FDA Regulation of Imaging Modalities

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Roles of FDA Centers and Offices

- **CDRH** – Ensures the availability, safety, and effectiveness of medical devices and radiological products
- **CDER** – Assures that all prescription and over-the-counter drugs are safe and effective
- **CBER** – Ensures the safety, purity, potency, and effectiveness of biological products including vaccines, blood and blood products, and cells, tissues, and gene therapies
- **OCP** – broad responsibilities covering the regulatory life cycle of drug-device, drug-biologic, and device-biologic combination products
Medical Devices Defined: FDCA 201(h)

• An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article:
  – recognized in the official National Formulary, or the United States Pharmacopeia,
  – 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 of any function of the body of man or other animals, or
• Which does not achieve any of its principal intended purposes through chemical action within the body or by being metabolized
Drugs Defined: FDCA 201(g)(1)

- Articles recognized in the official USP (or equivalent)
- 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 via chemical interaction
- Articles intended for use as a component of any article specified above
Biologics Defined:
Vague and multi-sourced (CBER site)

• Wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins
  – Can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances
  – Or may be living entities such as cells and tissues
• Isolated from a variety of natural sources — human, animal, or microorganism
• May be produced by biotechnology (but not synthesized) methods and other cutting-edge technologies
Key Legislation

- The Food and Drugs Act of 1906 was the first of more than 200 laws … [for] public health and consumer protections (did not include devices).

- Congressional milestones:
  - The Federal Food, Drug, and Cosmetic (FD&C) Act of 1938 was passed after a legally marketed toxic elixir killed 107 people, including many children. The law authorized the FDA to demand evidence of safety for new drugs, issue standards for food, and conduct factory inspections (again no devices).
  - The Kefauver-Harris Amendments of 1962, which were inspired by the thalidomide tragedy in Europe, strengthened the rules for drug safety and required manufacturers to prove their drugs’ effectiveness (still no device regulation).
  - The Medical Device Amendments of 1976 followed a U.S. Senate finding that faulty medical devices had caused 10,000 injuries, including 731 deaths. The law applied safety and effectiveness “safeguards” to new devices.
“There is 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.”

- Intended use plays a big role in evaluating safety
- Intended use is defined by the manufacturer
“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.”
Valid Scientific Evidence: 21 CFR 860.7(c)(2)

• Varies from device to device:
  – Well-controlled investigations,
  – Partially controlled studies,
  – Studies and objective trials without matched controls,
  – Well-documented case histories conducted by qualified experts, and
  – Reports of significant human experience [qualified experts] with a marketed device ...

• Not ignored, but not valid scientific evidence:
  – Isolated case reports
  – Random experience
  – Reports lacking sufficient details to permit scientific evaluation
  – Unsubstantiated opinions
Medical Devices

• Regulations only apply to devices to be marketed and sold (for labeled indication)
  – “FDA does not regulate clinical practice”

• Unexpected Device: Software
  – from electronic records to computer analysis and decision programs
  – includes software used to control imaging and therapeutic radiation devices

• Most Often Not a Device: Contrast agents
  – most are drugs (some biologics) because they are metabolized by the body
  – nanoparticles may be regulated as devices
Device Regulatory Pathways

- Premarket notification 510(k), unless exempt
  (21 CFR 807 Subpart E)

- Premarket approval (PMA)
  (21 CFR 814 Subpart C)

- Humanitarian Use Device
  (21 CFR 814 Subpart H)

- Emergency Use Authorization
  (FD&C Act Section 564)
Medical Device Classification

• Theoretically a Risk-Based Paradigm
  – Medical devices are classified and regulated according to their degree of risk to the public
  – Anomalies exist secondary to pathways/politics

Class I: Low Risk
Class II: High Risk
Class III: High Risk
Class I Devices

• General controls are sufficient to provide reasonable assurance of the safety and effectiveness
• Examples: elastic bandages, non-sterile examination gloves, and hand-held surgical instruments
Class I Devices: General Controls

- All or some may be required (some pre-market, some post-market)
  - Registration of manufacturing facilities
  - Listing of device types
  - Premarket notification 510(k)
  - Good Manufacturing Practices (GMPs)
  - Labeling
  - Record keeping
  - Reporting of device failures
  - Prohibition against adulterated or misbranded devices
Class II Devices

- General controls alone are insufficient to assure safety and effectiveness, and methods (special controls, performance standards) are available or are established to provide such assurances
- “Predicate(s) exist(s)” for 510(k) pathway
- Examples: powered wheelchairs, infusion pumps, CT, MRI, and most diagnostic ultrasound, CR/DR (exception, digital mammography which is (was) Class III)
- Most “cleared” by 510(k) pathway
Class II Devices: Special Controls

- All or some may be required (not always straightforward)
  - Performance standards (discretionary, voluntary national or international standard, recognized by rulemaking, and others)
  - Post-market surveillance
  - Patient registries
  - Guidance Documents
  - Design controls
  - Tracking requirements
510(k) Process

• Class II devices, for the most part
• Demonstrate “substantial equivalence” to predicate as previously defined
  – Same intended use
  AND
  – Similar technological characteristics OR does not raise new types of issues of safety and effectiveness
• When FDA finds a device substantially equivalent, it is “cleared”
Substantial Equivalence
FDCA 513(i)(1); 360c(i)(1)

• In order to be considered substantially equivalent, the device must:
  – have the same intended use, and
  – have the same technological characteristics

OR
  – have the same intended use, and
  – have different technological characteristics, which based on the information provided do not raise new “types of” questions of safety and effectiveness and demonstrate that the device is as safe and effective as the predicate.

• Substantial Equivalence provides entry to the 510(k) process

• Determination subject to wide variance
Class III Devices

• Insufficient information exists to determine that general and special controls (performance standards) are sufficient to provide reasonable assurance of the safety and effectiveness of such devices.

• Such devices are:
  – Life sustaining or life supporting;
  – Substantial importance in preventing impairment of human health; or which present a potential, unreasonable risk of illness or injury.

• Most “approved” by PMA pathway.
IDE: Investigational Device Exemption

- Permits unapproved/uncleared device use on humans in clinical studies to collect safety and effectiveness data (analogous to IND)
- Many imaging investigations are exempted because they do not have significant risk ("exempted" from an "Exemption" sounds confusing).
- Marketed devices used for labeled indication do not need IDE (includes "significant risk" devices)
IDE: Investigational Device Exemption

- “Significant risk” requires FDA-approved IDE
- “Nonsignificant risk” requires only IRB-approved IDE (*de facto* upon IRB approval)
- “Exempt” devices do not require an IDE
  - Legally marketed within indications;
  - Noninvasive diagnostic device w/o introducing energy
- Pre-IDE meeting to share information with and get feedback from CDRH
  - device design, intended use
  - clinical and pre-clinical protocols
  - may use device master file, if made available
PMA Process

• Class III devices for the most part
• Demonstrate reasonable assurance of safety and effectiveness
  – Very device and indication specific
• 180-day review timeframe
• When FDA finds a device safe and effective for its intended use, it is “approved”.
HDEs & EUAs

**Humanitarian Device Exemption**
- Requires sufficient information
  - Device does not pose unreasonable risk
  - Probable benefits outweigh risk
- No comparable devices available
- Restricted use
- Examples: Brain stimulator, Lung valve system, Device to repair lumbar spine pseudarthrosis, some neurointerventional devices in unusual clinical circumstances

**Emergency Use Authorization**
- Use of an unapproved product during a life-threatening or serious emergency; no alternative available
- Reasonable to believe the product may be effective
- Potential benefits outweigh potential risks
- Examples: First in 2005 - Anthrax Vaccine Absorbed
- 2009: InVitro Diagnostics, Antivirals, Personal Respiratory Protection Devices
Drugs
Drug and Biologic Regulation
The Alphabet Soup

- IND: Investigational New Drug (exemption)
- RDRC: Radioactive Drug Research Committee
- NDA: New Drug Application
  - Needs pre-clinical and clinical data
- ANDA: Abbreviated New Drug Application (generic version of approved drug)
  - No safety and effectiveness clinical trials required
    (only need to demonstrate equivalence)
- BLA: Biologic License Application
  - Generally an NDA for biologic agent
Investigational New Drug

• A drug that is not FDA approved for the indication being studied (with some exceptions)
  – Contrast agents and radiopharmaceuticals are drugs
  – Image-guided delivery of drugs may be a drug or a device-drug combination
Information Required in INDs

- Pharmacology/toxicology in animals
- Dosimetry for radiopharmaceuticals
- CMC: Chemistry, Manufacturing and Controls
- Some of these data may be referenced from existing INDs or the literature
- Clinical Information
Approach to Regulatory Requirements

• Regulations are the same for
  – Labeled therapeutic agents
  – Functional imaging agents
  – General imaging agents

• Strategy may differ with goal
  – Basic information about a therapeutic
  – Basic information about a tumor
  – Evaluating response to therapy
Types Of INDs

Three types of traditional INDs:
- An investigator-initiated IND
- Treatment (Compassionate-Use) IND
- Emergency use IND (E-IND)

And a relatively new type:
- Exploratory (“phase 0”, x-IND)
Investigational Drug Clinical Trials

- Sponsor must apply to FDA for permission to study drugs in humans
  - although this may not be needed for certain radioactive drug studies approved by institutional RDRC

- “Sponsor”
  - Individual physician
  - Institution
  - Industry
RDRC vs. IND for Radiopharmaceuticals

- **RDRC**: for basic research only
  - e.g., kinetics, distribution, dosimetry
  - NOT safety or efficacy or for FDA submission
  - Pediatric studies restricted
  - Only small doses and few patients (usually <30)
  - Drug must have been in humans before

- **IND**: not restricted to basic research
  - Can study safety and efficacy (i.e., clinical trials)
  - Can support FDA submission
  - Can do basic research
  - Pediatric studies less restricted
Why Exploratory INDs?

• <10% of new molecular entities progress beyond investigational stages
• Obtaining pre-clinical data required for typical IND is time-consuming and very expensive
• Animal testing does not always predict performance in humans
Goals of expINDs

• Gain an understanding of the relationship between a specific mechanism of action and the treatment of a disease.
• Provide information on PK
• Select the most promising lead product from a group of candidates designed to interact with a particular therapeutic target.
• Explore a product’s biodistribution characteristics using various imaging technologies.
What’s the difference?

• Traditional IND
  – Single agent
  – Plans for Phase 1, 2, 3 trials and NDA
  – Extensive pre-clinical data needed to begin
  – Dose escalation, therapeutic evaluation

• Exploratory IND
  – Multiple agents under one IND, go/no go
  – Microdosing, first-in-man studies
  – No therapeutic intent
  – Biodistribution, pharmacokinetics, safety
  – Less pre-clinical data required
  – **Resubmit as Traditional IND if successful**
Off-label Use of an FDA-Approved Drug in a Clinical Trial: Do I need an IND?

• Defined in FDA regulations (21 CFR 312.2(b))
• Exempt if:
  – Investigation not being done to “change the label”
  – Investigation does not involve dosage, route of administration, or use in a patient population that significantly increases risks

• Some IRBs will make the determination; others require that you ask FDA
Office of Combination Products

- Gets involved in drug/device combination products
- e.g., nanoparticle for drug delivery (therapy / imaging agent / both)
- e.g., software for DCE-MRI (CDRH / 510(k)) dependent on availability of contrast agent with a label approval for anatomic site and intended use!
FDA Guides the Process

• Three “Guidance for Industry” documents specifically for Medical Imaging drugs
  – Part 1: Conducting Safety Assessments
    www.fda.gov/cder/guidance/5742prt1.pdf
  – Part 2: Clinical Indications
    www.fda.gov/cder/guidance/5742prt2.pdf
  – Part 3: Design, Analysis, and Interpretation of Clinical Studies

• Guidances available for 510(k), PMA, device categories (some clinical, some not)
Where to get information

• FDA Guidance on the IND process with multiple links to other documentation:
  – http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm

• Comprehensive Guidance Page

• Pre-IND/IDE meeting (even when no IND/IDE planned or necessary)

Talk to your institutional experts (± FDA)!
Thank you.

Questions?