Regulations for medical device development

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Élan Pharmaceuticals
CT Scanning

Traditional Lateral Skull Film
The First Computer

ENIAC

- 10 tons
- 19000 vacuum tubes
- 30 x 50 feet

Functions:
+ - * / Square roots
For ... next
If ... then
Miniaturization of Electrical Stimulators

Pacemakers
Novel Imaging Devices
New Technology

Important Trends
- Miniaturization
- Intelligent Devices
- Designed for Consumer Use
- Minimally invasive
- Biotechnology Revolution
  - Genomics, Proteomics
  - Biological Medical Devices
- New Materials
- Combination Products
- Disruptive Technologies
  - That change how we do business
  - That change how medical devices deliver value
**Stent as RFID**

Preclinical Model of Self Monitoring Stent:

- Applications: Detect restenosis
- Measure Blood Pressure Continuously

Yogesh Gianchandani and his team at the University of Michigan
Innovation and Trust
New Therapeutic Technology

What regulatory burdens are required to bring innovative new medical technology to market?
FDA: 100 Years of Consumer Protection

Public Health Goals

- Safe Human Experimentation
- Marketing Products with demonstrated Effectiveness
- Manufacturing Quality
- Truthful Claims
- Prompt response to hazards
- Prompt response to unmet need
Definition of a Drug

The term "drug" means:

- ... articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals;
- ... articles (other than food) intended to affect the structure or any function of the body of man or other animals.
Food Drug and Cosmetic Act

Web:

FDA Home Page
http://www.fda.gov/

FD&C Act  (link on FDA Home Page)
http://www.fda.gov/opacom/laws/fdcact/fdctoc.htm

Definitions
http://www.fda.gov/opacom/laws/fdcact/fdactoc1.htm
Definition of a Devices

Instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory, which is -

- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and …
Definition of a Devices

... and,

which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.
Classification Heirarchy

Devices are:

- Drugs
  … which do not act by chemical or metabolic means …

Or:

- Instrument, apparatus, …
Rube Goldberg

An Automatic Back Scratcher
Safe Therapeutic Products

**Drugs**
- Pure molecules
- Toxicology
- Short half-life
- Long market life
- Drug interactions
- Wrong Drug / Dose
- Clinically studied
- Good Manufacturing Practices (cGMP)

**Devices**
- Complex components
- Biocompatibility
- Durable Equipment
- Rapid product cycles
- Malfunction
- User Error
- Bench studied
- Quality Systems (ISO 13485)
FDA Mission: Overview

- Safe Use of Experimental Products
- Assure Manufacturing Quality
- Approve Marketing Claims
  - Safety
  - Effectiveness
  - Product Characteristics

Claims Require Evidence
Device Regulatory Path

Pre Amendment Marketed Devices

Class I

Class II

Class III

1976
Device Regulatory Path

<table>
<thead>
<tr>
<th>1976</th>
<th>Pre Amendment Marketed Devices</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Class I</td>
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<td>Class II</td>
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<td>Class III</td>
</tr>
<tr>
<td>510(k) Predicates</td>
<td>“Substantially Equivalent”</td>
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- New Products based on Old Products
- "Substantially Equivalent"
Device Regulatory Path

- **Pre Amendment Marketed Devices**
- **1976**
- **510(k) Predicates**
  - Class I
  - Class II
  - Class III

- **New Novel Products**
- **New Products based on Old Products**
- **"Safe and Effective"**
- **Substantially Equivalent**

- **PMA**
- **New Novel Products**
Device Regulatory Path

Pre Amendment Marketed Devices

Class I

510(k) Predicates

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Reclassification

New Products based on Old Products

De novo Classification

PMA

New Novel Products

“Safe and Effective”

“Substantially Equivalent”
Device Regulatory Path

1976

Pre Amendment Marketed Devices

Class I

Class II

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510(k) Predicates

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Reclassification

New Products based on Old Products

“De novo Classification"

New Novel Products

“Safe and Effective"

“Substantially Equivalent”

HDE
Submissions to FDA by Year for Biologics and NME Drugs
Submissions to FDA by Year for Drugs, Devices and Biologics

- ALL NDA
- ALL BLA
- ALL PMA
- NME NDA
- PDUFA BLA


Number of submissions on the y-axis, ranging from 0 to 140.
Product Life Cycle
Consumer Protection

Premarket Safety
- Safe experimentation
- Premarket safety
- Premarket effectiveness
- Research Inspection

Postmarket Studies
- Truthful promotion
- Adverse Event Reporting
- Postmarket studies
- Manufacturing Inspection
Early Product Life Cycle

- What is the product?
  - Device, Pharmaceutical, Biological?
  - Combination product
- What makes the product new?
  - biomaterials?
  - design?
  - Indication?
- Are there critical performance specifications?
Toxicology / Immunogenicity

- What is already known?
- Does the product leech? Oxidize?
- Standards: ISO, CDER, CBER, CDRH
- Limitations of oral exposure models
Safe Human Experimentation

Preclinical Evaluation
- Biocompatibility, Toxicity, Immunogenicity
- Performance Characterization
  - Strength, Durability, Failure Mode
- Animal Testing, if useful

Prototype Manufacturing
First-in-Human Studies
- Risk of Harm
  - Compared to alternative treatments
  - Vulnerability of the patient population
  - Severity of the need
Clinical Evaluation

- With final manufactured product or prototype?
- Least burdensome source of clinical evidence?
  - Controls
  - Questions to be left for postmarketing period?
Full Scale Manufacturing

- Know your supplier
  - Can you detect changes in components
- Know your consignee’s
  - Dialysis unintended use
- Liability
End-of-Life Problems
- Customer complaints
- User Errors
- Product Failures
  - Failure analysis
Product Development Lifecycle
Product Development Lifecycle
Cross-Generations
Cell Phone EMC and Pacemakers
Product Development Lifecycle

The Pipeline
Regulatory Cycle

Request for Designation

Device Advice

Prototype

Early Planning Meetings

Preclinical

Clinical

IDEs

Agreement & Determination Meetings

Manufacturing

Marketing

PMA’s, 510(k)s

Guidance

Commercial Use

Post-Marketing Studies

MDR’s

Advisory Panels

Warning Letters

Safety Alerts

Recalls

Obsolescence

Concept
Life Cycle of a New Infection
Life Cycle of a New Infection

- Index Case
- Clustered Cases
- Specimens
- Pathogen Identified
- Initial Diagnostics
Life Cycle of a New Infection
Diagnostic Device Life-Cycle
Diagnostic Device Life-Cycle
Diagnostic Device Life-Cycle
IVD and Disease – Linked Cycles
Oversight of *In Vitro* Diagnostics

Center for Devices and Radiological Health

Medical Devices

Health Professionals

Health Facilities

IRB’s

States

Clinical Laboratories Improvement Amendments (CLIA) Program
## Comparison of Review Processes

<table>
<thead>
<tr>
<th></th>
<th>FDA</th>
<th>CLIA</th>
<th>NY State</th>
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<tbody>
<tr>
<td>Registration and Listing</td>
<td>By Device and Lab</td>
<td>By Lab</td>
<td>By Device and Lab</td>
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<tr>
<td>Informed Consent</td>
<td>As Appropriate</td>
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<tr>
<td>IRB Oversight</td>
<td>As Appropriate</td>
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<tr>
<td>Analytic Validation</td>
<td>By Device</td>
<td>By Lab</td>
<td>By Device</td>
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<tr>
<td>Clinical Validation</td>
<td>For Novel Devices</td>
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<td>Yes (but not requested to date)</td>
</tr>
<tr>
<td>Clinical Utility</td>
<td>For a utility claim (unusual)</td>
<td></td>
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Analyte Specific Reagents

Regulatory Status:

Lab
- Tests with ASRs are Medical devices
- FDA has not called for premarket applications of Home Brews with ASR’s
- Recognition of CLIA’s role

ASR Manufacturer
- Required to register and list
- Required to meet good manufacturing practices
- Required to report adverse events
- Restricted distribution, use, and labeling
Combination Products

Drug Eluting Disk

Drug Eluting Stent
Combination Product

Combination Product (21 CFR 3.2(e)):

- Two or more products:
  - … combined or mixed as a single entity
  - … packaged together
  - … packaged separately but … where both are required

Not:

- Drug-Drugs, Device-Devices
Combination Product Jurisdiction

Drug Eluting Stent

Primary Mode of Action:
- Stent opens artery

Secondary Actions
- Drug prevents inflammation and restenosis of artery

Regulated as a Device (PMA)

Drug Eluting Disk

Primary Mode of Action:
- Cancer Chemotherapy for brain tumor

Secondary Actions
- Local drug delivery of drug by device

Regulated as a Drug (NDA)