Lecture Notes – US Government Regulations on Medical Devices

Ying Sun, Biomedical Engineering, University of Rhode Island

I. Federal Organizations

Under the US Department of Health and Human Services (HHS) the US Public Health Service has the following operating divisions:

- Agency for Healthcare Research and Quality (AHRQ)
- Agency for Toxic Substances and Disease Registry (ATSDR)
- Centers for Disease Control and Prevention (CDC)
- Health Resources and Services Administration (HRSA)
- Indian Health Service (IHS)
- National Institutes of Health (NIH)
- Substance Abuse and Mental Health Services Administration (SAMHSA)
- Food and Drug Administration (FDA)

The FDA has the following centers:

- Center for Biologics Evaluation and Research (CBER)
- Center for Drug Evaluation and Research (CDER)
- Center for Food Safety and Applied Nutrition
- Center for Tobacco Products
- Center for Veterinary Medicine
- National Center for Toxicological Research
- Center for Devices and Radiological Health (CDRH)
  - Office of the Center Director
  - Office of Communication, Education, and Radiation Programs
  - Office of Compliance
  - Office of In Vitro Diagnostic Device Evaluation and Safety
  - Office of Management Operations
  - Office of Science and Engineering Laboratories
  - Office of Surveillance and Biometrics
  - Office of Device Evaluation

II. Office of Device Evaluation

Functions:

- Premarket Notifications (510(k))
- Premarket Approval Applications (PMAs) and Supplements
- Humanitarian Device Exemptions (HDEs)
- Investigational Device Exemptions (IDEs), Amendments and Supplements
- Product Development Protocols (PDPs)

Divisions:

- Division of Anesthesiology, General Hospital, Respiratory, Infection Control, and Dental Devices
- Division of Cardiovascular Devices

- Division of Ophthalmic and Ear, Nose, and Throat Devices
- Division of Neurological And Physical Medicine Devices
- Division of Orthopedic Devices
- Division of Surgical Devices
- Division of Reproductive, Gastro-Renal, and Urological Devices

III. Relevant Laws

- Public Health Service Act (1944): for preventing the introduction, transmission and spread of communicable diseases from foreign countries into the United States. Later amendments include: Family Planning Services and Population Research Act (1970), National Cancer Act (1971), Health Insurance Portability and Accountability Act (1996), Muscular Dystrophy Community Assistance Research and Education Amendments (2001), Hematological Cancer Research Investment and Education Act (2001), Newborn Screening Saves Lives Act (2007), Patient Protection and Affordable Care Act (2010), and Pandemic and All-Hazards Preparedness Reauthorization Act (2013).

- Fair Packaging and Labeling Act (1967) requires the labels on many consumer products to state: 1) identity of the product, 2) name and place of business of the manufacturer, packer, or distributor, and 3) net quantity of contents.

- Federal Food, Drug, and Cosmetic Act (1938) gave authority to the U.S. Food and Drug Administration (FDA) to oversee the safety of food, drugs, and cosmetics. **The Medical Device Amendments of 1976** required all medical devices be classified into one of three classes:
  - Class I: "general controls" type such as crutch, tape, glove, and dental floss.
  - Class II: "performance standards" type such as stethoscope, blood pressure meter, cardiac catheters, hearing aids, amalgam alloys used to fill cavities, and devices that are cleared using the 510(k) process.
  - Class III: "life sustaining or supporting" type such as cardiac pacemaker, implantable defibrillator, automated external defibrillator, cardiac assist devices, intrauterine devices, silicone breast implant, and devices that are approved by the Premarket Approval (PMA) process.
- Safe Medical Devices Act (SMDA) (1990) established Quality System requirements, supported postmarket surveillance, and allowed FDA discretion for PMAs brought to panel.

- FDA Modernization Act (1997) supported for early collaboration, expanded Class I and Class II exemptions, set the "least burdensome provision", supported dispute resolution, established evaluation of automatic Class III designation (giving the sponsor the opportunity to request lower classification due to a minimal risk device, known as "de novo" review), and mandated free and open participation by all interested persons.

- Medical Device User Fee and Modernization Act (MDUFMA) (2002) established a fee schedule for most types of device submissions to achieve shorter review times, and requires FDA to include pediatric experts on the panel for a product intended for pediatric use.

IV. Title 21 of the Code of Federal Regulations (21 CFR)

Title 21 is the portion of the Code of Federal Regulations that governs food and drugs within the United States for the Food and Drug Administration (FDA), the Drug Enforcement Administration (DEA), and the Office of National Drug Control Policy (ONDCP).

Codes from 21 CFR relevant to medical devices:

- Section 510 Good Laboratory Practice (GLP) – 21 CFR 58
- Section 510(k) Premarket Notification – 21 CFR 807
- Section 515 Premarket Approval (PMA) – 21 CFR 814
- Section 520(f) Good Manufacturing Practices (GMP) – 21 CFR 820
- Section 520(g) Investigational Device Exemption (GMP) – 21 CFR 812, 813, 50, 56
- Section 515A, 520(m) Humanitarian Use Devices (HUD) – CFR 814 subpart H

V. Two Pathways to Market

- Premarket Notification 510(k): To show substantial equivalence to a device that was on the market prior to 1976. (short cut, eventually will be phased out)
  - Do the new and the old devices have the same use?
  - Does the new device utilize new production techniques such as materials, structure, and energy source?
  - With new production techniques, are safety and effectiveness affected?
  - Do the new and the old devices have similar performances?
  - Does labeling show any new use or inaccuracy?

- Premarket Approval (PMA): To show safety and effectiveness such that the clinical benefit is higher than the risk.
  - Description of the device: detailed design, materials, manufacturing process, etc.
  - Information on nonclinical laboratory and animal studies.
  - Clinical test results.
  - Other relevant data.

VI. Before Clinical Trials

- Studies involving vertebrate animals require prior approvals from the local Institutional Animal Care and Use Committee (IACUC). (Studies involving invertebrate animals do not require IACUC approvals.)
- Nonsignificant Risk Devices require prior approvals from the local Institutional Review Board (IRB).
- Significant Risk Devices require the Investigation Device Exemption (IDE) from the FDA. The IDE application should:
  - provide all published papers showing laboratory, animal, and clinical studies, either supportive or non-supportive;
  - provide unpublished results, if available;
  - be in compliance with the Good Laboratory Practice (GLP) regulation;

- submit clinical study plan; and
- submit recommendation from the local IRB. (Key issues are human safety, ethical standards, integrity of data, and informed consent from human subjects.)

VII. Clinical Trials

Phase 1. Screening for safety

Testing within a small group of people (20–80) to evaluate safety, determine safe parameter ranges, and begin to identify side effects. A side effects could be subtle or long term, or may only happen with a few of people, so phase 1 trials are not expected to identify all side effects.

Phase 2. Establishing the efficacy

Against a placebo if applicable, testing with a larger group of people (100–300) to see if it is effective and to further evaluate its safety. The gradual increase in test group size, allows less common side effects to be progressively sought.

Phase 3. Final confirmation of safety and efficacy

Testing with large groups of people (1,000–3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely.

Phase 4. Sentry studies during sales

Postmarketing studies delineate additional information, including the treatment's risks, benefits, and optimal use. As such, they are ongoing during the lifetime of active medical use.

VIII. Randomized Controlled Trial and Double-Blinded Study

Randomized Controlled Trial

A randomized controlled trial (RCT) is a study in which people are allocated at random (by chance alone) to receive one of several clinical interventions. One of these interventions is the standard of comparison or control. The control may be a standard practice, a placebo ("sugar pill"), or no intervention at all. Someone who takes part in a randomized controlled trial (RCT) is called a participant or subject. RCTs seek to measure and compare the outcomes after the participants receive the interventions. Because the outcomes are measured, RCTs are quantitative studies. In sum, RCTs are quantitative, comparative, controlled experiments in which investigators study two or more interventions in a series of individuals who receive them in random order. The RCT is one of the simplest and most powerful tools in clinical research <www.medicinenet.com>.

Double-Blinded Study

A double-blinded study is a study in which both the subjects participating and the researchers are unaware of when the experimental medication or procedure has been given. Double-blinded studies are often used when initial studies shows particular promise. Double-blinding will remove any potential psychological effect from the participant sides or potential bias in the experimental procedure from the researcher side.