure change, which the company has determined does not affect the safety and effectiveness of the device.

1 – Is an amendment, supplement, or annual report appropriate for this type of change and why?

2 – Is prior approval from FDA required for this change and why or why not?

PMA Meetings

Types of Meetings

- Pre-PMA Meeting
  - A PMA is planned and the sponsor would like to obtain feedback on specific questions pertaining to PMA contents.
- Determination Meetings
  - A PMA is planned and the sponsor would like to understand the type of evidence required to demonstrate effectiveness.
- Day 100 Meeting
  - The PMA has been filed and the sponsor would like to discuss the PMA review status.
  - Request must be submitted within 70 days of PMA filing (not submission).
- Submission Issue Request (SIR) Meeting
  - A “hold” (major deficiency) letter has been issued and sponsor would like to discuss proposed approach to responding to deficiencies prior to submission.
- Advisory Panel Meeting (discussed later)

Advisory Panels

Advisory Committee (Panel) Overview

- Advisory committees are used by FDA to obtain independent expert advice on scientific, technical, and policy issues.
  - Medical Devices Advisory Committees: 18 panels based on therapeutic area (“panel meetings”)
- Specific to PMAs, advisory committees are utilized for:
  - First-of-a-kind devices
  - Clinical study results raise concerns
  - Public health interest
- Panel consists of voting and non-voting members, including chair and expert members, plus a consumer, industry, and often a patient representative.
- Panel meetings are public and provide a forum for public discussion.
- Panel recommendations are non-binding, but FDA generally follows them.

Panel Meeting Preparation

- Meeting scheduled and announced in Federal Register
- FDA and sponsor each prepare background materials ("panel pack") and provide to panel members
  - Executive Summaries from FDA and sponsor
  - FDA questions for the panel
  - Published literature relevant to the issues to be discussed
  - Information from the original PMA submission
- Panel preparation activities by sponsor and FDA

Panel Meeting and Follow-Up

- Panel meeting general agenda:
  - PMA Applicant and FDA Presentations
  - Open Public Hearing (OPH) session (21 CFR 14.29(a))
  - Deliberations by Panel
  - Voting by Panel (21 CFR 14.22(d))
    - Voting members only; consumer and industry representatives do not vote.
    - Should FDA approve the PMA?
      - Is there reasonable assurance that the device is safe?
      - Is there reasonable assurance that the device is effective?
      - Do the probable benefits of the device outweigh the probable risks?
- Meeting summary and transcript posted on FDA website.
- Following the meeting, FDA reviews panel proceedings to come to a decision.

Humanitarian Device Exemption (21CFR 814 Subpart H)

History and Definitions

- The Humanitarian Device Exemption (HDE) program was established in 1990 with passage of the Safe Medical Devices Act, and creates an alternative pathway for getting market approval for medical devices that may help people with rare diseases or conditions.
- Humanitarian Use Device (HUD): "Medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 8,000 individuals in the United States per year."
- Humanitarian Device Exemption: "premarket approval application ……seeking a humanitarian device exemption from the effectiveness requirements of sections 514 and 515 of the act……."
  - In contrast to PMA in which safety and effectiveness must be demonstrated, **safety and probable benefit** must be demonstrated in an HDE.

Humanitarian Device Exemption

- Two-steps
  1) HUD Designation
     - Sponsor prepares HUD designation with indications for use, description of disease, reasons for need for patient population, and justification that product meets definition of HUD.
     - FDA determines designation.
  2) HDE Application
     - Prerequisite – HUD designation (Step 1) and no comparable device to treat condition.
     - Sponsor prepares application with HUD designation letter, device description, product labeling, risk/benefit analysis, pre-clinical and clinical studies, labeling, Quality Systems procedures.
     - FDA Decision (75 day review timeframe)
       1) approval order
       2) “approvable” letter
       3) deficiency letter
       4) “not approvable” letter

Post-Approval Requirements

- Restrictions on use and profit
  - HUD can only be used in healthcare facilities with IRB oversight and upon IRB approval.
  - HUD cannot be sold for profit unless it treats or diagnoses a condition 1) that occurs in pediatric patients only and the device is labeled as such or 2) that occurs in adult patients only or occurs in pediatric patients and the device cannot be developed for the pediatric population.
  - Profit is limited to an annual distribution number (AND) by FDA.
- Submissions for changes
  - Supplement (21 CFR 814.108) – changes that affect safety and probably benefit
  - New HDE – changes that create new indication for use
- Advisory committee review of pediatric HUDs

Comparison of HDE to PMA

	PMA	HDE
Indication for Use	Proposed by Applicant	Based on HUD Designation
Safety	Reasonable Assurance of Safety	Will not expose patients to an unreasonable or significant risk of illness or injury
Effectiveness	Reasonable Assurance of Effectiveness	Demonstration of Probable Benefit. Exempt from demonstrating effectiveness.
FDA Review Days	180 days – if no panel 320 days – if panel	75 FDA days to determine a decision*
Institutional Review Board (IRB) Oversight After Approval	No	May only be used at facilities that have IRB oversight
Restrictions on Profit	No	Yes

Source: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/ucm563286.htm#HDE

Poll Question

- True or False – One difference between HDE and PMA is that, in a PMA, you are required to demonstrate probable benefit.

Breakthrough Devices

Breakthrough Device Program

- Voluntary program for medical devices and combination products with a device primary mode of action
- Intended to accelerate path to market and replaces expedited access pathway (EAP) and priority review programs
  - Sprint discussions, data development plan discussion, clinical protocol agreement
  - Prioritized review on future regulatory submissions
- Not a market access pathway. A device granted designation as a breakthrough device must still go through 510(k), PMA, or De Novo.
- Guidance documents:
  - “Breakthrough Devices Program” (Final)
  - “Select Updates for the Breakthrough Devices Program Guidance: Reducing Disparities in Health and Health Care” (Draft)

Breakthrough Device Criteria (515B(b) of the FD&C Act (21 U.S.C. 360e-3(b))

1 - The device provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions; and

2 - a) Represents Breakthrough Technology;

b) No Approved or Cleared Alternatives Exist;

c) Offers Significant Advantages over Existing Approved or Cleared Alternatives; or

d) Device Availability is in the Best Interest of Patients

Process and Timing

- Submit Q-submission for designation prior to market authorization submission
  - Device Description
  - Indications for Use
  - Regulatory History
  - Breakthrough Designation Criteria and Supporting Rationale
- FDA grants designation within 60 days, AI within 30 days
- FDA does not grant designation
  - Does not meet criteria or no response to request for AI
  - Safer Technologies Program may be an alternative.

Relevant Links

- Device Advice on PMA:

https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm050289.htm

- Quality System information in PMA:

https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM070899.pdf

- Real World Evidence:

https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM513027.pdf

- Modular PMA:

https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089767.pdf

- PMA Review Clock and PMA Amendments:

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm089734.pdf

- PMA/HDE Supplements:

https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM270606.pdf

https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089612.pdf

https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM080194.pdf

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/manufacturing-site-change-supplements-content-and-submission

Relevant Links

- PMA Annual Reports:

https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089398.pdf

- PMA Meetings:

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm609753.pdf

https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080191.pdf

- Advisory Panels:

https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm440348.pdf

- HUD/HDE:

https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/ucm563286.htm#HDE

- Breakthrough Devices:

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/breakthrough-devices-program

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/select-updates-breakthrough-devices-program-guidance-reducing-disparities-health-and-health-care