FDA and the Regulatory Pathway for Biomaterials in Medical Devices

Steven K. Pollack, Ph.D.
Director, Division of Chemistry and Materials Science
Office of Science and Engineering Laboratories
Center for Devices and Radiological Health
Food and Drug Administration

2nd Military Biomaterials Roadmap Workshop
Wednesday, November 8, New Brunswick NJ
Overview

- What is a Medical Device?
- What Do We Do at FDA/CDRH?
- Some Insights into Device Related Properties
- Some Examples
- Some War Stories
1938 Federal Food, Drug, and Cosmetic (FD&C) Act is enacted. One of the provisions of the new Act, which supersedes the original Food and Drugs Act of 1906, is to extend coverage to devices, making it illegal to sell therapeutic devices that are dangerous or marketed with false claims.

1976 May 28 – Medical Device Amendments to the Food, Drug, and Cosmetic Act of 1938 are enacted, to assure safety and effectiveness of medical devices, including certain diagnostic and laboratory products.

1997 Modernization Act mandates the most wide-ranging reforms in agency practices since 1938. Provisions include measures to accelerate review of devices.

2002 October - Medical Device User Fee and Modernization Act (MDUFMA)
A medical device defined

- intended for use in the **diagnosis** of disease or other conditions, or in the **cure**, **mitigation**, **treatment**, or **prevention of disease** in man, or

- intended to **affect the structure or any function** of the body of man, and which does not achieve its primary intended purposes through chemical action within or on the body of man and which is not dependent upon being metabolized for the achievement of its primary intended purposes.”

Section 201, Food Drug and Cosmetic Act
A medical device defined

- intended for use in the **diagnosis** of disease or other conditions, or in the **cure**, **mitigation**, **treatment**, or **prevention** of disease in man, or

- intended to **affect the structure or any function** of the body of man, and **which does not achieve its primary intended purposes** through **chemical action** within or on the body of man and **which is not dependent upon being metabolized** for the achievement of its primary intended purposes.”

Section 201, Food Drug and Cosmetic Act
Cochlear Implants
RETINAL IMPLANT
Bionic implant in retina simulates vision.
For Popular Mechanics Journal, © Edmond Alexander
CDRH Mission Today

CDRH promotes and protects the health of the public by ensuring the safety and effectiveness of medical devices and the safety of radiological products.

Protect

Promote
“There is reasonable assurance that a device is safe when it can be determined based on valid scientific evidence that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh the probable risks.”

21 CFR 860.7
Effectiveness

“There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.”

21 CFR 860.7
We Regulate Devices, Not Materials
Two important points:

We regulate Medical Devices...

... we don’t regulate medical procedures (aka “practice of medicine”).
Risk-Based Classification of Medical Devices

- Class I: simple, low risk devices
  - General controls
  - Most exempt from premarket submission
Class I: General Controls Sufficient

General Controls include:
- Prohibition against adulterated or misbranded devices
- Premarket notification (510(k)) requirements
- Banned devices
- Good Manufacturing Practices (GMPs)
- Listing of device types
- Record keeping
- Repair, replacement, refund
Class I Exemptions

- All Class I Devices are exempt *except*:
  - Those intended for a “use which is of substantial importance in preventing impairment of human health, or
  - Those that present a potential unreasonable risk of illness or injury

- **Examples:**
  - Ammonia test system
  - Dental handpiece and accessories
  - Protective restraint
Risk-Based Classification of Medical Devices

- Class II: more complex, higher risk
  - Special controls
  - Premarket Notification [510(k)]
  - Substantial equivalence
  - 10-15% require clinical data
  - 90 total FDA days to review
Class II:
Special Controls Sufficient

- Special Controls include:
  - Labeling
  - Guidance
  - Tracking
  - Design Controls
  - Performance Standards
  - Postmarket Surveillance
Risk-Based Classification of Medical Devices

- Class III: most complex, highest risk
  - Premarket Application [PMA]
  - Establish safety and effectiveness
  - Bench - Animal - Human
  - May include post-approval study requirements
  - 320 total FDA days to review
Class III
General and Special Controls are not sufficient

- Devices for which insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of such devices and

- Such devices are:
  - life sustaining of life supporting
  - substantial importance in preventing impairment of human health; or
  - present unreasonable risk of illness or injury
How do we decide which pathway is the right one for a particular device?
510k or PMA?

- Classified in the Code of Federal Regulations (CFR)
- Precedent
  - Previously found SE → 510(k)
  - Previously found NSE → PMA/HDE or “de novo” if low-risk device
  - Previously approved PMA → PMA
- 513(g) Request
Medical Device
Primary Pathways to Market

510(k)
510(k) Submission Required

When:

- Introducing a device to the market for the first time
- Change in intended use for a marketed device
- Making significant modification to a marketed device (aka Special 510k)
A Device is Substantially Equivalent (SE) if:

- In comparison to a legally marketed device, it:
  - Has the same intended use, and
  - Has the same technological characteristics as the predicate device, or:
SE (cont.)

- Has the same intended use, and
- Has different technological characteristics and the information in the 510(k):
  - Does not raise new types of questions of safety and effectiveness, and
  - Demonstrates it is as safe and effective as the predicate
Medical Device
Primary Pathways to Market
Four stages of PMA review

- Filing Review
- Substantive Review
  - Includes one or more cycles
  - May also include a prior module review
- Panel Process
- Closeout Process
PMA Review Process: Filing

- PMA Filing Reviews
- Filing Meeting
  - Expedited or not?
  - First discussion of panel meeting
  - Division or Office level signoff?
- Filing Review Memorandum
- Refuse to File/File Letter
  - Only FILED PMAs count towards MDUFMA goals
PMA Review Process: Substantive Review

- The “guts” of the PMA process
- Communication is key
  - Between team members
  - With the firm
  - With management (when needed)
The first BIG question

- Do we need to take the PMA to Panel?
  - First-of-a-kind
  - Data raises issues for Panel
- Preliminary decision by day 60
The second question

- Are the deficiencies significant enough to warrant a Major Deficiency Letter?
- Consulting reviews due day 80/70: need to decide soon after
Major Deficiency Letter

- Major Deficiency
  - Significant new or updated data
  - Significant previously omitted data
  - Resets 180 day clock

- MDUFMA requirements
  - Must issue within 150 days on first cycle
  - Must issue within 120 days on second cycle
PMA Review Process: Panel Process

- Must begin planning early
- Coordinate with Panel Exec Sec
- Selection of panel members
- Panel pack due out Day 100/90
  - Review memos
  - Company info
  - Panel questions
Medical Device Advisory Panels

- Provide broad clinical and scientific expertise to evaluate safety and effectiveness
  - PMAs, PDPs, 510(k)s
  - Device classification/reclassification
  - General issues (e.g. guidance documents, standards)
  - Homework assignments
- 7 voting members, non-voting industry & consumer representatives
- Provide recommendations only
CDRH Medical Devices
Advisory Committee Panels

- Anesthesiology and Respiratory
- Circulatory System
- Clinical Chemistry / Toxicology
- Dental Products
- Ear, Nose & Throat
- Gastroenterology / Urology
- General & Plastic Surgery
- General Hospital / Personal Use
- Hematology / Pathology
- Immunology
- Medical Devices Dispute Resolution
- Microbiology
- Molecular / Clinical Genetics
- Neurological
- Ob / Gyn
- Ophthalmic
- Orthopedic & Rehabilitation
- Radiological
PMA Review Process: Closeout:

- The BIGGEST question:
  - What is the final decision?
    - Approval
    - Approvable
    - Not Approvable
    - Denial
Investigational Device Exemptions (IDE)

- Patient protection and clinical study design considerations
IDE

- Allows investigational devices to be used in clinical studies to support PMA, 510(k)
- Exempts from certain provisions of FD&C Act
- Requirements for informed consent, labeling, monitoring, records/reports
- Requires approval by Institutional Review Board (IRB) and, for significant risk devices, FDA
- 30-day review period – if no action by FDA in 30 days, it is “deemed approved”
Polymers for Medical Devices

- **Primary**
  - Properties are critical to the function of the device
    - IOLs
    - Resorbable sutures
    - Hemostatic polymers

- **Secondary**
  - Properties are convenient
    - Housings on electronic devices
    - Components in non-implant devices
Physical Properties

- Thermoplasticity
- Reactivity
- Transparency
- Mechanical Strength
- Toughness
- Tribological Properties
- Interfacial Properties
Biocompatibility/Biostability

- Biocompatibility
  - Lack of toxicity/immunogeniticy
  - Minimal inflammatory response
  - Controlled encapsulation
  - Non-thrombogenic

- Biostability
  - Long term stability in the presence of high moisture
  - Resistance to Oxidation and Environmental Stress Cracking
Devices are Made of Multiple Materials
Wear Leads to Problems

Particles

Macrophages, Giant Cells, Prostaglandins, Interleukin-1, Stimulates Osteoclast, Bone Resorption
Polyethylene
Polyethylene
UHMWPE
UHMWPE
UHMWPE
Polypropylene
Polycarbonate

Cardiotomy reservoir
Polycarbonate
Polyethyleneterephthalate
Polyurethaness
Polyurethanes
Silicone
Silicones

Pre-operative X-ray

4 Months Post-operative
Silicones
Bioresorbable Polymers
Bioresorbable Polymers
Teflon

Wear particles led to severe bone loss
Storage of the Hollow Fiber Dialyzer At Elevated Temperatures Led to Depolymerization and Release of Neurotoxic Oligosacharrides
Repeated Defect in Heart Devices Exposes a History of Problems

By Barry Meier | October 20, 2005

It was March in the high desert West but the day felt more like early summer - warm, bright and breezy - as the young couple rode out on rented mountain bikes along a trail that ran through the majestic red rock canyons outside Moab, Utah.

The two college students met only a few months earlier, in late 2004. But the couple, Jessica Lemieux and Joshua Oukrop, had talked in recent days about their lives together and marriage. "I told him he had met his match," Ms. Lemieux recalled. "That I had started finishing his sentences for him."

It was one of the last things she told him. From behind, where Mr. Oukrop was riding, she heard him call out...
Non “Off-The Shelf” Polymers

- No device history
- Use in different device
- Use for different indication
- WE DON’T APPROVE MATERIALS
  - Sponsor must address the safety/efficacy of the Device.
  - Biocompatibility from earlier device can be sited, but use in different tissues (neurological versus bone) will certainly raise new safety questions.
An Example of Device Evolution
Ball Valve

Silicone

Dacron
Pyrolytic Graphite Disc Valve

Dacron

Pyrolytic Carbon (derived from PAN)
Pyrolytic Graphite
Fixed Porcine Xenograft Valve
Porcine Endocardium
Polyurethane Tricuspid Valve
What’s Next?

- Nanophase Materials
- Conducting Polymers in Electrophysiological Applications
- Tissue Engineered Medical Products with Synthetic Polymer Scaffolds
- New Bioreabsorbable Polymers
Acknowledgements

- Dr. Donna-Bea Tillman, Director, ODE
- Dr. Dan Schultz, Director, CDRH