FDA Regulatory Process for CAUTI Medical Devices: Premarket Review Processes

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Disclosures:
Outline I

- FDA and CDRH Overview
- Combination Products
- Premarket Review Processes
- Substantial Equivalence and Antimicrobials
- Clinical Data and Investigational Device Exemptions
- FDA Feedback and Pre-Submission
- Take Home Message
FDA Statutory Authority

• FDA’s authority is granted by Congress.
  – Without statutory authority, FDA has no jurisdiction.
FDA Regulatory Mandates

- 1938 Federal Food, Drug, and Cosmetic Act (FD&C)
- 1968 Radiation Control for Health & Safety Act (RCHSA)
- 1976 Medical Device Amendment of 1976
- 1988 Clinical Laboratory Improvement Amendments (CLIA)
- 1990 Safe Medical Devices Act (SMDA)
- 1992 Mammography Quality Standards Act (MQSA)
- 1992 Medical Device Amendments
- 1997 Food & Drug Administration Modernization Act (FDAMA)
- 2002 Medical Device User Fee and Modernization Act (MDUFMA)
- 2004 Project Bioshield Act
- 2005 Medical Device User Fee Stabilization Act (MDUFSA)
- 2007 Food and Drug Administration Amendments Act (FDAAA)
- 2012 Food and Drug Administration Safety and Innovation Act (FDASIA)
  - Medical Device User Fee and Modernization Act (MDUFMA III)
- 2016 21st Century Cures Act
Center for Devices and Radiological Health (CDRH)

Office of the Center Director (OCD)

- Office of Compliance (OC)
- Office of Device Evaluation (ODE)
- Office of In Vitro Diagnostics and Radiological Health (OIR)
- Office of Surveillance and Biometrics (OSB)

- Office of Communication and Education (OCE)
- Office of Management Operations (OMO)
- Office of Science and Engineering Laboratories (OSEL)
## Centers and Regulatory Responsibilities

<table>
<thead>
<tr>
<th>Center</th>
<th>Regulates</th>
<th>Definition</th>
<th>Examples</th>
</tr>
</thead>
</table>
| CDRH  | • Medical devices  
• Radiation emitting products | Section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) defines a medical device as any healthcare product that does not achieve its principal intended purposes by chemical action or by being metabolized. | • Catheter  
• Stents  
• Endoscopes  
• X-ray machines  
• Mammography |
| CDER  | • Over-the-counter and prescription drugs  
• Biological therapeutics  
• Generic drugs  
• Fluoride toothpaste*  
• Antiperspirants*  
• Dandruff shampoos*  
• Sunscreens* | Product is considered a drug if its primary intended use is achieved through chemical action or being metabolized by the body. | • Aspirin  
• Beta Blockers  
• Polymyxin B Sulfate |
| CBER  | • Blood and blood products  
• Blood banking equipment | “biological product” means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsenic compound or derivative of arsenic compound (or any other trivalent organic arsenic compound) | • Vaccine |
Combination Product

• It is a product composed of two or more different types of medical products (i.e., a combination of a drug, device, and/or biological product with one another). The medical products are referred to as “constituent parts” of the combination product.

• The FDA Office of Combination Products (OCP) covers the regulatory life cycle of combination products.

• OCP can be reached at either 301-796-8930 or combination@fda.gov
How Combination Products are Evaluated?

• Combination Products are assigned to a “Lead Center” having primary responsibility for their review.

• The Lead Center is selected based on the “primary mode of action” (PMOA) of the combination product.

• The PMOA refers to the single mode of action of a combination product that provides the greatest contribution to the product’s intended effects.
## Combination Product Example

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Foley Catheter with Silver Coating</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Constituents</strong></td>
<td>Foley Catheter (device) and Silver Coating (drug)</td>
</tr>
<tr>
<td><strong>PMOA</strong></td>
<td>Drainage of urine from the bladder (device)</td>
</tr>
<tr>
<td><strong>Secondary MOA</strong></td>
<td>Killing of microorganisms (drug)</td>
</tr>
<tr>
<td><strong>Lead Center</strong></td>
<td>CDRH</td>
</tr>
</tbody>
</table>
# CDRH Risk Base Classification

<table>
<thead>
<tr>
<th>Risk level</th>
<th>Sufficient information for controls?</th>
<th>Premarket review?</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong></td>
<td>Low</td>
<td>General</td>
<td>Tongue depressor, stethoscope</td>
</tr>
<tr>
<td><strong>Class II</strong></td>
<td>Moderate</td>
<td>General &amp; Special</td>
<td>Catheter with antimicrobial coating, Endoscopes</td>
</tr>
<tr>
<td><strong>Class III</strong></td>
<td>High</td>
<td>Insufficient</td>
<td>Cardiac ablation catheters, coronary artery stents</td>
</tr>
<tr>
<td></td>
<td>Class II</td>
<td>Class III</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Premarket Path</td>
<td>510(k)</td>
<td>De Novo</td>
<td></td>
</tr>
<tr>
<td>Predicate?</td>
<td>Identified</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Appropriate for ...</td>
<td>“me also”</td>
<td>Innovative lower risk</td>
<td></td>
</tr>
<tr>
<td>Regulatory standard</td>
<td>“substantial equivalence”</td>
<td>Controls provide reasonable assurance for reclassification</td>
<td></td>
</tr>
<tr>
<td>Permission</td>
<td>“cleared’”</td>
<td>“granted”</td>
<td></td>
</tr>
<tr>
<td>Clinical data?</td>
<td>10-15%</td>
<td>Most</td>
<td></td>
</tr>
<tr>
<td>Time to approval</td>
<td>4-6 months</td>
<td>6-9 months</td>
<td></td>
</tr>
<tr>
<td>2019 User Fees</td>
<td>$10, 953.00</td>
<td>$96,644.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$322,147.00</td>
<td></td>
</tr>
</tbody>
</table>
What is Substantial Equivalence?

• Demonstration that a new device (subject device), as compared to a legally marketed device (predicate device), has...
  – the same intended use and
  – the same technological characteristics,
  – Or differences in technological characteristics do not raise different questions regarding safety and effectiveness

Guidance document: The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]
510(k) Decision-Making Flowchart
## Determination of Substantial Equivalence

<table>
<thead>
<tr>
<th>Key Elements of Substantial Equivalence</th>
<th>Corresponding Decision Point in Flowchart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicate Device</td>
<td>1. Is the predicate device legally marketed?</td>
</tr>
<tr>
<td>Intended Use</td>
<td>2. Do the devices have the same intended use?</td>
</tr>
<tr>
<td>Technological Characteristics</td>
<td>3. Do the devices have the same technological characteristics?</td>
</tr>
<tr>
<td></td>
<td>4. Do the different technological characteristics of the devices raise questions of safety and effectiveness?</td>
</tr>
<tr>
<td>Performance</td>
<td>5a. Are the methods acceptable?</td>
</tr>
<tr>
<td></td>
<td>5b. Do the data demonstrate substantial equivalence?</td>
</tr>
</tbody>
</table>

Antimicrobial Agent

• Any substance that kills or inhibits the growth of microorganisms.

• These substances may or may not meet the statutory definition of a drug in section 201(g) of the Food Drug and Cosmetic Act, depending on their mechanism of action and intended use.
510(k)-Cleared Antimicrobial Coatings on Urological Catheters

- Silver
- Nitrofurazone
- Minocycline and rifampin
# Foley Catheter with Antimicrobial Coatings - 510(k) Decision Making

<table>
<thead>
<tr>
<th>Key Elements of Substantial Equivalence</th>
<th>Corresponding Decision Point in Flowchart</th>
<th>Foley Catheter with Silver, Nitrofurazone, or Minocycline/Rifampin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicate Device</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>Intended Use</td>
<td>2</td>
<td>Yes</td>
</tr>
<tr>
<td>Technological Characteristics</td>
<td>3 &amp; 4</td>
<td>Yes</td>
</tr>
<tr>
<td>Performance</td>
<td>5 a &amp; b</td>
<td>Yes</td>
</tr>
<tr>
<td>510(k) Appropriate</td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>
# Foley Catheter with Antimicrobial Coatings - 510(k) Decision Making

<table>
<thead>
<tr>
<th>Key Elements of Substantial Equivalence</th>
<th>Corresponding Decision Point in Flowchart</th>
<th>Foley Catheter with None or Different Antimicrobial Coating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicate Device</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>Intended Use</td>
<td>2</td>
<td>Yes</td>
</tr>
<tr>
<td>Technological Characteristics</td>
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<td>No</td>
</tr>
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<td>Performance</td>
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<td>510(k) Appropriate</td>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>
Examples of Different Questions

• What is the appropriate antimicrobial release profile?
• What is the antimicrobial safety and effectiveness at the specified range of concentrations?
• What is the safe and effective dose of the antimicrobial agent?
• What are the toxicity risks not present in the predicate product?
• What are the antimicrobial resistance (AMR) risks not present in the predicate product?
Regulatory Pathway Outcomes

• A subject device with an antimicrobial would not be able to be found substantially equivalent to a predicate with no antimicrobial.

• A subject device with different antimicrobial agent than that present in the predicate device would not be able to be found substantially equivalent.

• Therefore, the 510(k) regulatory pathway won’t be appropriate.

• Depending on the device characteristics, an alternative regulatory pathway such as De Novo or PMA should be considered.
Clinical Data and Investigational Device Exemption (IDE)

- Clinical data to support a premarket application depends on the risk of the device and the type of application.
  - Clinical studies are most often conducted to support a PMA
  - Most of De Novos and only a small percentage of 510(k)s require clinical data to support the application.

- The *investigational device exemption (IDE)* is a regulatory submission that allows clinical investigation of medical devices to collect safety and effectiveness data.
  - All clinical evaluations of investigational devices, unless exempt, must have an approved IDE before the study is initiated.
Feedback and Pre-submission

• Prospective applicants of future premarket submissions may request feedback from the FDA through Pre-Submission program.
• Detailed information regarding the program can be found in the 2017 FDA’s guidance document, “Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff” (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf.)
• There is no user fee associated with the Pre-Submission program
Division of Industry and Consumer Education (DICE)

- DICE provides education regarding medical device laws, regulations, guidances, and policies, covering both premarket and postmarket topics.

- Web Resources:
  - Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm)
  - CDRH Learn (https://www.fda.gov/Training/CDRHLearn/default.htm)

- DICE staff can be reached by email (dice@fda.hhs.gov) or phone at 1(800) 638-2041 or (301) 796-7100 between the hours of 9:00 am – 12:30 pm and 1:00 pm – 4:30 pm Eastern Time.
Take Home Message

• The FDA uses a risk-based process for the premarket evaluation of medical devices.
• Highest risk devices undergo the most rigorous review.
• For FDA Feedback, take advantage of the Pre-Submission Program.

www.fda.gov
Thank you!