Objectives

- Continued from …
- Understand the differences between the developmental demands and regulatory requirements for
  - Drugs & biologics
  - Medical devices
  - Dietary supplements

More Disasters ...

Medical Device Amendments of 1976

- 1969 HEW survey: 10 years 10,000 injuries & 751 fatalities
- FDA survey: 858 deaths
- Independent survey 36,000 complications in one year

FDA History - Medical Device Amendments of 1976

- Dalkon Shield, an IUD, marketed w/o proper testing:
  - removal rate of 26.4%
  - an infection rate of 5%
  - 25 miscarriages, 16 deaths
- Cardiac pacemakers defects necessitated 30 recalls involving 23,000 units
- May 28, 1976
Differentiate drug & device
Food, Drug & Cosmetic Act

- Drug/biologic 21USC201(g)(1)
  - USP/NF
  - INTENDED for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
  - intended to affect the structure or any function of the body of man or other animals;
  - Component
  - Not food or dietary supplement

- Medical device 21USC201(h)(1)
  - USP/NF
  - INTENDED for use in the diagnosis of disease or other conditions ..., or
  - intended to affect the structure or any function ..., does not achieve its primary intended purposes through chemical action within or on the body ... and which is not dependent upon being metabolized ....

FDA History - Medical Device Amendments of 1976

- Key features of the 1976 Amendments
  - Classification for regulatory purposes
  - Pre-market approval: implanted & life supporting devices
  - Interstate commerce is presumed in all cases
  - Authority to issue GMP's, Access to industry records
  - Registration and list, Authority to ban devices

Basis for Classification of Devices

- Amount of information known about device for intended use & indications for use
  - Scalpel: intended use - cut tissue. Indication in labeling "for making incisions in the cornea".

- What level of controls are necessary to assure Safety & Effectiveness of device

- Support or sustain human life OR important in preventing impairment of human health

- Risk of causing illness or injury

Medical Device Classification & Regulatory Requirements

- Class I - General Controls (with & w/o exemptions)

- Class II – General Controls and Special Controls (with & w/o exemptions)

- Class III – General Controls and Premarket Approval
Class I - General Controls

- Known information provides reasonable assurance of safety & effectiveness using General Controls
- Known information does not assure S & E, BUT the device
  - Does not support or sustain human life, OR
  - Is not used to prevent impairment of human health AND
  - No unreasonable risk of illness or injury

Examples of Class I Devices

- Examination Gloves 21CFR880.6250
- Dental Hand Instrument 21CFR872.4565
- Elastic Bandages 21CFR880.5075
- Pacemaker Charger 21CFR870.3670
- Ultrasonic Cleaner for Medical Instruments 21CFR880.6150
- Hand-held (Manual) Surgical Instruments 21CFR878.4800

Class II - Special Controls

- General Controls alone are insufficient to provide assurance of Safety & Effectiveness
  - BUT
- Information exists to establish Special Controls

Special Controls

- General Controls +
  - Special Labeling Requirements
  - Performance Standards
  - Postmarket Surveillance
  - Patient Registries
  - Guidelines, Recommendations
  - Any other appropriate actions
Examples of Class II Devices

- Cardiac Monitor 21CFR870.2300
- Elbow Joint Metal/Polymer Constrained Cemented Prosthesis 21CFR888.3150
- Pediatric hospital bed 21CFR880.5140
- Infusion Pump 21CFR880.5725
- Powered Wheelchair 21CFR890.3860
- Surgical Drapes 21CFR878.4370
- TENS device 21CFR882.5890

Class III - Premarket Approval

- Not enough information to classify as either Class I or II
- Device usually supports/sustains life,
  - is of substantial importance in preventing impairment of human health or
  - presents a potential, unreasonable risk of illness or injury

Examples of Class III Devices

- Implantable pacemaker pulse generator 21CFR870.3610
- Replacement heart valve 21CFR870.3925
- Cranial electrotherapy 21CFR882.5800
- Implantated electrical urinary continence device 21CFR876.5270
- Silicone gel-filled breast implant 21CFR878.3540
- Implantated cerebella stimulator 21CFR882.5820

Premarket Approval (PMA)

- Extensive submission including data showing Safety & Effectiveness
- Conditions of Approval
- Annual Reports
Device Pyramid (Classification)

- **Class I devices**
  - Low risk
  - 46% of all devices

- **Class II devices**
  - Moderate risk
  - 47% of all devices

- **Class III devices**
  - Moderate and high risk
  - <10% of all devices

**General Controls**

- Management Controls
- Design Controls
- Corrective and Preventive Actions (CAPA)
- Production and Process Controls

**Special Controls**

- Risk Analysis
- Design & Process
  - Verification
  - Validation

### Subsystems of a Quality System

- Design Controls
- Material Controls
- Corrective & Preventive Actions
- Production & Process Controls
- Management
- Equipment & Facility Controls
- Records, Documents, & Change Controls

### More history; different kind of disaster

**1976 VITAMINS AND MINERALS AMENDMENTS**
- “Proxmire Amendments” stop FDA from establishing standards limiting potency of vitamins and minerals in food supplements or regulating them as drugs based solely on potency.

**1989 FDA issued a nationwide recall of all over-the-counter dietary supplements providing 100 milligrams or more of L-TRYPTOPHAN.**

**1990 NUTRITION LABELING AND EDUCATION ACT**

**1994 DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT (DSHEA)**
- specific labeling requirements,
- provides a regulatory framework,
- good manufacturing practice regulations
- commission to recommend how to regulate claims.
**Dietary Supplement**

Food, Drug & Cosmetic Act – 21USC201(fff)

- product (other than tobacco) **intended to supplement the diet** that bears or contains one or more of the following dietary ingredients:
  
  (A) a vitamin;
  
  (B) a mineral;
  
  (C) an herb or other botanical;
  
  (D) an amino acid;
  
  (E) a dietary substance for use by man [but no other animals] to supplement the diet by increasing the total dietary intake; or
  
  (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E);

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**DSHEA-2**

- intended for ingestion in pill, capsule, tablet, or liquid form.

- not represented for use as a conventional food or as the sole item of a meal or diet.

- is labeled as a "dietary supplement."

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**Dietary Supplement Regulatory Requirements**

- No pre-market notification except for “new dietary ingredient”
  - Grandfathered all ingredients available through 10/15/94
  - Vetting for “new dietary ingredients”
  - Demonstration that product is unsafe for regulatory action

- Manufacturer/distributor responsible for safety and claims/representations made on label or in labeling

- No manufacturer/distributor registration

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**DSHEA Labeling Requirements**

- Descriptive name, including “supplement”

- Place of manufacture, etc.

- Complete list of ingredients

- Net quantity of contents

- NLEA-compliant “supplement facts” panel

- Certain “structure/function” claims permitted
  - Vitamin C – scurvy
  - Calcium – osteoporosis

- Otherwise, disclaimer required when claim is made
  - “This claim has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease”

[http://vm.cfsan.fda.gov/~dms/supplmnt.html](http://vm.cfsan.fda.gov/~dms/supplmnt.html)
Is Something Missing?

- Medical Products?
- Dietary Supplements?

Summing Up

- where was the science?
- phases of drug, device, dietary supplement development
- major regulatory events
- questions