Origins and Organizational Structure of FDA Overview of Regulation of Biological Products

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FDLI

Poll #1

- What animal do we have to thank for the first Biologics Law in the United States?
  - A. Rat
  - B. Monkey
  - C. Horse
  - D. Bat

Biologics Regulation—Where we start…

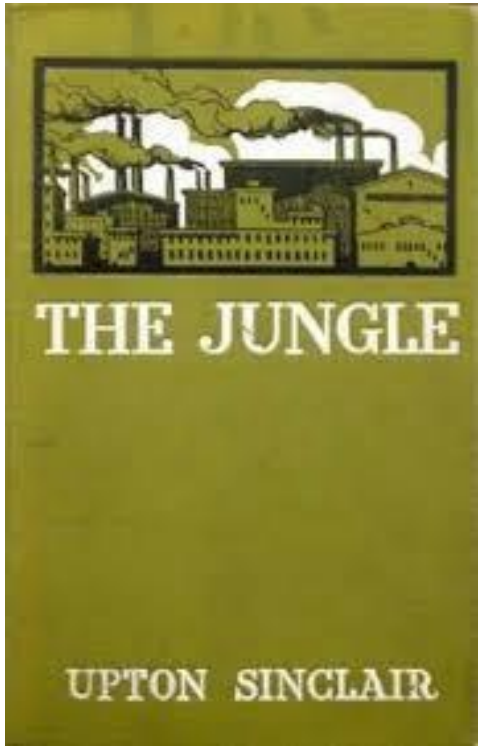
It started with a horse…

1902 Biologics Control Act:

In 1901, a 5-year-old girl died of tetanus in St. Louis, Missouri after being given a diphtheria anti-toxin. Investigations found that the St. Louis Board of Health produced the contaminated vaccine using the blood of a horse infected with tetanus. While the infected horse, Jim, was killed, the Board of Health continued to use the serum to treat diphtheria. It was later discovered that 12 other children had died from the same contaminated vaccines in St. Louis.

Biologics Regulation—Where we start…

- 1906 Food and Drugs Act
  - Banned adulterated or misbranded food and drugs
  - Regulated product labeling
  - No pre-market approval yet
    - Safety
    - Efficacy



Landmark Legislation—How did we get here…

- 1902—Biologics Control Act
- 1906—Pure Food and Drug Act
- 1938—Federal Food Drug and Cosmetic Act
- 1944—Public Health Service Act
- 2007—Food and Drug Administration Modernization Act (FDAMA)
- 2010—Biologics Price Competition and Innovation Act (BPCIA)
- 2012—Food and Drug Administration Safety and Innovation Act (FDASIA)
- 2016—21st Century Cures Act

True or False

- The FDA is an administrative agency with a confirmed Secretary who is part of the President's Cabinet?

False

- The FDA is sub-agency within the Department of Health and Human Services (HHS).
- The Commissioner of FDA reports to the Secretary of HHS – though typically they are given latitude. (This is not always the case however and toward end of the Trump administration HHS Sec. Azar took more significant control around rulemaking).

Poll #2

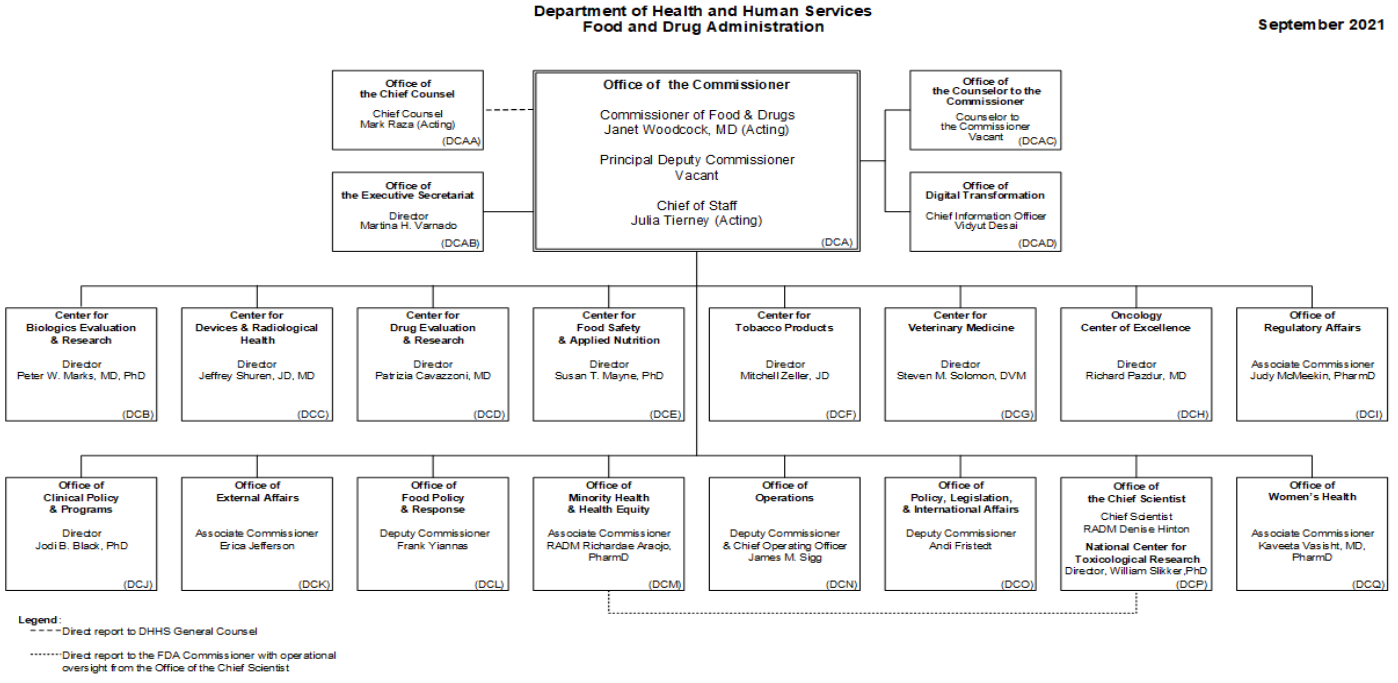
- The current FDA Commissioner is:
  - A. Dr. Stephen Hahn
  - B. Dr. David Kessler
  - C. Dr. Joshua Sharfstein
  - D. Dr. Janet Woodcock

Bonus points for naming current CBER Director

Food and Drug Administration

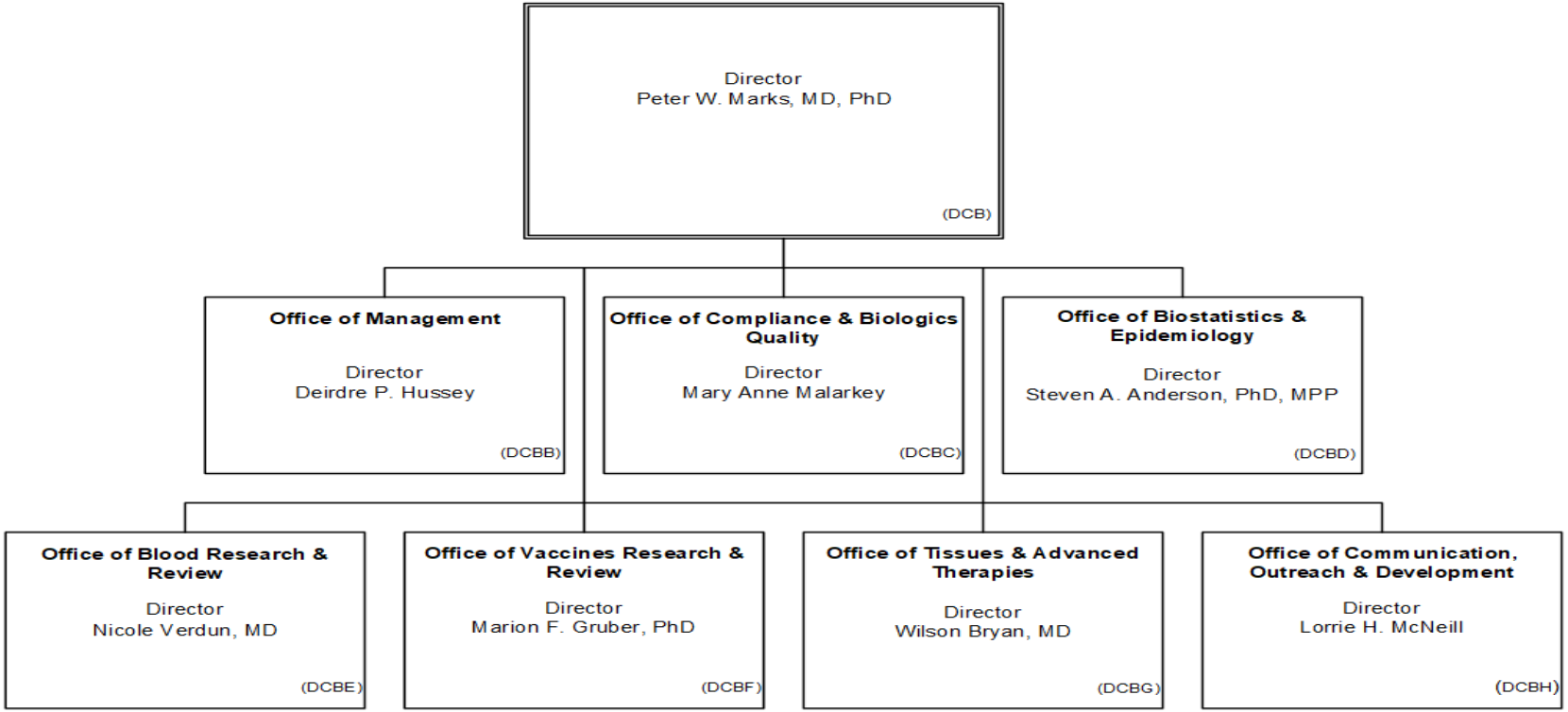
- FDA Mission
  - …protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, **biological products**, and medical devices; …

Current FDA Org Chart



June 2021

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research



FDA’s Place in Government

- The Department of Health and Human Services is a cabinet-level executive branch department of the U.S. federal government created to protect the health of all Americans and providing essential human services.
- Its motto is "Improving the health, safety, and well-being of America“
- FDA is a sub-agency within HHS.

Other HHS Sub-agencies

- Other HHS sub agencies also have roles involving biologics:
  - Center for Medicare and Medicaid Services (CMS)
  - HHS Office of Inspector General (OIG)
  - National Institutes of Health (NIH)
  - Centers for Disease Control and Prevention (CDC)
  - Animal and Plant Inspection Service (APHIS)

Animal Biologics

- Animal and Plant Inspection Service (APHIS)
  - Not actually a HHS sub-agency
  - Within the U.S. Department of Agriculture
  - APHIS regulates animal biologics (not FDA!) under the Virus Serum Toxin Act (21 USC 151 et seq.)
  - MOU between FDA and APHIS on topic (2019)

FDA’s Regulation of Biologics From Policy to Action

What is a Biologic?

In this Section:

- The term “biological product” means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, **protein** (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the **prevention, treatment, or cure of a disease or condition of human beings**.

42 U.S.C 262(i)(1)

What is a Biologic? (cont.)

- “Protein” definition changed by Further Consolidated Appropriations Act, 2020.
- BPCI Act amended biologics definition: a ‘‘protein (except any chemically synthesized polypeptide).’’
- FCA Act removed “(except any chemically synthesized polypeptide)”
- FDA Final Rule (Feb 2020) - the term protein means any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size.
- See https://www.govinfo.gov/content/pkg/FR-2020-02-21/pdf/2020-03505.pdf

Is a Biologic a Drug?

Yes.

- The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) **articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals**; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). …

21 U.S.C 321(g)(1)

FDA Legal Source of Authority to Regulate Biologics

- Acts of Congress (FDA Doesn't Write the Law)
  - Federal Food Drug and Cosmetic Act (FDCA)
    - New Drug Approval (NDA) (Section 505)
    - Abbreviated New Drug Application (ANDA) (Section 505(j))
  - Public Health Service Act (PHS Act)
    - Biologic License Application (BLA) (Section 351)
    - Abbreviated Biologic License Application (aBLA) (Section 351(k))

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March 23, 2020

- Biologics Price Competition and Innovation Act turns 10 years old

- **Biological Products** approved under Section 505 of the FFDCA “shall be deemed” to be licensed under Section 351 of the PHS Act. (Licensed BLA)
- All biologics must go through the BLA pathway.

Implementation of governing statute

- **Code of Federal Regulations**
  - Notice and Comment procedure
  - Must implement governing statute
- **Guidance documents**
  - Guidance for Industry (FDAs current thinking)
- **Compliance Policy Guides (CPGs)**
  - Guidance for FDA staff

Industry Participation in Shaping Policy

1) **Lobbying Congress—**new statute
2) **Comment** on proposed regulations (proposed guidance documents)
3) **FDA public meetings**
4) **Citizen Petitions—**seeking definite FDA action in a specific situation
5) **Judicial Review**
6) **Application Process—**e.g. Biosimilar Product Development (BPD) Program

Mechanisms in which FDA Regulatory Requirements are Solidified

1) **Enforcement Actions and letters**
2) **Citizen Petition Responses**
3) **Informal statements and advice**
4) **Miscellaneous publications**
5) **Product specific proceedings**

Policy in Action—Moving from Theory to Practice

Standards—Global harmonization and acceptance

1) **International Conference on Harmonization (ICH)**
   - ICH's mission is to achieve greater harmonization worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.
2) **United States Pharmacopeia (USP)**
   - 1906 Pure Food and Drug Act designated USP and National Formulary (NF) as official compendia.
   - Close collaboration of FDA and USP

Regulatory Proceedings

- Informal adjudications
  - I disagree with my reviewer, what do I do?
  - First discuss with review team and Division/Office Director, as appropriate
  - May next involve CBER Ombudsman, who reports directly to the Center Director.
    - Their function is to investigate what has happened and to facilitate a timely and equitable resolution.
    - A sponsor may avail themselves of the formal dispute process at any time after a division director has rendered an unfavorable decision regarding a sponsor's dispute, whereas a sponsor may contact the ombudsman informally at any time during the review process.
- Current CBER Ombudsman: Sheryl Lard-Whiteford, Ph.D. - cberombudsman@fda.hhs.gov

Regulatory Proceedings

- Formal Adjudications
  - I disagree with decision of division director – now what?
  - Guidance- Formal Dispute Resolution: Sponsor Appeals Above the Division Level
  - Appropriate action for formal dispute? (examples):
    - Complete response (CR)
    - IND clinical hold (partial or full)
    - Request for breakthrough therapy designation denied
    - Request for proprietary name review denied

Regulatory Proceedings

- Formal Adjudications
  - May continue to appeal to Center Director and then Commissioner.

- Judicial Review
  - Once there is final agency action – no further appeals may be taken – you may seek review in Federal District Court.
    - Either DC District Court or Maryland District Court

Freedom of Information Act (FOIA)

- Allows member of public to request access to records not normally prepared for public distribution
- Exceptions
  - Nine exemptions (created by Congress)
  - **No. 4-Trade secret or confidential commercial or financial information**
  - No. 5-Privileged inter- or intra- agency communication
  - No. 6-Individual Personal Privacy

Freedom of Information Act (FOIA)

Preventing disclosure of information submitted to FDA

- Under 21 CFR 20.61 FDA must notify a party of a FOIA request.
- 5 days to object to disclosure.
- If FDA decides to disclose, it must give notice to party.
- Party may then bring a reverse FOIA case in district court to seek relief from disclosure

True or False

- To date, three different COVID vaccines have been approved by FDA for use?

False

- FDA has “authorized” for use three vaccines. Only one (Pfizer) has been approved under the Public Health Service Act. Moderna and J&J are also expected to seek full approval for adult use as well.

What is an Emergency Use Authorization (EUA)

- Authorization of the emergency use of certain medical products under sections 564, 564A, and 564B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) as amended or added by the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA)

- Enacted to sustain and strengthen national preparedness for public health, military, and domestic emergencies involving chemical, biological, radiological, and nuclear (CBRN) agents, including emerging infectious disease threats such as pandemic influenza

EUA Authorizations

- Commissioner can authorize the emergency use of an unapproved medical product or an unapproved use of an approved medical product for certain emergency circumstances after the HHS Secretary has made a declaration of emergency or threat justifying authorization of emergency use

- The Commissioner may issue an EUA to allow an medical counter measures (MCM) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by a CBRN agent when there are no adequate, approved, and available alternatives.

EUA Authorizations

- Four statutory criteria:
  - Serious or life threating condition
  - Evidence of effectiveness (“may be effective”);
  - Risk – Benefits Analysis (known and potential benefits outweigh the known and potential risks);
  - No alternatives (may be considered unavailable if insufficient supplies).

Eligible FDA-approved Medical Products

- Empower FDA to extend the expiration date of an eligible FDA-approved MCM stockpiled for use in a CBRN emergency and to establish appropriate conditions relating to such extensions, such as appropriate storage, sampling, and labeling;
- Permit FDA to waive otherwise-applicable current good manufacturing practice (CGMP) requirements (e.g., storage or handling) to accommodate emergency response needs;
- Allow emergency dispensing of MCMs during an actual CBRN emergency event without requiring an individual prescription for each recipient of the MCM or all of the information otherwise required or by responders who may not otherwise be licensed to dispense, if permitted by state law in the state where such dispensing occurs or if in accordance with an order issued by FDA; and
- Permit the Centers for Disease Control and Prevention (CDC) to create and issue “emergency use instructions” (EUI) concerning the FDA-approved conditions of use for eligible product

Thank you

- Questions?
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