From Discovery to Marketplace Regulatory Oversight

Michael D. O'Hara, Ph.D.
Deputy Division Director
Division of Radiological Health
Office of In Vitro Diagnostic Devices and Radiological Health
Center for Devices and Radiological Health
Food and Drug Administration

Presentation Outline

- Summary of CDRH structure
- Pre-market review
- Medical device reporting
- Electronic Product Radiation Control
- Device Recall

How Does FDA (CDRH) get Involved with Advanced Technology Development

- FDA clears/approves new devices for market entry based on safety and effectiveness
- Depends on the Medical Device Type and the Office/Division that reviews the device
  - Radiological Devices –Division of Radiological Health
  - Surgical Oncology Devices –Division of Surgical Devices or Division of Reproductive, Gastro-Renal and Urological Devices

Center for Devices and Radiological Health (CDRH)

Component Offices

- Center Director
- Communication and Education
- Compliance
- Device Evaluation
- In Vitro Diagnostics and Radiological Health
- Management Operations
- Science and Engineering Laboratories
- Surveillance and Biometrics

Mission

The mission of the Center for Devices and Radiological Health (CDRH) is to protect and promote the public health. We assure that patients and providers have timely and continued access to safe, effective, and high-quality medical devices and safe radiation-emitting products. We provide consumers, patients, their caregivers, and providers with understandable and accessible science-based information about the products we oversee. We facilitate medical device innovation by advancing regulatory science, providing industry with predictable, consistent, transparent, and efficient regulatory pathways, and assuring consumer confidence in devices marketed in the U.S.

CDRH

- While all of the offices are involved with medical device evaluation, we are specifically concerned with the following divisions for this presentation:
  - Compliance
    - Analysis and Program Operations, Bioresearch Monitoring, Premarket and Labeling Compliance, Manufacturing and Quality, International Compliance
  - Device Evaluation
    - Anesthesiology, General Hospital, Respiratory, Infection Control, Dental, Cardiovascular Devices, Ophthalmic, Ear Nose and Throat Devices, Neurological and Physical Medicine Devices, Orthopedic Devices, Surgical Devices, Reproductive, Gastro-Renal and Urological Devices
  - In Vitro Diagnostics and Radiological Health
    - Program operations, Chemistry and Toxicology Devices, Immunology and Hematology devices, Molecular Genetics and Pathology, Microbiology Devices, Radiological Health, Mammography Quality Standards
  - Surveillance and Biometrics
    - Knowledge Management, Outreach, Epidemiology, Post-Market Surveillance, Biostatistics

CDRH interaction Before Market Approval / Clearance

- Similar for surgical oncology devices and radiological devices
- Calls to division management or branch management with questions
- The Pre-Submission Process
  - For a more detailed discussion on a potential medical device, clinical trial or submission issue;
  - Device sponsor briefly describes the device, how it will be used and tested and asks questions that can help them with the development of regulatory strategies;
  - Answers by FDA not binding but most divisions honor answers

Surgical Oncology Devices

- Division of Surgical Devices
  - Ablative devices
  - Software algorithms for tumor margins in breast cancer lumpectomy specimens (MarginProbe)
  - Melanoma diagnosis (Melafind)
- Division of Reproductive, Gastro-Renal, and Urological Devices
  - Drug eluting microspheres

Radiological Devices

- Device types reviewed by DRH
  - Linear accelerators
  - Co-60 Teletherapy
  - Proton Accelerators / Carbon Ion Accelerators
  - Treatment Planning Software
  - Brachytherapy devices
  - Y-90 microspheres (Therasphere, Sir Sphere)

Medical Device Classifications

- Class I (Low Risk Devices);
  - Subject to general controls
  - Many class I devices exempt from premarket notification
- Class II (Moderate Risk Devices);
  - Subject to general and special controls
  - Many class II devices require premarket notification (510(K))
- Class III (High Risk Devices)
  - Subject to general controls and premarket approval

Safety

- “There is a reasonable assurance that a device is safe when it can be determined, based upon 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 any probable risks.”

Defined in 21 CFR 860.7(d)1

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 significant results.”

Defined in 21CFR 860.7(e)1

Premarket Approval (PMA)

- Regulatory pathway to market highest risk devices (Class III devices)
- Requires scientific, regulatory and quality system review
- Requires reasonable assurance of safety and effectiveness
- Requires well-controlled clinical studies or other objective information
- Considers benefit vs. risk, conditions of device use, device safety, performance and reliability

Class III (PMA) Device examples

Product Code	Device	Definition	Example Sponcer	Review Office/ Department
NRZ	Ablation system, HIFU	MR-guided HIFU system to ablate tissues	Exablate system Insightec, inc.	ODE/DRGUD
MNB	Device Thermal Ablation	For endometrial ablation	Novasure impedence controlled ablation system Hologic, Inc.	ODE/DRGUD
OYO	Optical Diagnostic Device for Melanoma Detection	Detection of melanoma and high-grade lesions among atypical lesions	Melafind Mela Sciences, Inc.	ODE/DSD
NAW	Microsphere, radionuclide	Radioactive particles for liver tumor metastasis	Sir-Spheres microspheres Sirtex Medical Limited	OIR/DRH
OTE	3D mammography, screening/diagnosis	3D imaging of breast tissue	Selenia Demensions 3D Full Field Mammography Hologic, Inc.	OIR/DRH

510(K)

- It is a marketing clearance application
- Class II devices
- Demonstration that a new device is similar to a legally marketed predicate device that has:
  - The same intended use
  - The same technological characteristics or the differences in technological characteristics do not raise different questions regarding safety and effectiveness

Section 510(K) of Federal Food Drug and Cosmetic Act

Class II (510(K)) Device Examples

Product Code	Device	Definition	Example Sponsor	Review Office/Division
OAB	Oncobionic system with 6 probe outlets	Low energy direct current thermal ablation system	Oncobionics, Inc.	ODE/DRGUD
IYE	Varian high energy Linear accelerator	Linear accelerator	Varian Medical	OIR/DRH
LNH	Proton system	Particle Therapy	Ion Beam Applications S.a.	OIR/DRH

- Linear accelerators and Proton accelerators have a long history of medical use that pre-dates the medical device regulations of 1976
- Linear and Proton accelerators are usually cleared with a general indication for use
- IFU: Tumor treatment anywhere in the human body

Investigational Device Exemption (IDE)

- Regulatory authority & framework for device clinical investigation
- Types of studies
  - Sponsor-investigator studies
    - Not intended to support a marketing application
  - Feasibility study
    - Preliminary safety and effectiveness data in small number of patients
  - Pivotal study
    - Definitive evidence for safety and effectiveness for device's intended use
    - Statistically justified number of patients

IDE

- Can either be significant risk or non-significant risk
- Significant Risk
  - Potential for serious risk to the health, safety and welfare of a subject
  - An implantable device
  - Used in supporting or sustaining human life
  - Substantial importance in diagnosing, curing, mitigating or treating disease
- Non-significant risk
  - No IDE submission needed
  - Institutional Review Board serves as FDA's surrogate

Advanced Technologies use of the IDE Process

- IDE cannot be disapproved on the basis of FDA's belief that the study design is inadequate to support a future PMA, 510(K) or other regulatory submission
- Disapproval based upon subject safety and protection
- CDRH clinical trials enterprise goal is to conduct trials in a timely, efficient and cost-effective manner while maintaining appropriate patient protections
  - Office level Clinical Trials Director involved with disapprovals or approvals with conditions
  - Increase the interaction with device sponsors.
- Same basic procedure for surgical oncology devices and radiation oncology devices

Medical Device Reporting

- Surgical oncology device reports reviewed by OSB and discussed with ODE
- Radiation oncology device reports reviewed by DRH
- Federal Food, Drug and Cosmetic Act (Section 519) grants FDA authority to require mandatory medical device reports from:
  - Manufacturers
  - Importers
  - Device user facilities

MDR Report Timeframes

Reporter	Report What	To	When
Device Used Facility	Deaths	FDA and Manufacturer	Within 10 working days
Device Used Facility	Serious Injury	Manufacturer FDA if unknown	Within 10 working days
Manufacturer	Deaths, Serious Injuries, Malfunctions	FDA	Within 30 calendar days
Manufacturer	Remedial action events to prevent unreasonable risk of substantial harm	FDA	Within 5 working days
Manufacturer	Follow-up reports	FDA	Within 1 month
Importers	Deaths, Serious injuries	FDA and Manufacturer	Within 30 calendar days
Importers	Device Malfunctions	FDA and Manufacturer	As soon as practicable or 30 calendar days

Electronic Product Radiation Control (EPRC)

- Mostly pertains to electronic radiation emitting products not surgical oncology devices
- To protect the public from hazardous or unnecessary exposure to radiation from electronic products
- Applies to manufacturers
- Authority is from EPRC provisions of the Federal Food, Drug & Cosmetic Act and Title 21 CFR 1000-1050
- Have performance standards for some equipment
  - Televisions
  - Cabinet x-ray systems
  - Microwave ovens
  - Laser products
  - Sunlamps
  - Mercury vapor lamps
  - Therapy Ultrasound devices
  - Diagnostic x-ray systems

EPRC

Consumer & Industrial Electronic Products

- Old Style TV tubes
- X-ray security systems
- Microwave Ovens
- Laser products
- CD players, laser pointers, laser light shows
- Metal halide lighting

Medical Electronic Products

- Sunlamps
- Ultrasound therapy devices
- Laser therapy and surgical devices
- Radiation Therapy
- Diagnostic x-ray systems
  - Conventional x-ray equipment
  - Fluoroscopic equipment
  - Computed tomography (CT)
- Magnetic Resonance equipment

Medical Device Recalls

- Surgical devices usually handled as a medical device recall
- Radiation oncology devices can be a medical device recall or EPRC recall.
- Recalling firm has a responsibility to promptly notify its customers of the issue and provide instructions to prevent further problems
- FDA determines if the recall is:
  - Class I
    - Reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death
  - Class II
    - May cause temporary or medically reversible adverse health events
  - Class III
    - Not likely to cause adverse health events

Device Recalls

Medical Device

- Firm's voluntary removal or correction of a marketed product that FDA considers in violation of the FD&C Act and against which FDA would initiate legal action
- FDA can request or order a recall

EPRC

- For radiation emitting products
- Electronic product fails to comply with an applicable Federal standard or has a defect specified in CFR 1003.2,
- manufacturer required to notify FDA, customers and submit corrective action plan.

Are there differences in the way devices are regulated at CDRH

- Yes, some devices are regulated from “cradle to grave” by one division while other groups hand off regulatory responsibility
- Office of In Vitro Diagnostics and Radiological Health is a “Cradle to Grave” office
- Office of Device Evaluation is responsible for premarket review and hands off medical device reports to OSB and medical device manufacturer compliance activity to the Office of Compliance

Office of In Vitro Diagnostics and Radiological Health

- All aspects of medical device review handled by one division
- Division of Radiological Health reviews premarket submissions, medical device failure reports and medical device manufacture compliance
- Pros –Improves DRHs understanding of regulated devices, issues caught in post market or compliance can be quickly addressed in pre-market

Regulatory Review

Review Type	Surgical Oncology Devices		Radiation Oncology Devices	
	ODE Device Review Group	Organization outside review group	OIR/DRH	Organization outside review group
Pre-submission	X		X	
510(K)	X		X	
PMA	X		X	
IDE	X		X	
MDR review		OSB	X	
MedSun review		OSB	X	
Device recall		Office of Compliance	X	
Facility inspection		FDA District Offices		FDA District Offices

Conclusion

- FDA
  - clears/approves medical devices before they are marketed
  - Constantly using new methods to reduce regulatory burden and increase communication
  - Follows products once they are on the market
  - Works with firms to remove, repair or replace bad devices
  - Inspects firms quality systems.