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FDA Regulation of Medical Devices

Ronda Balham, O.D.

Presentation Outline

- Definition of “Device”
- Device Classification
  - General and Special Controls
- Major Regulatory Pathways
  - 510(k)
  - *de novo*
  - PMA

What is a "Device"?

- An instrument, apparatus, implement, machine, contrivance, implant, in-vitro reagent
- Intended to:
  - diagnose disease/conditions;
  - cure, mitigate, treat, or prevent disease;
  - affect the structure/function of the human body; and
- Does not achieve primary purpose through chemical action;
- Is not dependent upon being metabolized

Classification of Devices

- Risk-based and knowledge-based scheme that provides reasonable assurance of safety and effectiveness
- Determines level of regulation applied to the device
- Class I
  - Low risk devices
  - General controls are sufficient to assure safety and effectiveness
  - Generally exempt from pre-market review
  - Examples include: Handheld surgical instruments, elastic bandages, toothbrush

Classification of Devices (cont.)

- Class II
  - General controls alone are insufficient to assure safety and effectiveness
  - Sufficient information exists to establish special controls to provide such assurance (e.g., industry standards, guidance)
  - Moderate risk devices, premarket notification 510(k) generally required
  - Blood Pressure cuffs, powered wheelchairs, many diagnostic products, infusion pumps, daily wear contact lenses
  - Facility inspection is not required prior to clearance of a device

Classification of Devices (cont.)

- Class III
  - General/Special controls insufficient to assure safety and effectiveness
  - Products for use in supporting/sustaining human life, are of substantial importance in preventing impairment to human health, or present an unreasonable risk of illness or injury
  - Also includes technology with important new questions of safety or effectiveness (e.g., novel technology or indication)
  - Premarket approval (PMA) based upon “reasonable assurance” of safety and effectiveness
  - Pacemakers, silicone-filled breast implants, vascular grafts, lithotripters, lasers
  - Facility inspection, foreign or domestic, is required prior to approval of an application

General Controls: Applied to All Medical Devices

- Provide for a prohibition against adulteration and misbranding
- Include:
  - Establishment registration of the facility, listing of the device, and premarket notification
  - Labeling
  - Good Manufacturing Practices (GMPs)
  - Record keeping

Special Controls Apply to Class II Medical Devices

- Industry and other standards
- Postmarket surveillance
- Guidance documents (may require clinical data, special labeling for instructions for use, warnings, precautions, contraindications)
- Patient registries (traceability and/or collection of Adverse Device Events)

Regulatory Pathways

- Most widely utilized
  - Premarket Notification (Class I/II)
  - Premarket Approval (Class III)
  - *de novo* (for moderate risk devices previously unclassified)
- Less commonly utilized
  - Product Development Protocol

    (Class III)
  - Humanitarian Device Exemption

    (Class III)

Premarket Notification (510(k))

- "Me-too" devices
- Should demonstrate that the device to be marketed is as safe and as effective as an existing *legally marketed device* (predicate device)
- Over 90% of all devices are marketed via 510(k)s
- Fewer requirements than premarket approval
- Statutory 90 day process; often longer, depending upon whether questions are raised during the review
- Third party review option available for some devices

Substantial Equivalence

- The device has:
  - Same intended use, and
  - Same technological characteristics as the predicate device;
- ***OR***
  - Same intended use, and
  - Different technological characteristics from the predicate device
- ***BUT…***

Substantial Equivalence (cont'd.)

- **But**… the different technological characteristics do not raise new questions of safety and effectiveness, **and**
- There are accepted scientific methods for evaluating whether safety and effectiveness have been adversely affected by the new technological characteristics, and
- There are data or information to demonstrate that safety or effectiveness have not diminished

- Conformance with voluntary standards can be used to demonstrate substantial equivalence

Different Technological Characteristics

- Could include changes in:
  - Materials
  - Design
  - Energy sources
  - Principles of operation
- Examples:
  - Non-absorbable sutures
    - Type of polymer
  - Surgical Mesh
    - Collagen source
    - Suture pull-out strength

New Questions of Safety and Effectiveness

- Not defined in legislative history or guidance
- Provides FDA with substantial discretion
- Examples:
  - Non-absorbable suture
    - Immunologic reaction
  - Surgical mesh
    - Safety of collagen source – bovine versus porcine

Who Must Submit a 510(k)?

- Domestic manufacturers, specification developers, or foreign manufacturers/exporters (or their U.S. representatives) who are introducing a device to the U.S. market for the first time, proposing a new or different intended use for a device already in commercial distribution , or significantly changing or modifying a device already in commercial distribution
- Re-packers or re-labelers who modify the labeling or significantly change the device

Contents of a 510(k)

- Device name*;* classification
- SE Statement and comparison to predicate:
  - Indication(s) for use
  - Description of device/technology
  - Performance data – bench data, animal trials and/or human clinical trials (approximately 10% of submissions)
  - Compliance with voluntary standards
  - Draft labels, labeling, advertising
  - Sterilization and packaging

Alternatives to Traditional 510(k)s

- Special
  - For certain changes to a 510(k) cleared device
  - Intended to be processed within 30 days of receipt
- Abbreviated
  - When device-specific guidance, special control or recognized standard exists
  - Less data-intensive facilitating a more rapid review
- Third party review
  - Could yield a more rapid marketing clearance
  - Not available for all device types
- Summary Technical Document (STED) format
  - Voluntary pilot program currently underway for certain submissions

FDA Action on 510(k)s

- Refuse to accept incomplete submissions
- Issue determination declaring the device to be substantially equivalent to legally marketed predicate device
- Issue not substantially equivalent order (NSE)
  - *de novo* application
  - PMA application
- Request additional information
- Advise applicant that 510(k) is not required (exempt)

510(k) Process Undergoing Reform

- In January 2011, following a lengthy internal review, the FDA released a report detailing proposed reforms to the 510(k() process
  - It includes 25 action items that the FDA intends to implement in 2011
  - Mostly administrative in nature: guidance documents to clarify the process, addressing staffing needs and training, streamlining the *de novo* process, and implementing the Unique Device Identification system
- The most controversial items cited in the report including the authority to rescind a 510(k) clearance, requiring postmarket studies for Class II device as a condition of clearance, and establishing a Class IIb device category, all of which would likely require legislative approval to accomplish, have been referred to the Institute of Medicine for further independent assessment and possible inclusion in their study report due out this summer

Class IIb Proposal has Received Little Support from Industry

- This proposal would require manufacturers of a subset of higher-risk Class II devices to submit clinical data and/or undergo a manufacturing facility inspection before receiving 510(k) clearance. The devices could also be subject to post-market study requirements.
  - There are currently a few Class II devices that need to submit clinical data for review (daily wear contact lenses) or to have a premarketing inspection (infusion pumps). This has been accomplished through guidance documents

de novo Classification

- Also known as Automatic Class III designation
- For “low risk” devices with no predicate that are found to be NSE through the 510(k) process
- Submitter must request *de novo* classification within 30 days of receipt of NSE
- The *de novo* process has a 60 day review period

Premarket Approval (PMA)

- Premarket approval required for Class III medical devices
- Sufficient valid scientific evidence to assure that the device is safe and effective for its intended use
  - Safety - probable benefits outweigh the probable risks
  - Effectiveness - in a significant portion of the target population, provides clinically significant results
- PMA approval provides a confidential, proprietary marketing registration

“Valid Scientific Evidence”

- The valid scientific evidence used to determine effectiveness shall consist of:
  - Well-controlled studies
  - Partially controlled studies
  - Objective trials without matched controls
  - Case histories
  - Significant human experience

Contents of a PMA

- Device description & principle of operation
- Preclinical (bench/animal testing)
- Clinical studies
- Bibliography of all known information
- Manufacturing information
- Professional and patient labeling

Review of PMA

- Team: medical officer, engineer, biologist, statistician, labeling expert, manufacturing expert
- 45 days to file; 180 day review period
  - Many submissions are not filed initially due to information presented unclearly or incompletely
  - 180 day statutory review period begins on the date of the filing determination
- Advisory committee input is often required

Advisory Committees

- 17 panels by medical specialty
- Independent, contemporaneous input
- Voting members/consultants
- Recommendation not binding; however, FDA generally follows
- Especially important for new technology

Expedited Review

- For devices intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition and that:
  - Represent a breakthrough technology
  - Have no existing approved alternative
  - Offer significant advantages over existing approved alternatives, or
  - Whose availability is in the best interest of patients
- Applications receive priority review before other pending applications

PMA Amendments

- Additional submissions to the PMA/PMA supplement before approval
  - Revise existing information
  - Provide additional information
- Can add up to 180 days to the review clock if it is substantial
  - Contains significant new data from a previously unreported study of significant updated data from a previously reported study
  - Detailed new analyses of previously submitted data
  - Significant required information previously omitted

PMA Supplements

- Submission required for a change affecting the safety or effectiveness of the device for which the applicant has an approved PMA
- Changes must meet the requirements of the quality system requirements
- Numerous changes require submission of a supplement
  - New indication for use of the device, labeling changes, use of a different facility to manufacture, process, sterilize or package the device, changes in sterilization procedures, changes in packaging

Types of PMA Supplements

- PMA Supplement – 180 days
  - For significant changes requiring an in-depth review and approval prior to implementation of the change
  - Some may qualify for a Real Time Review
    - Minor design or component change, labeling, expiration dating
- Special PMA Supplement – Changes Being Effected
  - For any change that enhances the safety of the device or the safety in the use of the device – usually a labeling change
  - May be placed into effect by the applicant prior to receipt of written FDA order approving the supplement
- 30-day Notice and 135-day PMA Supplement
  - Changes to the manufacturing process or changes in the method of manufacture


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