FDA Advises on How to Improve Your 510(k) Submission Process

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Device Submission Review Process

Approaching a 510(k) submission, recent changes, and moving forward

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Orthopaedic Manufacturing & Technology Exposition and Conference (OMTEC)
June 18, 2015
Overview

• 510(k) Basics

• 510(k) Program under MDUFA III
  – Timelines
  – Refuse-to-Accept (RTA) and checklist tips
  – Substantive Review and common deficiencies

• Guidance Documents
510(k) Basics
Regulatory Classes: I, II, and III

- Three regulatory Classes – based on the level of control necessary to provide reasonable assurance of safety and effectiveness:
  - Class I – General Controls
  - Class II – General Controls & Special Controls
  - Class III – General Controls and Premarket Approval
Regulatory Classes

- Class determines type of premarket submission required by FDA
- *510(k) for preamendment devices (pre-1976) until 515(b) calls for PMA or the device type is reclassified
- Class I, II: 510(k) required
- Class I, II Exempt: no 510(k) required, subject to limitations of exemption (xxx.9)
Regulatory Options to Market

**510(k)**
- Most common way to market
- “me too” process

**de novo**
- Newer pathway to market
- Innovative, lower to moderate risk devices

**PMA**
- Most stringent data requirement
- Reserved for high risk devices or when general & special controls can’t be written
So a 510(k) is…

• Premarket Notification per Section 510(k) of FFD&C Act
  – Outlined in 21 CFR 807 Subpart E
• The 510(k) process is used to classify individual post-amendment devices:
  – Either find a device substantially equivalent (SE) to a predicate; or
  – Find a new device that must be placed automatically into class III and require PMA, de novo, or reclassification before marketing in U.S.
• FDA receives ~3000 510(k) submissions per year (largest premarket program)
  – ~90% are found SE and go to market
A Device Must be Compared to…

• A legally marketed predicate* device that does not require a PMA, i.e.:
  – A pre-amendment device
  – A device found by FDA to be Substantially Equivalent (SE)
  – A reclassified device
  – A device classified by a *de novo* petition

*21 CFR 807.92(a)(3)
A 510(k) is required when...

- Introducing device to the market for the first time
- Changing a device’s indications for use/intended use
- Making modification(s) to device that could significantly affect safety or effectiveness
  
  - Guidance Document: “Deciding When to Submit a 510(k) for a Change to an Existing Device” (issued January 10, 1997)
  
  - E.g., change in design, materials, chemical composition, energy source, or manufacturing process
A 510(k) is NOT required when…

• Private Label Distributor
  – who does not modify device or labeling
  – only adds company name or language like “distributed by__”

• Re-packager or re-labeler who does not alter the labeling

• Not selling device in US

• Manufacturer of parts
Types of 510(k)s

• Traditional
  – New devices, modifications that require complete review of test reports, changes in indications for use

• Special*
  – Modifications that do not require complete review of test reports

• Abbreviated*
  – Relies on meeting acceptance criteria from consensus standards, device-specific guidance (rarely seen in orthopedics)

510(k) Program under MDUFA III
MDUFA III Review Process Overview

1. **510(k) Submission received by DCC**
   - User Fee Paid & valid eCopy?
     - No: User fee and/or eCopy hold. FDA clock does not begin.
     - Yes: Submission assigned & RTA review begins

2. **Submission assigned & RTA review begins**
   - Accepted? (by day 15)
     - No: FDA clock does not begin. Submitter sends in missing info
     - Yes: Reviewer begins substantive review. FDA clock ticking

3. **Reviewer begins substantive review. FDA clock ticking**
   - SI decision? (by day 60)
     - No: Work interactively to resolve remaining issues. FDA clock ticking
     - Yes: Hold
       - FDA clock stops. Clock resumes when additional info received.

4. **FDA works with submitter to resolve remaining issues. FDA clock ticking**
   - Final Decision

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No: IR
Yes: Hold
Processing Timeline: Traditional

1. Refuse to Accept (RTA) Decision  Day 15
2. Substantive Interaction  Day 60
3. Final Decision  Day 90
4. Missed MDUFA Decision Process  Day 100
Processing Timeline: Special

1. Refuse to Accept (RTA) Decision       Day 15
2. Substantive Interaction                Day 30
3. Final Decision                         Day 30/60/90

Note: Only 1 round of Substantial Interaction
**Timeframes**

- Under the Medical Device User Fee Amendments (MDUFA III), FDA is subject to the following performance goals:

<table>
<thead>
<tr>
<th></th>
<th>FY13</th>
<th>FY14</th>
<th>FY15</th>
<th>FY16</th>
<th>FY17</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Substantive Interaction</strong></td>
<td>65% in 60 days</td>
<td>75% in 60 days</td>
<td>85% in 60 days</td>
<td>95% in 60 days</td>
<td>95% in 60 days</td>
</tr>
<tr>
<td><strong>MDUFA</strong></td>
<td>91% in 90 days</td>
<td>93% in 90 days</td>
<td>95% in 90 days</td>
<td>95% in 90 days</td>
<td>95% in 90 days</td>
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<tr>
<td><strong>Average Total Time</strong></td>
<td>135 days</td>
<td>135 days</td>
<td>130 days</td>
<td>130 days</td>
<td>124 days</td>
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MDUFA III Review Process Overview

510(k) Submission received by DCC

User Fee Paid & valid eCopy?

Yes

Submission assigned & RTA review begins

No

User fee and/or eCopy hold. FDA clock does not begin.
510(k) Refuse to Accept

- Guidance Document: Refuse to Accept Policy for 510(k)s (issued December 31, 2012)
  - Outlines policy & timelines
  - Includes traditional, special, and abbreviated checklists
- Steady improvement in submission quality and rate of acceptance since implementation
Using the Checklists

• RTA criteria: present or not present
  – *Present*: item wholly provided OR rationale provided for omission or alternative
  – *Not Present*: item not provided (either wholly or partially) AND rationale not provided for alternative/omission
  – Not an evaluation of adequacy

• Comments:
  – Not needed for every “not present” criteria
  – Should be included to clarify what is missing (e.g., guidance partially followed)
- All checklist criteria are present
- Begin Substantive Review
- No effect on clock
- Notification to submitter

- One or more missing criteria
- Clock stops, resets to Day 0
- Notification to submitter w/ checklist

- Very rare occurrence
- Day 16: notification sent to submitter
- Begin Substantive Review
- No effect on clock
What Happens if Rejected?

- Email sent to submitter
  - Reviewer completed checklist is provided
  - Lead Reviewer identified
- Submitter has 180 days to respond to RTA
  - Response should address all missing criteria; no piecemeal response & no need to resend entire submission (please don’t!)
    - FDA Clock resets to Day 0 when DCC receives response
    - Submitter has option to withdraw the file
    - File closed on day 181 due to lack of response
- Reviewer conducts RTA review again with add’l info
Tips & Best Practices

• Make a good first impression
  – Be organized
    • Page numbers, headings, table of contents
    • Hyperlinks/bookmarks within eCopy are very helpful
    • Ensure eCopy text and figures are all legible and clear
  – Avoid data dump
    • Follow the order of the checklist
    • Provided info should have a purpose
      – Too much information can delay the review
  – Proofread everything
    • Ensure consistency throughout submission
      – (e.g., IFU consistency with labeling, device name consistency)
    • Tell the story of equivalence
Tips & Best Practices (cont’d)

• Include the checklist in the submission and indicate page numbers for where each respective criterion is addressed

• Address each checklist criterion fully
  – Be sure to include a rationale for alternative approaches or omissions
  – Don’t allow the reviewer to make any assumptions about whether a criterion is applicable or not

• Make sure contact information is correct

• Contact reviewer for clarification after RTA, if needed

• Contact 510(k) Staff immediately if…
  – You don’t receive an RTA status email by day 16
    • First check your “junk” folder
  – If you disagree with the “not accepted” decision
RTA’s Most Wanted

- #28 SHELF LIFE: Submission includes summary of methods used to establish that device performance is not adversely affected by aging or includes a rationale for why the storage conditions are not expected to affect device safety or effectiveness.
- #9: ADMINISTRATIVE: submission identifies prior submission for the same device for which FDA provided feedback…or states that there were no prior submissions for the subject device.
- #36: PERFORMANCE DATA: Full test report is provided for each completed test. A full test report includes…an explanation of how the data generated from the test supports a finding of substantial equivalence.
  - Device specific or special controls guidance documents
- #4a: ADMINISTRATIVE: submission contains all elements of 510(k) Summary
RTA’s Most Wanted (cont’d)

- #17a: LABELING: Indications for use are stated in the labeling and are identical to Indications for Use form and 510k Summary
- #13c DEVICE DESCRIPTION: List of compatible components and accessories (instruments) with 510(k) number
- #22 STERILIZATION: Assessment for the need for sterilization
- #29 BIOCOMPATIBILITY: Submission includes list of patient-contacting device components and associated materials of construction, including identification of color additives, if present
- #31 BIOCOMPATIBILITY: Submission includes: Test protocol (including identification and description of test article), methods, pass/fail criteria, and results provided for each completed test, OR a statement that biocompatibility testing is not needed with a rationale (e.g., materials and manufacturing/processing are identical to the predicate)
Special 510(k): RTA Checklist Tips

• Indications for use unchanged
• Fundamental scientific technology unchanged
• Only summary-level performance information provided – test reports not necessary to establish SE

➔Will convert to a Traditional 510(k) if it does not meet these criteria. After conversion, reviewer completes Traditional 510(k) RTA checklist

#18a LABELING: All changes in proposed labeling resulting from device modification(s) are highlighted or prominently identified.
  – Recommend red-lined tracked changes version or a summary of changes with a copy of the labeling
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The Review

• The information requested by FDA varies based on the device type, indications for use, technology, etc.
  – Descriptive Characteristics
  – Labeling
  – Sterilization & Shelf Life
  – Biocompatibility
  – Performance Testing
    • Bench Testing
    • Animal Testing
    • Clinical Studies

Guidance Document: Format for Traditional and Abbreviated 510(k)s (issued August 12, 2005)
Evaluating Substantial Equivalence in Premarket Notifications [510(k)] Guidance

- The final guidance issued on July 28, 2014
  - Replaces only K86-3 Blue Book Memorandum
- Describes FDA’s current review practices for 510(k) submissions by describing the regulatory framework, policies and underlying practices
- Does not address the Special and Abbreviated 510(k) programs

NOTE: These sections will be finalized separately. Until then, the recommendations for Special and Abbreviated 510(k)s contained in the “New 510(k) Paradigm” guidance remain in effect for these types
Updates and Changes

• A revision of the 510(k) Decision Flowchart
• New terms with definitions
• Clarification on “Split Predicate”
• Discussion on Intended Use and Indications for Use
• Explanation of 510(k) Summary content
The 510(k) Flowchart

- 2014 Guidance: Evaluating Substantial Equivalence in Premarket Notifications
- Flowchart not intended to be used as a stand-alone document
- Decision questions are answered in order
- Walk through with 1 predicate at a time
Decision 1

• A “legally marketed predicate” is one that either:
  - Was cleared in a 510(k)
  - Is a pre-amendment device
  - Was down-classified from Class III to II or I
  - Was classified by a *de novo* petition

• Devices that are the subject of a recall or are no longer marketed are **still** considered legally marketed predicates
Decision 2

- **Intended Use** means the general purpose of the device or its function, and encompasses the indications for use.

- **Indications for Use** describes the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended.
Example (Intended Use)

- A new device’s instructions for use describes general surgery use in a body cavity
- The predicate is used only to treat external injuries
- A comparison may not be adequate due to risk of infection
- An independent infection risk assessment of the predicate was not evaluated or was significantly less concerning during the predicate review
- New device may constitute a new intended use
- PMA (or alternative submission type), or if appropriate, a De Novo request is required
Discussion on Intended Use and Indication For Use (IFU)

• “Only a change in the indications for use that raises different questions of safety and effectiveness … constitutes a new intended use.”

• Examples of when a new Indication for Use may result in a new Intended Use
  – A change from a function/performance indication to a treatment or aesthetic indication
  – A change from a diagnostic indication to a screening indication, or vice versa;
  – A change in the anatomical structure of use;
  – A change in the patient population (e.g. adult versus pediatric)
  – A change in the clinical context or setting (e.g. hospital versus home use)
Decision 3

- The old flowchart asked if the technological characteristics were the same, were the descriptive characteristics enough for SE?

- The new flowchart asks if the technological characteristics are the same, then the device is SE; however, descriptive characteristics are still taken into account.

- The descriptive characteristics may include brief summary-level analyses (e.g. engineering analyses) to show that the technological characteristics are the same.

- Answering yes implies the descriptive characteristics are precise enough to ensure equivalence.

- Finding a device SE based on descriptive characteristics alone may be rare.
Example (Decision 3)

• A manufacturer seeks clearance for a bone screw that is larger than what valid predicates offer
  – A basic engineering analysis and clinical rationale was provided showing that the new screw does not introduce a new worst case and a performance evaluation is not needed
  – It can be determined that the technological characteristics are the same -> SE
Example (Decision 3)

• A different manufacturer seeks clearance for a bone screw that is smaller than what valid predicates offer
  – The provided descriptive and engineering analyses were not sufficient to establish equivalent technological characteristics
  – Move on to Decision 4 (Do the technological differences raise different questions of safety and effectiveness?)
A “different question of safety and effectiveness” is a question raised by the technological characteristics of the new device that was not applicable to the predicate device, and poses a unique safety or effectiveness concern for the new device.

FDA is responsible for coming up with the different question

It only takes 1 different question
Example (Decision 4)

- A new device externally applies vacuum around the neck to move soft tissue and “open” the airway
- The predicate device (Decision 1) is a tube inserted into the patient’s pharynx through the mouth to provide an airway by mechanically moving soft tissue
- The intended use is the same (Decision 2)
- There are different technological characteristics (Decision 3)
- The new device exerts continuous pressure on all soft tissue in neck and the predicate does not
- The new device raises concerns with potential adverse events associated with the stimulation of nerve structures in the neck and the predicate does not raise this type of question
- Because these types of questions were not necessary to take into account for the predicate device, the new device would be found NSE
Decisions 5a & 5b

• If there are no different questions of S&E, can data be used to evaluate the differences?

• 5a: “Are the methods acceptable?”
  • It has been rare that a device falls off the chart at this stage

• 5b: Review the data
New Terminology: Primary Predicate

- **Primary Predicate** — the identified predicate with indications and technology **most similar** to the subject device when multiple predicates are identified
  - Sponsor should suggest the primary predicate; however, final decision is up to reviewer
  - Must be able to address Decision points 1-4 with one primary predicate
  - Identifying a Primary Predicate can facilitate a timely review and well-supported decision
    - identify the minimum number of predicates to demonstrate SE
    - help track predicate lineage and technology changes
Example (Multiple Predicates)

- New hemodialysis catheter with an extension piece similar to legally marketed (Decision 1) predicate A and a tip similar to legally marketed predicate B
  - Both predicates have same intended use (Decision 2)
  - The technological characteristics of the new device are not the same as the predicates (Decision 3)
  - The technological characteristics do not raise different questions of safety and effectiveness in regard to the predicates (Decision 4)
- Either predicate can serve as primary predicate
New Terminology: Reference Device

• **Reference Device** — a legally marketed device intended to provide scientific information to support safety and effectiveness.
  
  – Reference devices may be used to support scientific methodology or standard reference values at Decision Point 5a
  
  – Reviewer still has authority to decide what data is necessary
  
  – Reference device is NOT a predicate and cannot be used to support decision points 1-4 on the Flowchart.
Example (Reference Predicate)

- Total knee implant with new coating X
  - Other total knee implants with coatings A, B, and C are legally marketed and have the same intended use (Decisions 1 and 2)
  - A total hip implant is cleared with coating X

- New implant does not have the same technological characteristics due to a different coating than other knee implants (Decision 3), but do not raise different questions of safety and effectiveness (Decision 4).

- Predicate knee implant with coating A has served as a comparator for Decisions 1-4 in the Flowchart and can be the Primary Predicate

- Total hip implant with coating X can be the Reference Device for support of appropriate scientific methods for characterization (Decision 5)

- The review team decides the extent to which the data from the hip implant can be used to support the subject device
Split Predicate

- Refers to demonstrating the 510(k) decision making process by combining the intended use of one device with technological characteristics of another.

- The guidance clarifies “The use of a ‘split predicate’ is inconsistent with the 510(k) regulatory standard.”

- To obtain SE, FDA should be able to walk down the flowchart (at least Decisions 1-4) using the primary predicate.
Top Deficiencies in Orthopedics

• Inadequate performance testing
  – Low performance values
  – No discussion of data in comparison to predicates (data dumps)
  – Incomplete tests (e.g., inadequate fatigue testing/characterization)
  – Poor worst-case analysis, or tests not conducted on worst case constructs
Top Deficiencies in Orthopedics

• Inadequate performance testing
  – Incomplete test reports
    • Lacking detailed methodology (e.g., sample size justification, test procedures, test conditions, etc.)
    • No pre- and post-test images
  – Testing not conducted in accordance with recognized consensus standard (or absence of justification for any deviations from standard)
Top Deficiencies in Orthopedics

• Inadequate cleaning instructions for reusable devices (i.e., instruments)
• Insufficient retrospective literature review (e.g., to support an expansion of indications)
• Inadequate risk analysis (especially in Special 510(k)s)
• Inadequate Device Description
  – Inadequate and/or conflicting device descriptions/parts listings
  – Lack of information regarding device specific accessories/instruments
  – Inappropriate add-to-file changes that lead to additional questions/clarification
Top Deficiencies in Orthopedics

Need comprehensive data on color additives

• Basic Colorant Information
  – Commercial name of the colored material
  – Chemical name and the Chemical Abstract Services (CAS) number of each key colorant in the formulation.
  – Estimated absolute amount of colorant per device
  – Evidence of biocompatibility of the base resin

• Identification of other US marketed medical devices by device name, manufacturer, submission #, where the colorants have been previously used, if known.

• Additional Colorant Information
  – Additional information may be required (e.g., Size range of colorant, Purity level of colorant, Material Safety Data Sheet (MSDS) for each colorant, Release capability of colorant, Toxicity assessment of the colorant or a rational for why additional toxicity testing for the device containing the colorant is unnecessary.
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     - IR: FDA works with submitter to resolve remaining issues. FDA clock ticking

4. **FDA works with submitter to resolve remaining issues. FDA clock ticking**
   - Work interactively to resolve remaining issues
Interactive Review

• Guidance Document - Types of Communication During the Review of Medical Device Submissions (issued on April 4, 2014)

• After first hold, issues should be resolved interactively

• FDA aims to offer 2-5 days to respond to any remaining deficiencies (depending on nature of requests, time remaining)

• Final decision based on information submitted by date specified by reviewer
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Final Decision

IR

FDA works with submitter to resolve remaining issues. FDA clock ticking

Work interactively to resolve remaining issues
510(k) Outcomes

**SE**
- Green light to go to market
- FDA Classifies & assigns regulation and product code

**NSE**
- NSE for inadequate performance data or inadequate response
- Can’t go to market yet
- Try again with a new 510(k) (inc. data, responses to address NSE issues)

**NSE, try again**
- NSE for lack of predicate, new intended use, or different questions
- Can’t go to market
- Possible *de novo* or PMA
Guidance Documents
Guidance for Industry and Staff

• Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling (issued March 17, 2015)
  – Considerations for reprocessing instructions, methods
  – Validation should be completed prior to submission of 510(k)
  – FDA does not routinely review validation data (only for devices in Appendix E of the guidance)
  – FDA *may* still request validation data for devices with unique reprocessing concerns (i.e., “shaft-within-a-lumen” which can’t be disassembled)

• Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile (DRAFT*)
  *not for implementation
Guidance for Industry and Staff

- Medical Device Accessories: Defining Accessories and Classification Pathway for New Accessory Types (DRAFT*)
- Reporting of Computational Modeling Studies in Medical Device Submissions (DRAFT*)
- Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications with Different Technological Characteristics (DRAFT*)

*not for implementation
For more information…

- [Constance.Soves@fda.hhs.gov](mailto:Constance.Soves@fda.hhs.gov)
- Division of Orthopedic Devices: 301-796-5650
- General questions – contact Division of Industry and Consumer Education (DICE)
  - **Email**: [DICE@fda.hhs.gov](mailto:DICE@fda.hhs.gov)
  - **Phone**: 1(800) 638-2041
  - (301) 796-7100
- Questions about an anticipated submission – submit a Pre-Submission**!!

**Guidance Document - Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff (issued February 18, 2014)**
Questions?
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