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Presentation

Stockholm, Sweden

November 13, 2007

# Preparing Successful Pre- Market Submissions

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# Framework: Risk-Based Flexibility

- FDA classifies devices into one of three classes based on risk (Class I = lowest risk; Class III = highest risk)
- FDA regulations are written according to the principle that devices are to be regulated at the lowest possible level
- Ways to bring a device to market:
  - Class I or II exempt device
  - Section 510(k) Premarket Notification
  - Premarket Approval (PMA) Application
  - *De Novo* classification

# How Do 510(k)s and PMAs Differ?

- Volume of Information
- Need for Clinical Data
- Manufacturing Information and Pre-Approval Inspections
- Panel Review
- Time to Clearance or Approval
- Exclusivity / Barriers to Entry

# Basics of 510(k) Submissions

- FDA receives approximately 4,500 510(k) submissions per year
- “Substantial Equivalence” to a legally-marketed device
  - Same intended use
  - Similar technological characteristics
  - OR different technological characteristics but no ***new types*** of safety and effectiveness questions
- No requirement that devices be identical
  - Technology and indication for use can be different
  - 510(k) can rely on more than one predicate device

# Basics of 510(k) Submissions

- Performance testing (i.e., bench, and in some cases, animal) is often required and is usually sufficient to address issues
- Clinical data may be needed depending on differences from predicate device
- No pre-approval inspection of manufacturing facilities
- No annual reporting requirements (other than MDRs)
- Types of 510(k)s:
  - Traditional
  - Special
  - Abbreviated

# Basics of 510(k) Submissions

- Review Clock
  - Performance goal – decision within 90 days (cumulative FDA review time)
- Actions
  - SE Letter (substantially equivalent)
  - NSE Letter (not substantially equivalent)
  - Request for additional information
  - Advise submitter that 510(k) is not required (not a device or otherwise exempt)
- Formal request for additional information (e.g., in writing) stops review clock

# Preparing a 510(k)

- Identify device classification
  - Device classifications found in FDA regulations at 21 CFR Parts 862-892 according to panels
    - Anesthesiology
    - Cardiovascular
    - Dental
    - General and Plastic Surgery
- Identify similar devices that have been cleared by FDA
  - 510(k) database – panel, 510(k) number, applicant and device name, device type, decision date, etc.

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>

# Submit a 513(g)?

- Section 513(g) of Food, Drug and Cosmetic Act: FDA will provide a written statement of the classification (if any) of a device and the requirements of the Act applicable to the device if a party submits a request that contains device description, indication for use, and labeling
- Most 513(g) requests are submitted to:
  - Determine whether a product is subject to FDA regulation (e.g., software that may have medical applications)
  - Determine whether a device is exempt from 510(k)
  - Determine the appropriate classification (to assist in identifying predicate)
- FDA responses do not constitute clearance or approval!

# Importance of Guidance Documents

- Identify any device-specific guidance documents
  - <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfggp/search.cfm>
- Guidances are voluntary and represent FDA recommendation and “current thinking”
- Following device-specific guidance will make the review process more efficient and reduce FDA requests for additional information
- Identify general guidance documents that may apply to device
  - Sterility: <http://www.fda.gov/cdrh/ode/guidance/361.html>
  - Software: <http://www.fda.gov/cdrh/ode/guidance/337.html>
  - Biocompatibility: <http://www.fda.gov/cdrh/g951.html>

# Importance of Recognized Standards

- Standards that have been officially recognized by FDA (in *Federal Register*) to meet one or more requirements of the Act
  - ASTM F623-99: Standard Performance Specification for Foley Catheter
  - ISO 10555-3: Sterile Single-Use Intravascular Catheters - Part 3: Central Venous Catheter
- Searchable database of Recognized Consensus Standards  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/search.cfm>
- Applicant provides – instead of actual test data – a Declaration of Conformity to one or more standards applicable to device

# Importance of Recognized Standards

- Completely voluntary – conformity declarations can be provided in any premarket submission (key is acceptance and applicability)
- Conformity to standards has become a de-facto requirement in many countries outside the U.S.
  - Strategic use of standards can have substantial impact on worldwide regulatory strategy
  - Example: ISO 10555-1 is both an FDA-recognized consensus standard and an EU harmonized standard

# Third-Party Review Program

- Use of “Accredited Persons” to review 510(k)s
  - Began as pilot program in 1996
  - Codified and expanded in 1997 (FDAMA) – expanded again in 2001 to include many Class II devices not previously eligible
- Intended to allow FDA to devote review resources to higher-risk devices by allowing “accredited persons” to conduct initial review of select low- to moderate-risk devices (combination products and devices requiring clinical data not eligible)
- No user fee – payment of fee to third party reviewer
- 510(k) is submitted to Accredited Person with a letter that authorizes that person to discuss the submission with FDA and to forward it to the Agency
- Guidance page: <http://www.fda.gov/cdrh/thirdparty/>

# Drafting a 510(k)

- Utilize FDA's "Device Advice" website for basic information

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

- Follow FDA's guidance document on the format and content of Traditional and Abbreviated 510(k)s

<http://www.fda.gov/cdrh/ode/guidance/1567.pdf>

- Step-by-step guide to drafting 510(k)s
- Will help organize information prior to drafting
- FDA reviewers will be able to find information quickly

# Format and Content of 510(k)s

- Sections include:
  - Recommended forms and administrative information
  - Device description
  - Substantial equivalence discussion
  - Proposed labeling
  - Sterility and shelf life
  - Biocompatibility
  - Software
  - Electromagnetic Compatibility and Electrical Safety
  - Performance Testing – Bench
  - Performance Testing – Animal
  - Performance Testing – Clinical

# STED Format?

- FDA Device Center is encouraging submitters of 510(k)s (and PMAs) to participating in “STED Pilot Program”
- STED = Summary Technical Document format for regulatory submissions
  - Harmonized submission format developed by Global Harmonization Task Force (U.S., EU, Canada, Australia and Japan)
  - Proposed document issued in December 2003
- While use of STED format is still in early stages, it is already accepted by multiple regulatory authorities worldwide
- FDA Pilot Program ongoing

# STED Format?

- Use of STED preparation process in U.S. may help streamline international approvals for devices
- Accredited persons may reviewed STED-formatted 510(k)s for devices eligible for third-party review
- FDA guidance identifies devices eligible for STED, other devices will be considered on case-by-case basis
- Contact FDA review division for device type prior to preparing submission to ensure that device is suitable for STED submission

<http://www.fda.gov/cdrh/ode/guidance/1347.html>

# Common Problems with 510(k) Submissions

- Inconsistency in documentation
- Testing not complete at time of submission
- Failure to respond to questions
- Incomplete responses to questions
- Changing device design or indication for use during review process
- Keep in mind:
  - Prioritize finding the right predicate device
  - Provide a complete submission
  - Follow FDA guidance
  - Be available for FDA questions
  - Ask for clarification when necessary

## No Predicate? *De Novo* Classification

- Low risk, new devices may not have a predicate that will support a finding of substantial equivalence (510(k))
  - FDA will issue “not substantially equivalent” (NSE) determination
- Following NSE determination, devices are automatically placed in Class III (requiring PMA)
- FDA established *de novo* process in 1997 to limit unnecessary expenditure of resources that would occur if low risk devices are subject to PMA review
- Manufacturer may request *de novo* classification within 30 days of receiving an NSE determination
  - Submission should include necessary data and proposed special controls
- Eligible devices: simple technology, low risk intended use, well-accepted methods

# PMA Submission Basics

- The most complex submissions made to FDA Device Center
- Required Elements
  - Device Description
  - Non-clinical laboratory studies
  - Clinical investigations
  - Manufacturing
  - Labeling
  - Summary of Safety and Effectiveness Data
  - Other minor sections

# Preparing a PMA – Key Sections

- Non-clinical laboratory testing (biocompatibility, software validation, sterilization, bench tests, animal tests, etc.)
  - Follow FDA-recognized consensus standards and guidance documents
  - Refer to “SSEDs” for similar devices to determine the types of testing that may be needed
- Clinical Investigations
  - Present data clearly and accurately
  - Present all data, including data from studies outside U.S.
  - Explain the purpose of each study and whether it is meant to serve as a key data set for safety or efficacy
  - Be prepared to justify inconsistent results

# Preparing a PMA – Key Sections

- Manufacturing
  - Reviews are on “parallel track” to scientific review (Office of Compliance)
  - FDA will not approve device until it is assured that facility is compliant with QSR requirements
  - Consider:
    - Is your facility ready?
    - Have you completed validation activities?
    - Have you identified all facilities used in the manufacture of your device?
- Labeling (user manual, patient labeling, etc.)
  - One of the final steps in review and approval process
- SSEDs
  - Posted on FDA website (applicant submits first draft)

# PMAs – Key Considerations

- Clinical data are most important
  - Discuss clinical strategy with FDA
  - Conduct study you proposed doing
  - If you have IDE, address all issues raised by FDA in correspondence
- If relying on data from non-U.S. sites, ensure compliance with FDA requirements for acceptability of foreign data
- Be available to answer questions
  - Do not sacrifice quality for speed
  - Avoid excessive status checks

# Engaging FDA - Meetings

- Manufacturers have several opportunities to engage FDA in product development and clearance / approval process:
  - Pre-IDE meeting – early, informal FDA input on regulatory strategy and pathway to market
    - Important for new sponsors and new technologies
  - Pre-510(k) meeting
    - Recommended if device has new features or indication; or if multiple predicates will be identified
    - Prepare focused questions

# Engaging FDA - Meetings

- Pre-PMA Submission Meetings
  - FDA input on submission / discussion of changes since last meeting
  - FDA input on clinical data presentation
  - Discussion of need for advisory panel review
- Day 100 Meetings
  - Update on status of FDA review
  - Used to clarify review issues and to discuss major problems with PMA