# U.S. -- History of Regulation

## OCRA RAC Study Group U.S.
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- These slides are intended to provide general educational information and are not intended to convey legal advice.

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# What Will You Learn

- History of FDA
- Overview of US Legal System
- General Structure of FDA
- FDA Definitions

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# History of FDA

# Once upon a time…

Dr. Mixer's Condition
After Cured by
his Cancer and Scrofula Syrup.

DRS. MIXER,

SOLE MANUFACTURERS
AND PROPRIETORS OF

SPECIAL TREATMENT GIVEN

MIXER'S CANCER AND SCROFULA SYRUP

Cancer, Tumors,
Erysipelas,
Abscesses, Ulcers,
Fever Sores, Goiter,
Catarrh, Salt Rheum,
Scald Head, Piles,
Rheumatism,
and ALL BLOOD DISEASES.

The World Renowned
BLOOD PURIFIER.

ESTABLISHED 1862

DR. CHAS. W. MIXER.
GEN'L MANAGER.

Not a Physician.

# Once upon a time…

- Food and drug laws varied state to state
- Misleading claims and adulteration of food were commonplace
- Science's ability to detect fraud was advancing
- Legitimate manufacturers were worried about loss of reputation
- The general public wanted safer food and drugs

# Mr. Harvey Wiley

- Wrote paper on methods to determine if pure cane sugar had been diluted with glucose
- Became Chief Chemist (USDA) in 1883

# Wiley's "Poison Squad"

- 5-year human feeding experiment
- Sets of 12 men ate 3 meals a day
- Compounds studied were: borax, salicylic acid, sulfuric acid, sodium benzoate, and formaldehyde
- Participants agreed not to consume any outside food or drink (except water) and to be checked by doctors weekly

# Another Tragedy

- In the early 1900's diphtheria patients were routinely treated with antitoxin from horse blood serum
- In St. Louis, Jim (the horse) was used as a source of serum
- 13 children died of tetanus

# The Biologics Control Act - 1902

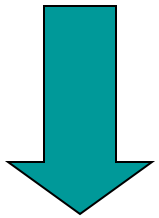
- **"Virus Toxin Law" had the following purposes:**
  - Authorized the regulation of the sale of viruses, serums, toxins, and analogous products
  - Authorized the promulgation of biologics regulations
  - Required licensing of manufacturing establishments
  - Provided inspection authority to the federal government

# Pure Food and Drug Act (1906)

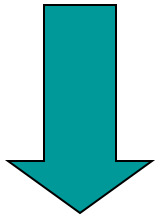
- 1906: Upton Sinclair's The Jungle is published, exposing the horrors of the meat-packing industry.
- Harvey Wiley is able to pull together a coalition in support of a National Food and Drug Law
- Prohibited interstate transport of unlawful – misbranded or adulterated -- food and drugs, added product labeling requirements

# Time passes…

**Bureau of Chemistry**



**Food, Drug and Insecticide Administration**



**Food and Drug Administration**

# The 1937 Elixir Sulfanilamide Incident

- Over 100 people died in 15 states
- Formulation contained 72% diethylene glycol
- Only "misbranded"
- Hastened the passage of the Food, Drug, and Cosmetic Act
- Signed by FDR into law in June 1938

# Food, Drug, and Cosmetic Act (1938)

- Required labels to include directions for safe use
- Brought medical devices and cosmetics under FDA control
- Mandated pre-market submission for drugs before marketing
- Prohibited false claims
- Addressed food packaging and quality as well as factory inspections

# Thalidomide in the 1960's

- Marketed in Europe since 1957 as a sleep aid
- Found to cause birth defects in thousands
- Kept from the U.S. market by Dr. Frances Kelsey
- Stronger drug regulation in Kefauver-Harris Amendments (1962)

# Kefauver-Harris Amendments (1962)

- Mandated efficacy as well as safety
- Instituted stricter FDA control over drug trials (including a requirement that patients must give their informed consent)
- Transferred from the FTC the regulation of $R_x$ drug advertising
- Established good manufacturing practices by the drug industry
- Granted FDA greater powers to access company production and control records to verify practices

# FDA EVOLUTION

- **Safety alone**
  - (1938) Food, Drug & Cosmetic Act
- **Safety & Efficacy**
  - (1962) Kefauver-Harris Amendment
- **Safety & Efficacy Expanded Access Exclusivity**
  - (1983) Orphan Drug Act
  - (1984) Generics (Waxman-Hatch)
  - Accelerated Approval (late 1980s, AIDS and other life threatening)
  - Pediatric Initiatives (mid-90's)
  - Institute Review Timelines (mid-90's: PDUFA, FDAMA)

***For more info, read:***

***http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm056044.htm***

# History of US Laws and Regulations

- Biologics Act of 1902
- Federal Pure Food and Drugs Act of 1906
- Food, Drug, and Cosmetic Act of 1938
- Durham-Humphrey Amendment of 1951
- Food Additive Amendments of 1958
- Color Additive Amendment of 1960
- Kefauver-Harris Amendment of 1962
- Controlled Substance Act of 1970
- Medical Device Amendments of 1976
- Infant Formula Act of 1980
- Orphan Drug Act of 1983
- Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman)
- Prescription Drug Marketing Act of 1987
- Generic Animal Drug and Patent Term Restoration Act of 1988
- Nutrition Labeling and Education Act of 1990
- Safe Medical Device Act of 1990
- Prescription Drug User Fee Act of 1992
- Dietary Supplement Health and Education Act of 1994
- FDA Export Reform and Enhancement Act of 1996
- FDA Modernization Act of 1997 (FDAMA)
- Medical Device User Fee and Modernization Act of 2002
- Best Pharmaceuticals for Children Act of 2002
- Pediatric Research Equity Act of 2003
- Project BioShield Act of 2004
- Food Allergen Labeling and Consumer Protection Act of 2004
- Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2007 (GMPs)
- Food and Drug Administration Amendment Act of 2007 (FDAAA)
- Family Smoking Prevention and Tobacco Control Act
- Biosimilars Price Competition and Innovation Act of 2009 (enacted in 2010 as part of ACA)
- Food Safety Modernization Act of 2011
- Food & Drug Administration Safety & Innovation Act of 2012 (FDASIA)
- Drug Quality & Security Act of 2013

# Question #1

**Which law, for the first time in U.S. history, required the preapproval of drugs?**

a. Kefauver-Harris Amendments (1962)
b. Food, Drug, and Cosmetic Act of 1938
c. Pure Food and Drug Act (1906)
d. Drug Price Competition & Patent Restoration Act of 1984

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# Overview of U.S. Legal System

# Federal Government - Separation of Powers

- The Legislative Branch
- The Executive Branch
- The Judicial Branch

# The Executive Branch

- **President - enforces laws passed by Congress**
  - Enforcement through various agencies
- **Where does FDA fit in?**
  - Not an independent agency

# Department of Health and Human Services

- **<u>Mission</u>: Protect public health and provide essential human services (e.g., welfare)**
- **Largest grant-making agency**
- **Medicare is nation's largest health insurer**
- **Organization –**
  - Public Health Service
    - FDA is part of
  - Human Services

# Public Health Service

- **National Institutes of Health (NIH)**
- **Centers for Disease Control and Prevention (CDC)**
- **Food and Drug Administration (FDA)**
  - and others

# Food and Drug Administration

- **Commissioner is political appointee**
  - Nominated by President and Confirmed by Senate (since 1988)
- **FDA budget approved by Congress**

# Food and Drug Law and Regulation

- **Federal power**
  - Right to regulate interstate commerce -- U.S. Constitution
  - Product or one of its ingredients must have traveled in interstate commerce for FDA jurisdiction
- **Shared power with the states**
  - Police power to protect the public health and safety

# From Laws to Regulations

- **Laws – binding as written**
- **Regulations**
  - Have force and effect of law
  - FDA promulgates regulations to assure compliance with the word and intent of either and existing or new statute enacted by Congress conferring power on FDA to regulate
  - New regulations published in Federal Register

# Notice and Comment Rulemaking

- **Notice of Proposed Rulemaking**
  - Publication of proposed regulation –
    - Comment period – 60 to 90 days
  - Requests written comments about the proposed action
- **Final rule**
  - Final regulation published
  - Preamble discusses how FDA resolved public comments
    - Binding – on FDA -- as an advisory opinion
  - Specifies effective date
  - Rule must be consistent with statute upon which it is based

# The Federal Register

- **Contains**
  - All proposed and finalized regulations and legal notices issued by all federal agencies
  - Presidential proclamations
  - Executive orders

# FDA Information in the Federal Register

- **New Rules (regulations)**
  - Preambles
- **Regulatory Agenda**
- **Guidances**
- **Announcements of Meetings and Hearings**
  - FDA advisory committee meetings, public meetings, administrative and public hearings
- **Information Collection Notices**

**Example citation: 74 FR 29490**

# Code of Federal Regulations

- All of the federal agencies' regulations, covering all of the regulated areas, are organized/codified into the Code of Federal Regulations (CFR)
- FDA's regulations -- Title 21

Example citation: 21 CFR Part 211 (Drug GMP reg.)

# 21 CFR …

- Sections 1-99 -- General
- Sections 100-169 -- Foods
- Sections 170-199 -- Food additives
- Sections 200-299 -- Drugs general
- Sections 300-499 -- Drugs for human use
- Sections 500-599 -- Animal drugs, feeds
- Sections 600-799 -- Biologics, cosmetics
- Sections 800-1299 -- Devices, Tissue Regs, misc.
- Sections 1300-end -- Controlled substances

# Guidance Documents

- **FDA publication issued under "Good Guidance Practices" –** "*best advice on how to comply with law*"
- **Intended to assist industry in carrying out their obligations under laws and regulations**
- **Do not *legally* bind the FDA or the public.**

# FDA and Other Federal Agencies

- **FDA authority not always exclusive**
- **FDA authority may:**
  - Overlap with other agencies
  - Be complimentary to other agencies
- **MOU – between agencies to clarify**
  - Regulatory responsibilities
  - Areas of primary jurisdiction
  - Reciprocal regulatory and information roles
  - Funding responsibilities

# Federal Advisory Committee Act

- Passed in 1972
- Requires renewal of all standing committees every two years
- Requires meetings be open to the public and transcripts available
- Portions of the meeting may be closed to protect trade secret information
- Meetings must be announced in the Federal Register

# FDA Advisory Committees

- **FDA has approximately 30 standing advisory committees**
- **Each is assigned an executive secretary (FDA employee) to provide administrative management and operation of the committee**
- **Each Center has their own committees**
  - Organized for specific therapeutic areas

# FDA Advisory Committees

- **21 CFR 14**
- **Asked to recommend whether a product should be approved**
- **Asked for advice or policy, may be used to help develop guidelines**
- **FDA may or may not follow committee's advice**
- **Presentations to committees can be made by:**
  - Manufacturers
  - FDA
  - Any member of the public
- **Transcripts, videos available**

# Question #2

**True or False – Guidance documents are legally binding?**

a. True
b. False

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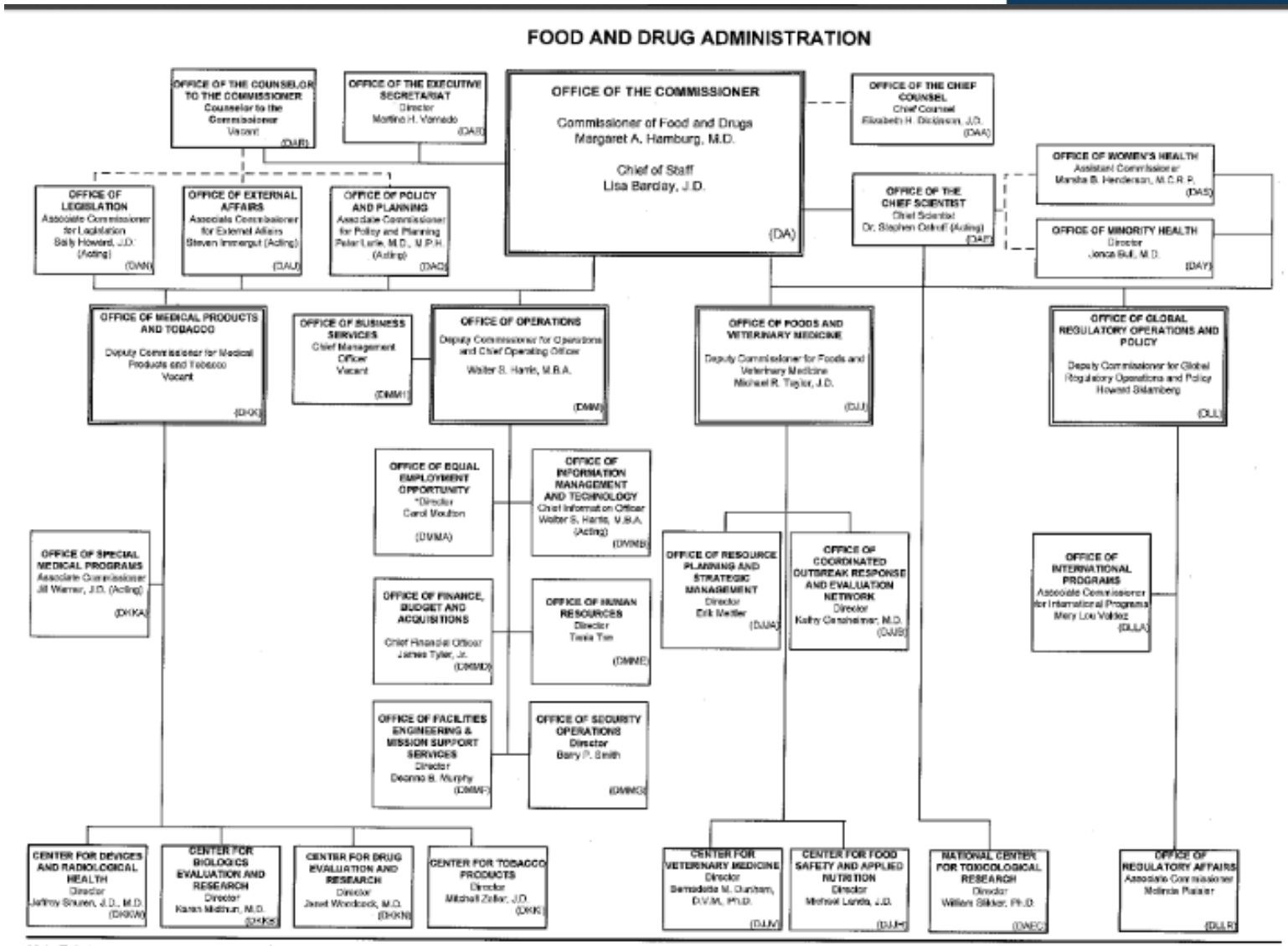
# Structure of FDA


FOOD AND DRUG ADMINISTRATION
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Counselor to the Commissioner
Vacant
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OFFICE OF THE EXECUTIVE SECRETARIAT
Director
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Chief of Staff
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Chief Scientist
Dr. Stephen Ostroff (Acting)
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Deputy Commissioner for Medical Products and Tobacco
Vacant
(DHK)
OFFICE OF BUSINESS SERVICES
Chief Management Officer
Vacant
(DMM)
OFFICE OF OPERATIONS
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*Director Reports to the Agency Head
4/11/14
Approved by the FDA Reorganization Coordinator and Principal Delegation Control Officer

# The Mission of the FDA

The FDA promotes, protects, and enhances public health through the medical product development and evaluation process.

The FDA's mission is to:

Approve products for marketing that are effective for the labeled indications, provide benefits that outweigh their risks, are of high quality, and have directions for use that are complete and honestly communicated.

# Core FDA Functions

- **Gatekeeper to Marketplace – product approval/clearance**
- **Cop on the Beat – enforcement and compliance**
- **Sentinel of Health Concerns – adverse event monitoring**
  - partly in coordination with CDC and other federal, state and local health authorities

# Who Regulates What at FDA?

- ***Drugs and Therapeutic Biologics***: Center for Drug Evaluation and Research (CDER)
- ***Biologics, Including Blood, Cell & Gene Therapy***: Center for Biologics Evaluation and Research (CBER)
- ***Medical Devices and Radiological Products***: Center for Devices and Radiological Health (CDRH)
- ***Foods, Dietary Supplements, and Cosmetics:*** Center for Food Safety and Applied Nutrition (CFSAN)
- ***Tobacco:*** Center for Tobacco Products (CTP)

# Who Regulates Medical Products ?

**Regulating US Medical Products involves more than just the FDA**

- ***Domestic*** **—** includes FDA, BATF, EPA, FTC, DEA, CPSC, FSIS, CDC; Commerce, Agriculture, Transportation Departments.
- ***International*** **—** add USTR, Agency for International Development, US Treasury (Customs), State Department

# Question #3

**Which Center within the FDA would regulate a dietary supplement for human use?**

a. CDER
b. CDRH
c. CBER
d. CFSAN
e. CTP

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# FDA Definitions

# "Biologic"

- "... any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product ... applicable to the prevention, treatment, or cure of diseases or injuries of man..."

- Biologics include such vitally important products as polio and measles vaccines, diphtheria and tetanus toxoids, and skin test substances, as well as whole blood and blood components for transfusion.

# Drug

**Section 201(g)(1): an article (other than food)**

- **Recognized in USP or other compendia;**
- **Intended to diagnose, cure, mitigate, treat or prevent disease;**
- **Intended to affect structure or function of body of man; or**
- **Intended as component of these**

**FD&C Act, as amended, can be found at**
**http://www.fda.gov/opacom/laws/fdcact/fdctoc.htm**

# Drug vs. Biologic (in general)

## Drug

- Chemical synthesis
- MW less than 500 kD
- Screen base on similarity to other chemical structures
- Not extremely heat sensitive

## Biologic

- Composed of or extracted from a living organism
- MW greater than 500 kD
- Complex structures
- Less well-defined
- Heat and shear sensitive
- Immunogenic

# "Device"

- **"an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including a component part, or accessory which is:**
  - recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
  - 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 or any function of the body of man or other animals, and which does not achieve any of it's primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

# Food

- (f) The term "food" means (1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article.

# Dietary Supplement

- **Dietary Supplement Health and Education Act (DSHEA) of 1994**
- **Taken by mouth that contains a "dietary ingredient" to supplement the diet.**
- **"Dietary ingredient" -- must be one or any combination of the following substances:**
  - a vitamin,
  - a mineral,
  - an herb or other botanical,
  - an amino acid,
  - a dietary substance for use by man to supplement the diet by increasing the total dietary intake (e.g., enzymes or tissues from organs or glands), or
  - a concentrate, metabolite, constituent or extract.
- **"New dietary ingredient" -- a "dietary ingredient" not marketed in the U.S. in a dietary supplement before October 15, 1994.**
  - ***Prior market clause*** – if in an IND or approved, can not be a dietary supplement

# Cosmetic

- (1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles; except that such term shall not include soap.

# Question #4

**Human platelet rich plasma intended for human infusion meets the definition of a:**

a. Drug
b. Device
c. Biologic
d. Dietary Supplement

# Acknowledgements


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# Questions?

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