

PMAAs: The Good, the Bad, the Ugly

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Topics for This Session - 1

- Brief Review of Product Development; When Clinical Studies are Required
- Safety and Effectiveness; Definition of Valid Scientific Evidence
- Marketing Submissions
- What is a PMA; Contents of a PMA; Supplements

Topics for this Session - 2

- The FDA Review Process for PMAs
- Pre-approval Inspections: clinical and manufacturing
- FDA Decisions
- PMA Supplements
- Postmarketing Surveillance
- Alternatives to a PMA Submission:
 - PDP
 - HDE
 - Custom Devices

Brief Review of Product Development Process

Review of Product Development Process for Medical Devices

- Product specifications: components
- Classification of medical devices; controls
- Testing: nonclinical/bench and animal
- Clinical Testing: IRBs, IDEs
- Pilot plant - scale up - manufacturing
- Quality Assurance: clinical, manufacturing
- PMA Application

Safety and Effectiveness

Safety and Effectiveness

21 CFR 860.7

- Considerations:
 - Persons for whom the device is intended
 - Conditions of use for the device
 - Possible benefit to health vs. probable injury or illness from use
 - Reliability of the device
- Reliance on valid scientific evidence only (may include objective performance criteria)

Valid Scientific Evidence

21 CFR 860.7(c)(2)

- Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use.

What Valid Scientific Evidence is NOT

- Isolated case reports and testimonials
- Random experience
- Unsubstantiated opinions
- Reports lacking sufficient details to permit scientific evaluation

Review of Medical Devices Marketing Submissions - 1

- Class I products

- no risk

- Class I products

- Minimal risk

- Establishment
Registration (ER)

- Medical Device Listing
(MDL)

- ER

- MDL

- 510(k)

Review of Medical Devices Marketing Submissions - 2

- Class II

- Minimal risk

- ER, MDL

- 510(k)

- Performance Standards (PS)

- Class II

- Moderate risk

- ER, MDL, 510(k), PS

- IDE

Review of Medical Devices Marketing Submissions - 3

- Class III
 - High risk
 - ER, MDL, IDE
 - Safety and Effectiveness (S&E) data
 - PMA
- Class III
 - New product, few safety issues
 - De novo [510(k) – NSE]

Review of Medical Devices Marketing Submissions - 4

■ CBER

- 510(k) – BK#
 - IVDs
 - Medical devices relating to Biologics

- PMA – BP#
 - IVDs
 - High risk medical devices relating to biologics

■ CDRH

- 510(k) – K#
 - Most IVDs
 - Most medical devices

- PMA – P#
 - Some IVDs
 - High risk medical devices

The PMA

Why is a PMA Needed?

- When substantial equivalence is not enough; FDA wants data on safety and effectiveness (S&E)
- When general and special controls are insufficient to assure S&E
- When the device supports or sustains life, or is of significant importance in preventing impairment of human health, or presents a potential unreasonable risk of illness or injury

What is an Approved PMA?

An Approved PMA is:

a private license granted by FDA to an applicant to manufacture and market a particular medical device for a specific intended use.

Premarket Approval Application (PMA)

- 180 day review period by CDRH
- demonstrates safety and effectiveness of product
- provides manufacturing procedures
- contains Operators Manual, Training program (if needed)
- preapproval inspections by FDA required for clinical and manufacturing data

PMA Contents - 1

- Applicant's name and address; signature of US representative
- Table of Contents – do this last; must have volume and page
- Summary of Safety and Effectiveness Data
 - Do this next to last to ensure all late arriving data have been included
- Device Description; Manufacturing Section
 - Provide flow charts of product through the facility
 - Can provide lists of tests and testing procedures; include critical ones; be prepared to send rest upon request

PMA Contents - 2

- Reference to Performance Standards that are recognized
 - More are being recognized every week; keep current on these
- Technical Sections of non-clinical and clinical data
 - Most important section; must be complete and persuasive
- Justification for one Investigator/Site
 - Almost never used, but insert as a placeholder anyhow

PMA Contents - 3

- Bibliography; other relevant info
 - Include copies of articles; alphabetically
 - Include nonpublished manuscripts and texts or “personal communications”
 - Put them in one (or more) volumes at end of submission;
- Samples (if requested by FDA)

PMA Contents - 4

- Copies of Proposed Labeling
 - Includes outer box label, label on product; Operators Manual or Instructions for Use; Information for Patients (or end consumer) and Training material
- Environmental Impact Statement or Assessment or claim of categorical exclusion
 - Information must apply to manufacturing facility and end disposal if appropriate

PMA Contents - 5

- Financial Certification or Disclosure
 - See 21 CFR Part 54
- Any other Information Requested by FDA
 - Examples: Other training information, initial advertising materials

Acceptance of Foreign Clinical Data

- Greater protection: Declaration of Helsinki or laws/regulations of that country
- Applicable to US population/medical practice
- Clinical investigators of recognized competence
- Valid Scientific Evidence (21 CFR 860.7)
- Guidance document
<http://www.fda.gov/cder/guidance/fstud.pdf>

FDA Review Process

Items Affecting Review Process

- IDEs and PMAs have priority
- 510(k)s and PMAs granted expedited status are reviewed first
- If additional data are requested by FDA, the application is put on hold
- Consulting review of the application may require another Division or Center

PMA Review Phases

- Filing review: to file or not to file (21 CFR 814.42)
- Substantive review
- Communication to PMA applicant
 - 90 day letter
 - 100 day meeting
- Panel Meeting
- FDA decision

Panel Review

- Get names of people on Panel (available on FDA website)
- Prepare slides for what you will present and slides to respond to requests for more information
- Have experts and consultants “act” as the Panel to elicit possible questions.
- Rehearse, rehearse and rehearse some more
- Take two laptops, disks or memory sticks, and sets of handouts – Murphy’s law concerning electronics!

Pre-Approval Inspections: QSR

- New guidance document issued last month
- Pre-approval inspections of facilities where final assembly occurs
- May also do inspection where critical subassemblies are made
- Note: must also have a pre-approval inspection before moving manufacturing (lessons of Hurricane Katrina)

Pre-Approval Inspections: Clinical Investigational Sites

- Prepare sites – have monitors assist in organizing files for possible inspections
- Conduct a practice inspection with personnel at sites; ensure preparedness!
- Ensure personnel understand what can and cannot be asked by FDA inspectors
- If investigator moves prior to inspection, ensure the hospital/clinic and sponsor all know where the records will be and how long the retention period is.

FDA Decisions

Approvable

- Pending QSR inspection
- Pending minor deficiencies
- Agreeable to “Conditions of Approval”
- Agreeable to post-approval study

Not Approvable

- Identify what is needed to put application in approvable form
- Response resets 180 day clock

Approval

- Decision based on FDA review panel recommendation, GMP and BiMo inspections
- Can go to market; FR notice of approval

PMA Decisions

- FDA decisions
 - approvable
 - not approvable
 - approval
 - denial
- 21 CFR 814.2 “to facilitate the approval of _____ or _____ ensure the disapproval of _____”

Expedited Review Criteria

- Is intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition, and is breakthrough technology
 - No approved alternative exists
 - Significant advantages over available approved alternative
 - Availability of device is in best interests of the patient
 - www.fda.gov/cdrh/modact/expedite.html

PMA Supplements

PMA Supplements

21 CFR 814.39

- A PMA amendment is information to modify a pending PMA or supplement.
- A PMA amendment must include the number assigned to the original submission and the reason for the amendment.
- FDA may extend the PMA review time if:
 - the PMA amendment is major (significant new or updated data, revised or previously omitted)
 - an applicant declines to submit a major amendment as requested by FDA

Changes to a PMA Device - 1

[21 CFR §814.39(a)]

- After FDA's approval of a PMA, an applicant shall submit a PMA supplement for review and approval by FDA before making a change affecting the safety or effectiveness of the device for which the applicant has an approved PMA unless...

Changes to a PMA Device - 2

- ... unless the change does not affect the device's safety and effectiveness AND the change is reported to FDA in an Annual Report OR
- unless the change is of a type for which the FDA has advised that an alternate submission is permitted [21 CFR 814.39(e)] OR
- unless the change is of a type which can be reported in a 30-day notice [21CFR 814.39(f)]
- Guidance document: Modifications to a device subject to PMA approval
<http://www.fda.gov/cdrh/ode/pmasuppl.pdf>

Types of PMA Supplements

- Panel Track: new clinical trial to support new indication for use, or a change in the device design or performance that could significantly affect clinical outcome
- 180-Day Supplement: “traditional” review cycle with 180 days being the target
- Special: implemented before FDA review, usually under urgent circumstances
- 30-Day Notice: limited types of manufacturing changes that could affect safety or effectiveness
- Real-Time: compressed review cycle, by express permission of the ODE review branch

Who Decides if a
Supplement is Needed?
YOU DO!!!

Alternatives to a PMA

HUMANITARIAN DEVICE EXEMPTIONS (HDE)

- treatment or diagnosis in disease affecting less than 4,000 people in the U.S. per year
- effectiveness data not required; reasonable assurance of safety
- two-step process
 - must obtain designation from FDA's Office of Orphan Products (Humanitarian Device Use – HDU)
 - Submit the HDE to Office of Device Evaluation
- approval for use is limited to 18 months
- 21 CFR 814.100

Product Development Protocols (PDP) 21 CFR 814.19

- The option exists to have Panel Review at the beginning and come to agreements for milestones. As each milestone is reached, the applicant submits full reports and data.
- When the last milestone has been reached and the last report has been submitted, reviewed and approved, the PDP is declared "complete". It is considered to be the equivalent of an approved PMA.
- In the years since the PDP option became available (over 15 years), only 1 PDP and 2 amendments have been approved under this regulation.

Custom Devices - 1

21 CFR 812.3 (b)

- (1) Necessarily deviates from devices generally available or from an applicable performance standard or PMA requirement in order to comply with the order of an individual physician or dentist;
- (2) Is not generally available to, or generally used by, other MD/DDS;
- (3) Is not generally available in finished form for purchase or for dispensing upon prescription;
- (4) Is not offered for commercial distribution through labeling or advertising; and
- (5) Is intended for use by an individual patient named in the order of an MD/DDS, and is to be made in a specific form for that patient, or is intended to meet the special needs of the MD/DDS in practice.

Custom Devices - 2

- Certain devices ordered by members of the health professions to conform to their own special needs or to those of their patients are considered custom devices and are exempt from registration and from otherwise applicable performance standards or premarket approval requirements (Sec. 520(b)).

Custom Devices - 3

- The exemption applies only to devices not generally available to or used by other health professionals. Custom devices are not exempt from other provisions of the Federal FD & C Act and regulations.
- Examples: Patients - orthotics, dental appliances; Doctors - surgical instruments designed for small hands

Post-marketing Surveillance

Postmarketing Requirements

- FDA may require post approval conditions
- Such conditions may include
 - restriction of the sale, distribution or use of the device
 - evaluation and periodic reporting on the safety, effectiveness, and reliability of the device
 - prominent display in the labeling and advertising of warnings, hazards or precautions
 - maintenance of records to enable tracking of patients
 - maintenance of records to enable FDA to determine if there is continued safety and effectiveness
 - batch testing of the device

Postmarketing Surveillance

<http://www.fda.gov/cdrh/postsurv/>

- Evaluation and reporting on safety, effectiveness, and reliability of device
- May requires submission of protocol to FDA for review and approval
- Often formal clinical trial with protocol and case report forms, although less extensive than study performed under IDE regulations

Purpose of Postmarket Surveillance

- Identify problems
- Provide safety warnings
- Provide information not available from the medical device reporting regulation
- Provide actual use of safety and effectiveness information.

When is postmarket surveillance mandatory

- The FDA can now order postmarket surveillance for any Class II and Class III device:
 - the failure of which would be reasonably likely to have serious adverse health consequences; or
 - which is intended to be implanted in the human body for more than one year; or
 - which is intended to be a life sustaining or life supporting device used outside a device user facility.

Summary

PMAs: The Good

- Competitors must file a PMA also for similar product with same indication
- Confidentiality – only SSED is available to the public
- Perception of expertise by the medical community when you have a PMA
- Limit on product liability because the product is “approved” by the FDA

PMAAs: the Bad

- Clinical studies are expensive
- Clinical studies take a long time
- Must have pre-approval inspection of facility before manufacturing for sale
- Must have pre-approval for new facility before moving
- Review time of PMA is usually > 6 months
- Expense of preparation for and meeting with Panel

PMAAs: The Ugly

- Panel can recommend approval and FDA can deny it for many reasons
- Panel may not recommend approval for nonscientific and/or nonmedical reasons
- More frequent and intensive inspections
- Very high User Fees
- Post-marketing requirements