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Origins and Overview of the Food and Drug Administration and the Regulation of Drugs

November 9, 2022

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Outline

- Administrative Organization
- Navigating FDA Systems
- Major Statutes
  - Three heroes – a muckracker, a woman scientist, and an obscure English mathematician-agronomist
- Product Specific Regulator Proceedings

FDLI Food and Drug Law Institute

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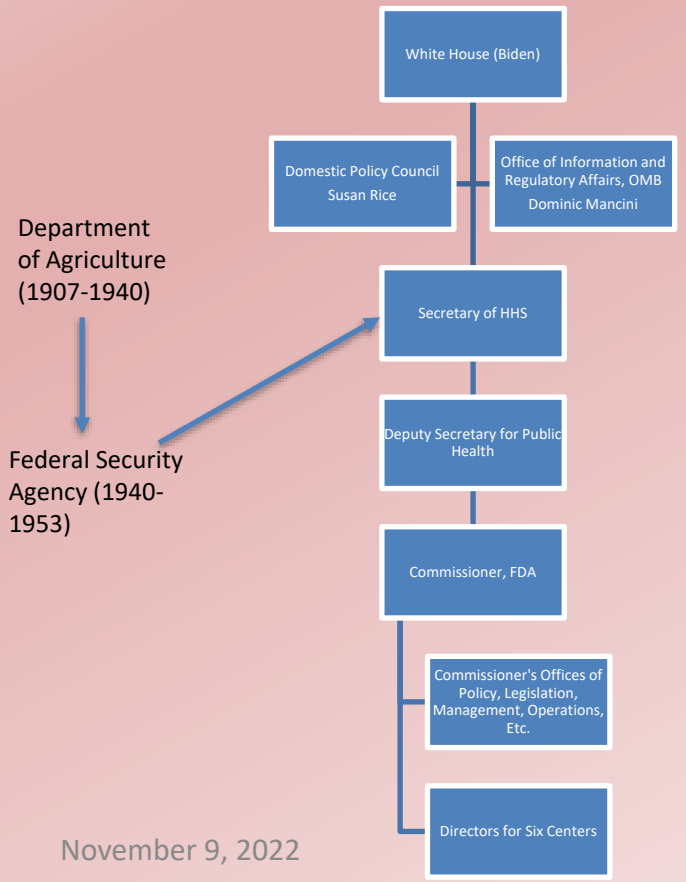
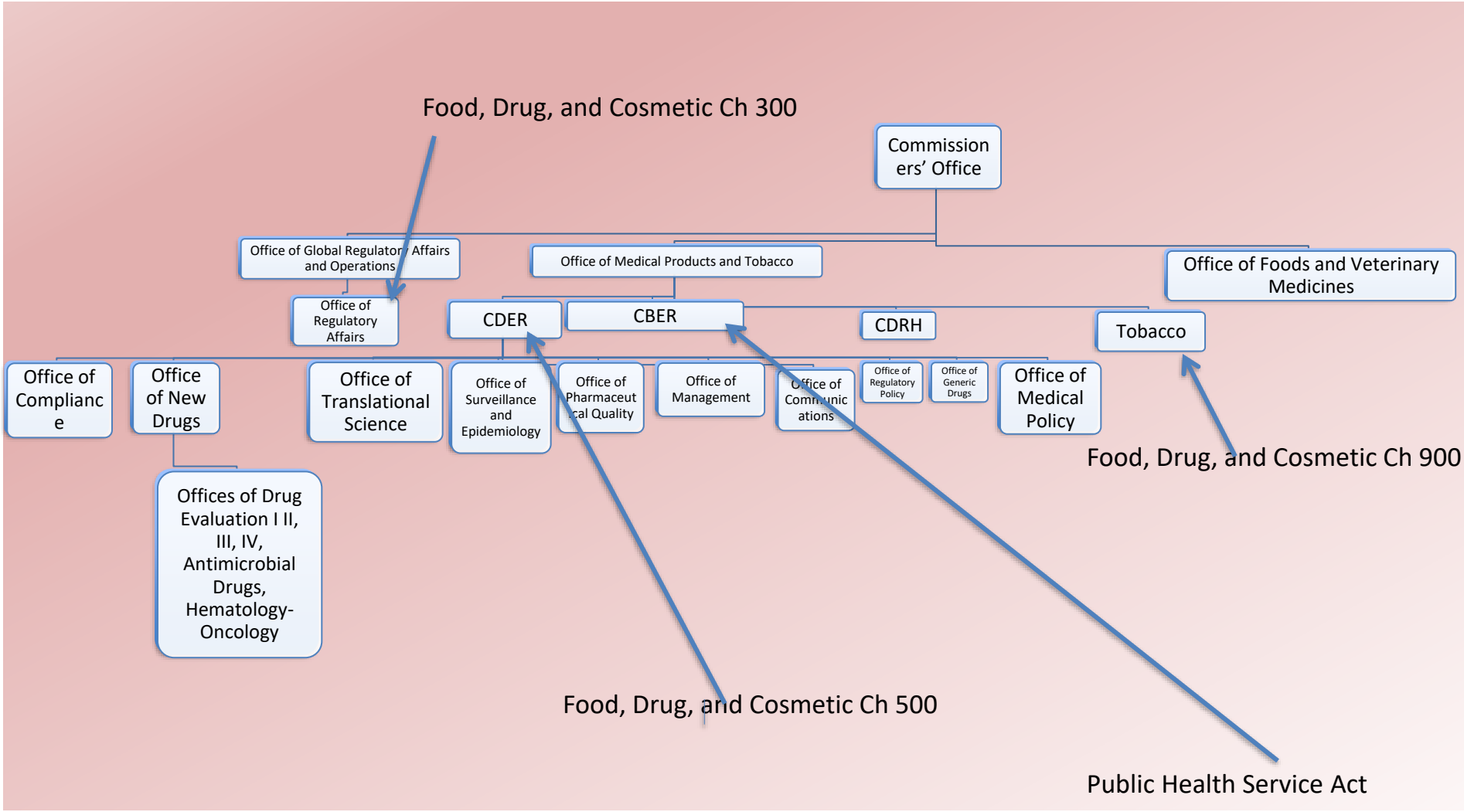


- Secretary Xavier Becerra JD (conf'd March 19, 2021)
- Deputy Secretary Andrea Palm MSW (conf'd May 11, 2021)
- Commissioner Robert Califf MD (conf'd Feb. 17, 2022)
- Deputy Comm'rs (historically, political; currently all career SES)
  - Janet Woodcock, Principal Deputy Comm'r (2022)
  - Anna Abram, Deputy Comm'r Policy, Planning, Legislation and Analysis (2017)
  - Walter Harris, Deputy Comm'r Operations/COO (2012)
  - Stephen Ostroff, Food (2016)
  - David Corrigan, Acting Deputy for Global Regulatory Operations and Policy (2017)
- Center Directors (historically and generally, career scientists)
  - Patrizia Cavazzoni (CDER) (2020)
  - Jeff Shuren (CDRH) (2008)
  - Peter Marks (CBER) (2016)
  - Brian King (Tobacco) (July 2022)
  - Susan Mayne (CFSAN) (2016)
  - Steven Solomon (CVM) (2017)(retiring)


Food, Drug, and Cosmetic Ch 300
Commissioners' Office
Office of Global Regulatory Affairs and Operations
Office of Medical Products and Tobacco
Office of Foods and Veterinary Medicines
Office of Regulatory Affairs
CDER
CBER
CDRH
Tobacco
Office of Compliance
Office of New Drugs
Office of Translational Science
Office of Surveillance and Epidemiology
Office of Pharmaceutical Quality
Office of Management
Office of Communications
Office of Regulatory Policy
Office of Generic Drugs
Office of Medical Policy
Offices of Drug Evaluation I II, III, IV, Antimicrobial Drugs, Hematology-Oncology
Food, Drug, and Cosmetic Ch 900
Food, Drug, and Cosmetic Ch 500
Public Health Service Act

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Navigating FDA

- Constitution, Statute, Regulation, Federal Register
- Industry Guidance and Responses to Citizen's Petitions
- Internal Operating Manuals
- Advisory Committees and Drugs@FDA
- Enforcement Actions
- FDA statements, publications, website, webinars
- Citizen's Petitions
- FOIA documents

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Binding on FDA and Public

- Statutes Relevant to Drug Regulations
  - Title 21 U.S.C. Chap 9 (Food, Drug, and Cosmetic Act)
  - 42 U.S.C § 263 (Public Health Service Act of 1944 § 351)
  - 21 U.S.C. Chap 13 (Controlled Substances Act of 1970)
  - 42 U.S.C. Chap 6A (Bioterrorism Act of 2002)
  - 42 U.S.C. § 243 et seq (Project Bioshield 2004)
- Regulations
  - Title 21 C.F.R.
- Guidance issued under Good Guidance Practice pursuant to the Food and Drug Administration Modernization Act?
- Interpretative
  - Applicable Congressional Reports
  - Applicable Federal Register Notices – Preambles and Responses to Comments
  - Responses to Citizens Petitions

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Non-Binding Formal Resources

- Manual of Compliance Policy Guide (CPG)
  - Unique approach to an issue or scope of enforcement discretion
- Investigators Operations Manual (IOM)
  - Required procedures for an inspection and report.
- Regulatory Procedures Manual (RPM)
  - Agency internal rules for generating compliance action
- Manual of Administrative Policies and Procedures (MAPP)
- Draft Guidance
- Statements, Press Releases, Website, Webinars, Agency Publications

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Enforcement and Decisions

- Inspections
  - Establishment Inspection Report (EIR)
  - FDA Form 483 Investigational Findings
  - Warning or Untitled Letters
- FDA Review Policies
  - Summary Bases of Approval at Drugs@FDA
  - Advisory Committee Transcripts
  - Regulatory Hearings and adjudications
- External to FDA
  - Case Law
  - Congressional Hearings
  - Congressional Research Services and Institute of Medicine Reports

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Citizen's Petition (21 CFR § 10.30)

- Any person who wants the agency ***to issue***, amend, or revoke a regulation.
  - Unique to FDA
  - Docket established
  - 90 days for mandated response (§ 10.30(e)(2))
- Work around to arrive at exhaustion, fitness for review, and finality pursuant to the Administrative Procedures Act
  - "Unreasonably delayed" 5 U.S.C. § 706(1)
  - "Final" 5 U.S.C. § 704

Freedom of Information Act Requests

- Public access to agency records, processes and decisions
- Electronic filing: https://www.accessdata.fda.gov/scripts/foi/FOIRequest/index.cfm
- Response times and costs vary by scope and applicant
- Personal, trade secrets, deliberative processes, and commercial or financial information that are privileged or confidential are segregated or redacted
- Sets up opportunity for judicial review.

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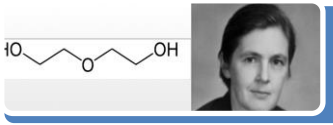
Major Statutes

Federal Food and Drugs Act of 1906 (Wiley / Pure Food and Drug Act)



Federal Food, Drug, and Cosmetic Act of 1938 (FDCA) HO

Durham-Humphries Act of 1951 (Prescription Drugs)

Kefauver-Harris Drug Amendments of 1962

Hatch-Waxman Drug Price Competition and Patent Term Restoration Act of 1984 (Generic Drugs)

Prescription Drug User Fee Act of 1992 and Quinquennial Reauthorizations (through 2022)

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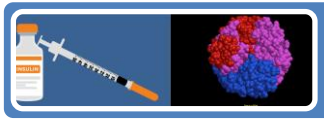
Major Statutes

Food and Drug Administration Modernization Act of 1997



Biologics Price Competition and Innovation Act of 2009

FDA Safety and Innovation Act of 2012

Drug Quality and Security Act of 2013 (successor to Prescription Drug Marketing Act of 1987)

21st Century Cures Act of 2016

The CARES Act of 2020

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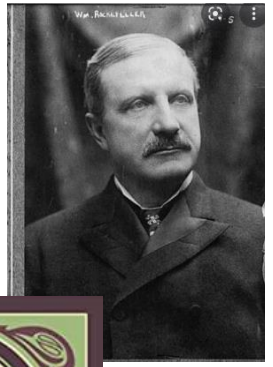
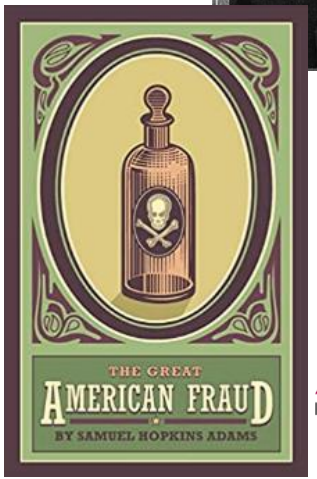
Origins of Food and Drug Regulation

- Toadstool Millionaires (19th Century)
  - Patent Medicine shows – Wm A Rockefeller
  - Alcohol and opium for cancer, meningitis, etc.
- Muckrakers
  - Collier's The Great American Fraud
    - Samuel Avery Hopkins (Oct 1905 – Feb 1906)
      - Chemical testing and false claims
  - Upton Sinclair *The Jungle* (1906)
  - Harvey Wiley – Dept. of Agriculture





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Federal Food and Drugs Act

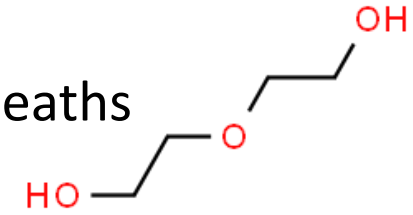
June 30, 1906

- Prevention of Fraud
  - "any substance … *intended to be used* for the cure, mitigation, or prevention of disease of either man or other animals" (§ 6 – Definition of Drug)
- Introduction from one state into another
  - *In rem* seizure or refusal of import entry
- Burden of proof on government
  - "Satisfactory evidence"
  - Bureau of Chemistry USDA

Sulfanilamide Tragedy (Fall 1937)

- Antibiotic, *e.g.*, Bactrim®
- Manufacture simplified by chemist at Messengill by dissolution in diethylene glycol
- Frances Kelsey
  - PhD Student in Pharmacology at U. of Chicago
  - DEG presence

  associated with deaths



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Federal Food, Drug, and Cosmetic Act (June 1938)

- New Drug Application
  - "Introduction … into interstate commerce … in violation of § 505" is a "prohibited act."
  - "No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an application … is effective" and "such drug is safe for use" §§ 505(a), (b)
- Burden on sponsor to demonstrate safety.
- "Generic" marketing based on approval of innovator active ingredient without pre-market authorization, including combinations.
  - Identical, Related or Similar (IRS)

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Durham-Humphries Act (1951)

- Philosophical shift from the concept of targeted "magic bullet" antimicrobial (e.g., penicillin) to drugs as interfering with human chemical and metabolic systems.
  - ACTH (suicide), corticosteroids, cocaine, narcotics, live polio vaccine, radiation therapy for cancer
- FDCA § 503(b)
  - Need for practitioner management of drug therapy (Rx Only)
  - Balancing of risks and benefits by provider supervision
    - Physicians assumed capable of keeping up with drug manufacturers

Kefauver Antitrust and Corruption Hearings (1957-1962)

- Anti-competitive drug pricing
  - Promotion of trade names for same drug
  - Promotion of unnecessary fixed combinations
- Misleading lack of good efficacy studies
- Lack of authority to assess efficacy?
  - Inherently unsafe → Risk/Benefit information
- Unknown drug manufacturers and drugs

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Developments in Academic Medicine and Application of RA Fisher to Clinical Testing

- Evolving Concern about Substantiation of Efficacy
- AMA Council on Drugs – Starr Report
- Particular Academics
  - Pharmacology – Dr. Louis Goodman
  - Dr. Louis Lasagna
- Causal
- Randomized, Placebo-Controlled, Blinded Studies
  - Ronald A Fisher (1890 – 1962)
  - Design of Experiments (1936)

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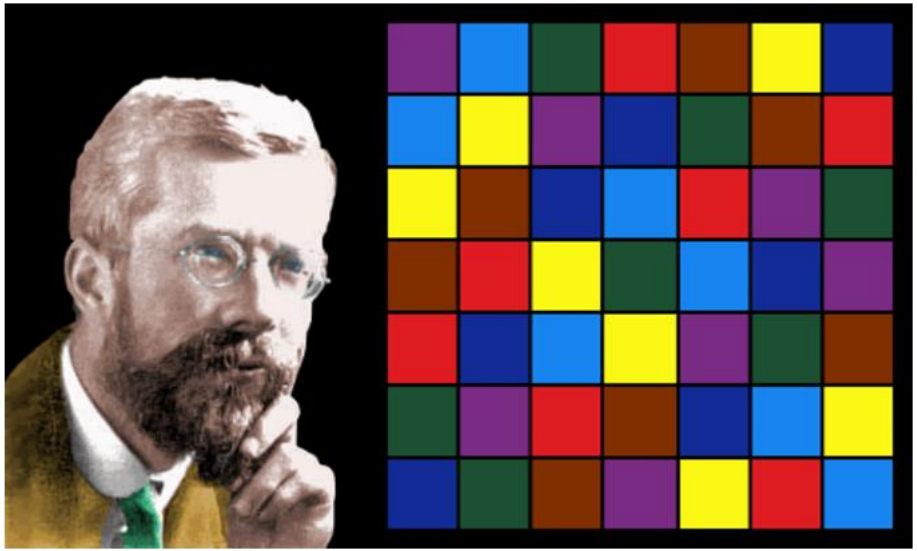

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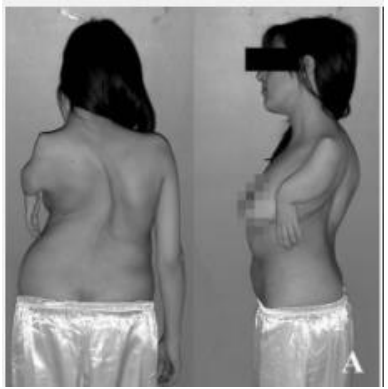
The Thalidomide Tragedy – "Mother's Little Helper"

- Frances Kelsey
  - Ph.D. in placental transmission of drugs
  - Her pharmacology review raised issue of placental transfer
- Phocomelia:



Dr. Frances Kelsey

(1914 – 2015)

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Drug Amendments (Oct 10, 1962)

- Registration of all drug manufacturers
- Broad inspectional authority
- Generic names
- Fixed combinations required

4-arm studies

- Efficacy review added to NDA
  - Retrospective
    - Drug Efficacy Study Implementation (DESI) by FDA.
  - Prospective as part of NDA review by sponsor.

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Expanded New Drug Application

- "Introduction … into interstate commerce any new drug unless an approval … is effective." § 505(a)
  - Marketing " in violation of section . . . 505" is a "prohibited act." § 301(d)
- Approval conditional on:
  - "Such drug is safe for use under the condition prescribed" § 505(d)(1).
  - "Will have the effect it purports to have" based on "substantial evidence" § 505(d)(5).
- Efficacy based on "substantial evidence" which means "evidence consisting of adequate and well-controlled investigations, including clinical investigation***s***, by experts" § 505(d)(7)

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Drug Efficacy Study Implementation (DESI)

- Retrospective evaluation of efficacy
- National Academy of Science/National Research Council (1966-1969)
  - ≈5000 products with >10,000 indications
- Category
  - I Safe and effective
  - II Not safe or not effective
  - III Indeterminate
- Advanced Notice of Proposed Rulemaking
- Notice of Proposed Rulemaking (Tentative Final Monograph)
- Proposed Rulemaking (Final Monograph)
  - 21 CFR Parts 331-358
- Revisited in CARES Act of 2020

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Competitive Effect of Efficacy Standard

- Loss of patent term
  - Longer development time to conduct clinical studies and longer review times (*cf.*, consumer such as electronics)
- Loss of generic competition
  - Loss of "IRS" status
  - 100% Data Exclusivity = regulatory patent
- Virtually complete privatization of drug development (*cf.*, NIH clinical budget [$1-2B] to JPMorgan SF Conference annual private investment [north of $100B])
- How would you think investors react on approvals?

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Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman)

- Patent term restoration for FDA review time ≤5 yrs.
- Limited data exclusivity
  - NCE = 5 years + review time
  - New indication = 2 years + review time
- Abbreviated New Drug Application
  - No clinical or nonclinical studies
  - Three requirements
    - Identical labeling
    - Bioequivalence on Human Use
    - Chemistry, Manufacturing, and Controls, and Good Manufacturing Practices

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Prescription Drug User Fee Act of 1992

- Origins: Delays and inadequacy in review, precedence in patent review, chronic understaffing, unwillingness to use tax receipts, perceived profitability of pharmaceutical industry
- Commitment Letters on review timeframes (and later for other aspects of agency action and for other Centers) in exchange for a "user fee"
  - Currently, $2M paid in advance of NDA filing used to fund increased personnel
- Five Year Reauthorization Required as a "test" (and comparable to federal transportation and agriculture budgets)
  - Created a five-year vehicle for easy substantive amendment of FDCA on "must-pass" legislation

Reauthorized and expanded: 1997, 2002, 2007, 2012, 2017, 2022

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Food and Drug Administration Modernization Act (FDAMA) of 1997

- First and exemplary reauthorization
- Substantive additions:
  - Pediatric study requirements
  - Permissible lessened clinical study requirements
  - PET and diagnostic radiopharmaceutical regulatory relief
  - Fast track and expanded access made statutory
  - Information dissemination in face of First Amendment challenges
  - Good Guidance Practices
  - PDUFA Meetings formalized
  - Combination product reform in light of agency recalcitrance
  - First statutory foray into regulation of compounding
- Multiple amendments to medical device and food regulation

Public Health Security and Bioterrorism Preparedness Act of 2002

- Second reauthorization
- Significant expansion of FDA's role in security of food supply, agency role in development of medical countermeasures, and controls on dangerous biological agents
- Agency manpower concerns and limitations go out the window

Food and Drug Administration Amendments Act of 2007

- Third reauthorization
- Pediatric studies made mandatory
- Enhanced authority when safety issues arise in post-market setting (e.g., Vioxx)
- Fees extended to medical devices
- Support for new antimicrobials

Biologics Price Competition and Innovation Act of 2009

- Program for generic or "biosimilar" biologics finally enacted after many tries.
- Definition of biologics updated to include any and all proteins above certain size with movement of historic drug products (e.g., heparin, insulin) to BLAs by March 2022
  - Should have the impact of moving all protein INDs as well . . .
- Biologics user fees
- Marketing exclusivity for new biologics (12 years)

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FDA Safety and Innovation Act of 2012 (FDASIA)

- Fourth drug user fee reauthorization
- Follows wholesale changes in the country's approach to food safety with corresponding significant increase in agency responsibilities and funding found in Food Safety Modernization Act of 2011
- Numerous other small changes in drug regulations:
  - More on pediatric study plans
  - Shortage reporting
  - Supply chain security
  - Breakthrough designation
  - New antibiotic support

Drug Quality and Security Act of 2013

- Successor to, and largely supersedes, Prescription Drug Marketing Act of 1987
- Second foray into compounding and outsourcing of pharmaceuticals in shortage
- Extensive cradle-to-pharmacy track-and-tracing of all prescription drugs
- Direct federal regulation of wholesale drug distributors, third-party logistics providers, and more indirectly, pharmacies
  - Proposed rule issued on May 24, 2022

21st Century Cures Act of 2016

- Passed on December on eve of President Trump's inauguration in January
- Another User Fee Reauthorization
- Number of substantive changes
  - Direct patient engagement by FDA
  - Real World Evidence Standards
  - More on new antimicrobials and medical countermeasures support

The CARES Act of 2020

- Largely focused on pandemic reliefPassed on December on eve of President Trump's inauguration in January
- An outstanding change in the DESI or OTC review program (and adding user fees)
  - FDA permitted to finalize DESI drug programs by order without notice-and-comment rulemaking

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Product Specific Proceedings

- CDER Dispute Resolution
  - Senior personnel technical review
- Ombudsperson
  - Procedural review and mediation
- Regulatory Hearings or Adjudications
- FDLI or Other Meetings
  - Various forms of “jaw-boning” are a fact of life
- Congressional committee staff or Member

Lawfully-Marketed Drugs

- Approved New Drug Application
- Monograph compliant
- No determination of lack of safety, in a pending monograph, and without a final order
  - *E.g.*, alcohol handwash
- Pre-1938 "old drugs" if not subject to Special Order (Prescription Drug Wrap-Up)
  - *E.g.*, Donnatol® (atropine, hyoscyamine, scopolamine, phenobarbital)

Intention v. Effect

- Did 1938 Act assure safety and did it limit review to safety?
- Did the 1951 Act provide for a comprehensible package insert?
- Did 1962 Act make drug pricing competitive, would its earlier enactment have changed thalidomide review, did Congress intend that "substantial evidence" be prospective, randomized, blinded, placebo-controlled, clinical studies with a single, predefined statistical endpoint?[1]
- Have generic approvals lived up to the promise of lower drug costs?
- Did PDUFA result in an agency subservient to industry or loosen the guardrails on regulators?

[1]21 CFR § 314.126

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~ *fin* ~

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Questions