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FDA’s Clinical Investigator Course

Cosponsored by

FDA’s Office of Critical Path Programs (OCPP)
and
The Clinical Trials Transformation Initiative (CTTI)
Medical Device Clinical Trials: An FDA Perspective

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Director
Division of Cardiovascular Devices
CDRH
Today’s Topics

1. Introduction
2. Premarket Device Trials
3. Off-Label Use
What does the U.S. medical device industry look like?

According to the US Census Bureau, there are over 12,000 medical device manufacturing firms in the US.*

* Source: Census Bureau, Number of Firms, Number of Establishments, Employment, and Annual Payroll by Employment Size of the Enterprise for the United States, All Industries 2005 using NAICS codes 339111, 339112, 339113, 339114, 339115, 339116, 334517, 334510, 325413 [http://www.census.gov/csd/susb/susb05.htm](http://www.census.gov/csd/susb/susb05.htm)
Medical Devices

The Section 201(h) of the Food, Drugs and Cosmetics Act defines a medical device as any healthcare product that does not achieve its principal intended purposes by chemical action or by being metabolized.

– As simple as a tongue depressor or a thermometer
– As complex robotic surgery devices

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The Total Product Life Cycle

- Regulation of device technologies requires a total product life cycle approach.
## Device vs. drug development

<table>
<thead>
<tr>
<th>Developmental Feature</th>
<th>Device</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of technology change</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Ease of <em>in vitro</em> assessment</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Influence of physician technique on results</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Ease of blinding</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Definition of “Orphan” (number of patients)</td>
<td>4,000</td>
<td>200,000</td>
</tr>
<tr>
<td>Number of full scale studies usually required</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Number of Regulatory Classes</td>
<td>3</td>
<td>1*</td>
</tr>
</tbody>
</table>

*Note: Regulatory Class 1 for drugs includes a requirement for approval by the American Health System for Use (AHSU) program.
1. Pre-clinical Testing
   - Are bench and animal studies acceptable?

2. Pivotal Trial
   - Design: Minimize bias and confounding
   - Execution: Minimize amount of missing data
   - Analysis: Rule out chance (i.e., several prospectively chosen, clinically relevant hypotheses with plan for alpha allocation)
   - Have clinically meaningful results been clearly demonstrated?

3. Manufacturing
   - Can device be built safely for commercial distribution?

4. Is the Device Label truthful and accurate?
Analysis of Pivotal Device Trials

- Statistical significance is different from clinical significance
- There is no perfect device surrogate –
  - CDRH frequently deals with partial device surrogates
  - Understand their limitations
- Composite endpoints have limitations –
  - A combined endpoint needs to retain its interpretability
- The basic unit of analysis is the patient and not the device
- Advisory panels offer advice to the FDA in an open and transparent environment
- Totality of data in a device trial should indicate a beneficial risk/benefit ratio
### Four Studies all with the same P-value

<table>
<thead>
<tr>
<th>Number of Patients Receiving A and B</th>
<th>Proportion preferring A</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>15:5</td>
<td>0.04</td>
</tr>
<tr>
<td>200</td>
<td>114:86</td>
<td>0.04</td>
</tr>
<tr>
<td>2,000</td>
<td>1,046:954</td>
<td>0.04</td>
</tr>
<tr>
<td>2,000,000</td>
<td>1,001,445:998,5555</td>
<td>0.04</td>
</tr>
</tbody>
</table>
CDRH Case Study on Composite Endpoints

Cordis Checkmate Intracoronary Brachytherapy System

• Ref.

  – PMA SSED

  FDA Approval of Coronary-Artery Brachytherapy
In-Stent Restenosis (2001)

- Over 725,000 percutaneous coronary interventions will be completed in the U.S. each year, of which > 80% will receive a new stent
- Over 100,000 U.S. (20-40%) of patients will develop recurrent symptoms due to in-stent restenosis
- Often no effective minimally therapies are available
Intravascular Brachytherapy RX

Stent Segment
22.7 ± 10.7 mm

Analysis Segment
40.8 ± 9.4 mm
Cordis Gamma I Results

<table>
<thead>
<tr>
<th>Event</th>
<th>IRT</th>
<th>Placebo</th>
<th>95% CI OF DIFFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 Month MACE</td>
<td>28.2%</td>
<td>43.8%</td>
<td>(-27.3, -3.8%)</td>
</tr>
<tr>
<td>Death</td>
<td>3.1%</td>
<td>0.8%</td>
<td>(-1.1, 5.6%)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--Q wave MI</td>
<td>5.3%</td>
<td>3.3%</td>
<td>(-3.0, 7.0%)</td>
</tr>
<tr>
<td>--Non Q wave MI</td>
<td>6.9%</td>
<td>3.3%</td>
<td>(-1.8, 8.9%)</td>
</tr>
<tr>
<td>Target Lesion Revascularization</td>
<td>24.4%</td>
<td>42.1%</td>
<td>(-29.2, -6.3%)</td>
</tr>
</tbody>
</table>
The Total Product Life Cycle

- Regulation of device technologies requires a total product life cycle approach.
Striking the Right Balance Between Pre- and Postmarket Evaluation

• Use appropriate amount of pre-market data to make primary decisions about approvability of new devices (safety, effectiveness)

• Use postmarket data to
  – supplement our understanding about device and operator performance
  – identify device malfunctions and take corrective action as necessary
  – modify pre-market expectations for next generation devices.
Premarket Device Trials
FDA’s Approach to Medical Device Regulation

1. Base degree of control on risk
2. Weigh benefit vs. risk to determine safety and effectiveness
3. Use valid scientific evidence
4. Consider least burdensome means
5. Provide “reasonable assurance”
Device Classification

Medical Device Classes

- Class I
  - General Controls
  - Most exempt from premarket submission

- Class II
  - Special Controls
  - Premarket Notification [510(k)]

- Class III
  - Premarket Approval
  - Require Premarket Application [PMA]
## Valid Scientific Evidence

### 21CFR860.7

<table>
<thead>
<tr>
<th>Includes</th>
<th>Does NOT include</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Well-controlled investigations</td>
<td>• Isolated case reports</td>
</tr>
<tr>
<td>• Partially controlled studies</td>
<td>• Random experience</td>
</tr>
<tr>
<td>• Studies and objective trials without matched controls</td>
<td>• Reports lacking sufficient details</td>
</tr>
<tr>
<td>• Well-documented case histories</td>
<td>• Unsubstantiated opinions</td>
</tr>
<tr>
<td>• Reports of significant human experience with a marketed device</td>
<td></td>
</tr>
</tbody>
</table>
510(k)
Premarket Notification

- Substantial equivalence
- 10-15% require clinical data
- Performance testing
- Usually confirmatory
- Type of study dictated by:
  - Ability of bench and animal testing to answer questions
  - Amount of difference between subject device and predicate
PMA
Premarket Approval Application

- Establish safety and effectiveness
- Bench-Animal-Human
- Similar to NDA (New Drug Application)
- Clinical Studies
  - Reasonable assurance of safety & effectiveness
Investigational Device Exemption (IDE) Process

• Applies to significant risk studies
• Allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification [510(k)] submission to FDA
• Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices
Some challenges in the development of cardiovascular device trials
Device-specific challenges: Drug-eluting stents (DES)

Pharmacologic Agent (‘Drug’)  

Carrier (e.g., Polymer)

Stent Design

Drug Eluting Stent
## Device-specific challenges

### Clinical studies

<table>
<thead>
<tr>
<th>Feature</th>
<th>DES “A”</th>
<th>DES “B”</th>
<th>DES “C”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>NME</td>
<td>Approved for systemic indication</td>
<td>paclitaxel sirolimus</td>
</tr>
<tr>
<td><strong>Drug formulation</strong></td>
<td>Novel drug formulation</td>
<td>Similar drug release profile (local/systemic)</td>
<td>Same drug formulation as approved DES</td>
</tr>
<tr>
<td><strong>Stent</strong></td>
<td>New stent material</td>
<td>316L, CoCr, nitinol platform</td>
<td>Approved stent platform</td>
</tr>
</tbody>
</table>

**Serial Iteration of existing DES**

**Entirely New Product**

**New & old technologies**
Evaluation of New Coronary Stents

One Size Does Not Fit All

- Randomized Control
- Nonrandomized Concurrent Control
- Historical control
- Operating Performance Characteristic (e.g., heart valve evaluation, LVAD BTT Trial)
Sample Size and the Binomial Distribution

Tx Effect = 25%, Power = 80%, Alpha error = 5%
Role of Bayesian Statistics in Medical Device Trials

- Combines information in the current trial with prior information accepted by the FDA: can be very useful in medical device clinical trials
- Not a substitute for poor trial design and/or execution
- Needs careful planning (prespecification of methods and validation of code is critical)
- Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials – 2006
- Examples: Circulatory Systems Advisory Panels (March 18, 2009; April 23, 2009; November 20, 2008)

http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm
Off-Label Use
After product approval…

What is “off-label use” according to the FDA?

• Use of a medical device for treatments other than for what the device was initially approved.

• Use not explicitly included in product labeling.

• Also referred to as “unlabeled,” “out-of-label,” “extra label” and “unapproved” use.
Off-label use

FDA concerns regarding off-label use:

- Off-label uses are not subject to a rigorous pre-market approval process.
- Off-label uses may diminish or eliminate the incentive to study or seek FDA approval for the indication for which the therapy is being used off-label.
- Adverse events associated with off-label use may not be captured and analyzed; patients not informed properly.
What is FDA’s interpretation of “practice of medicine”?

- Discussing treatment with patient
- Using treatment on patient
- Discussing treatment with other physicians in course of professional activity

FDA does not regulate the practice of medicine (Sec 906, FDAMA)
Practice of Medicine and Physicians

• Recognition of the importance of evidence-based medicine and patient informed consent in guiding clinical decision-making.

• If physicians use a product for an indication not in the approved labeling, they have the responsibility to:
  
  – Be well-informed about the product
  – Base its use on firm scientific rationale and on sound medical evidence
  – Maintain records of the product’s use and effects