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

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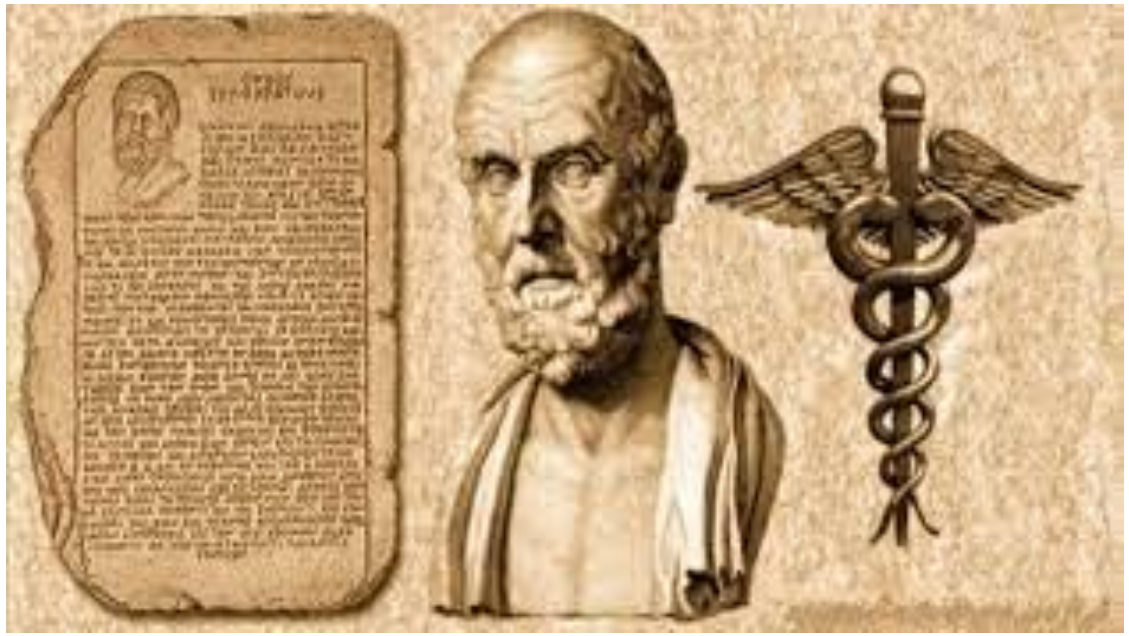
Major Topics

- Historical Context, FDA's Origin and Place in Government
- Major Statutory Underpinnings of Today's Legal and Regulatory Framework
- Sources of Legal and Regulatory Requirements and FDA Policies
- Participating in FDA Policymaking
- Product-Specific Regulatory Proceedings
- FDA Appointments in the Biden Administration, FDA Organization.

“Pre-History” of Drug Regulation

- Ancient regulation around “adulteration”.
- Recreational drugs allowed. Intoxicants regulated by “society”.
- Few medicines with real efficacy (opium for pain), some anti-microbial herbs, poisons, contraceptives/abortifacients.



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Early Western Drug Regulation

- Medieval Church attempts to limit Laudanum.
- 1729 – China bans opium imports, leads to 19th century wars and foundation of Hong Kong.
- 1828 – Case fought in Scotland over insurance pay out of an opium addict.
- 1868 – Pharmacy Act in the UK. Limited the sale of poisons and dangerous drugs to pharmacists, who were required to register.

Early Pharmacopeias

- Ancient Egyptian, Chinese, formularies known.
- Florence – 1498
- Spain – 1588
- London – 1618
- USA - 1820

Early US Drug Law

- Early laws were a patchwork of state and local enactments.
- Reluctance to regulate business.
- 1848 – Drug Importation Act, attempts to prevent import of adulterated medicines.
- 1902 – Biologics Control Act. Two dozen children died from contaminated vaccines/serums. ***Established the precedent in the USA of inspection and regulation of drug manufacturers.***
- Early inspections by Treasury Department agents.
- Medicine is separating from “food” in concept. The idea that medicines might actually work is growing. Diphtheria serum, aspirin, Salvarsan, Quinine.

Pure Food and Drug Act of 1906

- America is in a “reform” period. Mass newspapers are new.
- Upton Sinclair and *The Jungle*. Attempt to expose working class misery leads to outrage over food manufacturing practices.

A NAUSEATING JOB, BUT IT MUST BE DONE

Pure Food and Drug Act of 1906

- Prohibited introduction into interstate commerce of misbranded or adulterated food and drugs.
- Regulation based on product labeling.
- No premarket approval provisions.
- No requirement for safety or efficacy.
- Gave “Bureau of Chemistry” power to inspect drug manufacturing facilities. Most inspections (if any) still in the hands of state boards of pharmacy.

Bureau of Chemistry

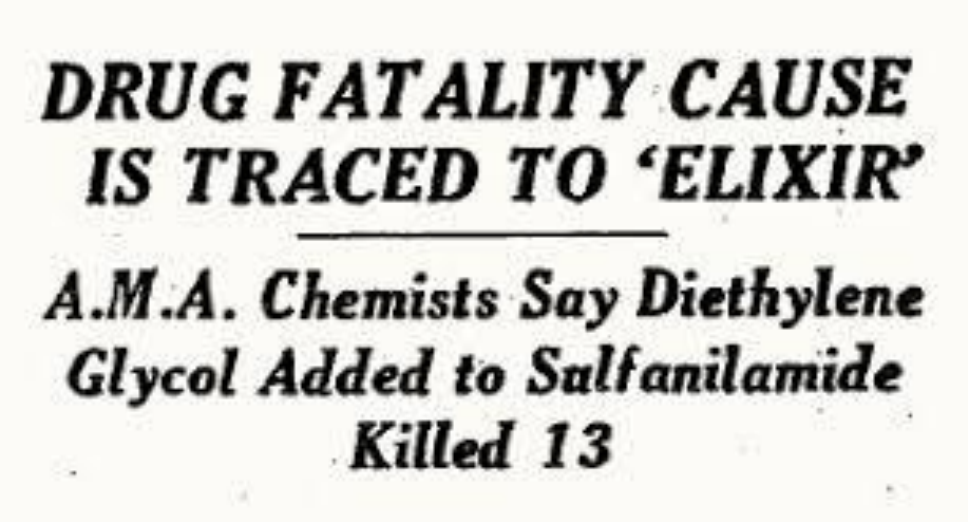
- Began in the Department of Agriculture in 1862 with a single scientist. Became “Division of Chemistry” then Bureau in 1901.
- Regulatory function began in 1906.
- Converted to “Food, Drug and Insecticide Division” in 1927, then the “Food and Drug Administration” in 1930.

Elixir Sulfanilamide

- Antibacterial compound discovered through the work of Paul Erlich at Bayer, saved FDR's son from infection.
- Active ingredient was off patent. Sold and used in pill and powder form. Poor water solubility.
- S. E. Massingill Company prepared liquid form. Chemist did not research toxicity of solvent, though it was known. Diethylene glycol.

Elixir Sulfanilamide

- Deaths began to be reported. Eventually over 100.
- One of the first mass recalls initiated. Field agents tracked down individual bottles, even in patient's trash.
- Frances Oldham Kelsey worked in agency as a young scientist. Her memory of the incident is important.
- FDA had no enforcement power except labeling. Massengill was fined $100 because "elixirs" must contain ethanol. Some further state level fines.



DRUG FATALITY CAUSE IS TRACED TO 'ELIXIR'

A.M.A. Chemists Say Diethylene Glycol Added to Salfanilamide Killed 13

More Fallout

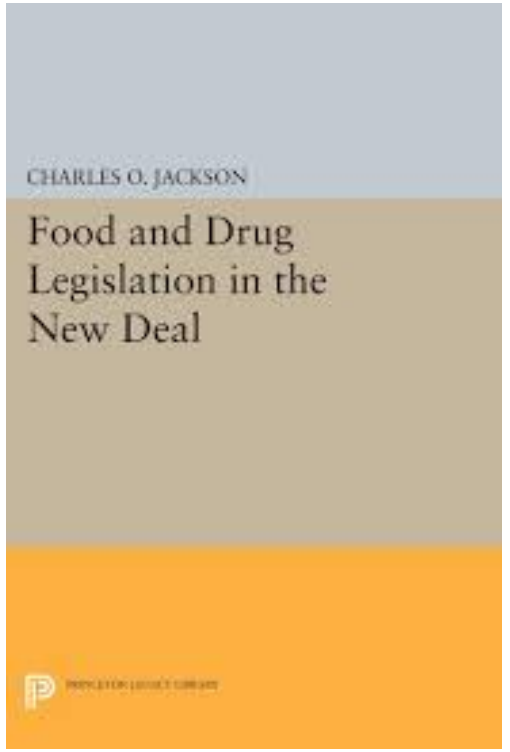
- Chemist from Massengill, Harold Watkins committed suicide.
- However, the owner of the company told congress, “We have been supplying a legitimate professional demand and not once could have foreseen the unlooked-for results. I do not feel that there was any responsibility on our part.”
- Toxicity of diethylene glycol had been known for years. No one bothered to check.
- Public outrage led to the passage of the Food, Drug and Cosmetic Act of 1938. Foundation of modern drug law.

Food Drug and Cosmetic Act of 1938

- Relied on the “commerce clause” to give FDA jurisdiction.
- Required “New Drug Applications (NDAs).
- FDA had only 60 days to intervene, otherwise approval was automatic.
- Did not affect products already on the market.
- Required drug manufacturers to submit an application showing that new drugs were safe [note, NOT effective] before they could be marketed.
- Gave FDA the authority to regulate cosmetics and medical devices.

Food Drug and Cosmetic Act of 1938

- Gave some statutory authority to the USP and National Formulary (which are still quasi-private.)
- Gave FDA power to regulate Homeopathic medicines.
- FDA's power still very limited. FTC regulates advertising.
- First mention of "current Good Manufacturing Practices.



Sulfathiazole Scandal

- Less well known due to following Elixir Sulfanilamide and just preceding World War 2 in the USA.
- March 1941 FDA's Boston office learns of a 3 year old girl in a coma following being medicated with Sulfathiazole. Investigation led to knowledge of the death of a 4 year old in California the previous month.
- FDA eventually discovered 300 related deaths.
- Winthrop Chemical Company had accidently mixed sulfathiazole with phenobarbital, a sedative toxic in large enough doses

Sulfathiazole Scandal

- Winthrop had discovered the error and was quietly trying to recall the material. Two lots were implicated.
- Normal practices at the time included lack of documentation, no cleaning standards.
- This led to the birth of GMP. Eventually the mantra, “if it wasn’t documented, it wasn’t done.”

FD&C Act Developments

- Early on, FDA required to test antibiotics and insulin themselves. Leads to current understanding that “FDA tests”, which it does NOT do normally.
- 1944 – Public Health Service Act sets framework for Biologics Licenses. Distinction between small discrete molecule and complex biological matrix.
- 1951 – Durham Humphrey amendment defines which drugs can be sold “over the counter” OTC.
- 1955 – FDA rejects first drug that has not proven “efficacy”, determining that ineffective drugs are not safe.

Thalidomide

- Developed in Europe to treat morning sickness. No evidence of toxicity in trials. Used from 1957 to 1961.
- Frances Oldham Kelsey delayed FDA approval, even under pressure. Limited free samples distributed in the USA.
- 4000 still births and 6000 profound birth defects in Europe. Less than 20 in the USA.
- Led to Harris – Kefauver Amendment.

Harris – Kefauver Amendment - 1962

- First time in statute that drugs must be “effective” to be approved.
- Many drugs already on the market are exempted.
- FDA contracts with the National Academy of Sciences to evaluate the effectiveness of 4000 drugs already marketed.

Over the Counter Reform/Review

- Difference between prescription and over the counter further clarified in 1972.
- Review of drugs marketed before May 1972.
- Key questions:
  Can a drug be used in self-treatment?
  Is it “Generally recognized as safe and effective (GRASE)?
- Public rulemaking to describe how a drug will become GRASE.
- Drugs become over the counter (OTC) by compliance with published rule, approved NDA/ANDA or supplemental NDA to switch status.

Generic Drugs

- “Drug Price Competition and Patent Term Restoration Act of 1984”
- Commonly “Hatch-Waxman”.
- Tries to balance need for profit to drive new drugs versus price competition.
- Formalizes the ANDA, introduces the 505(b)(2).
- 505(b)(2) – new formulation of an existing drug.

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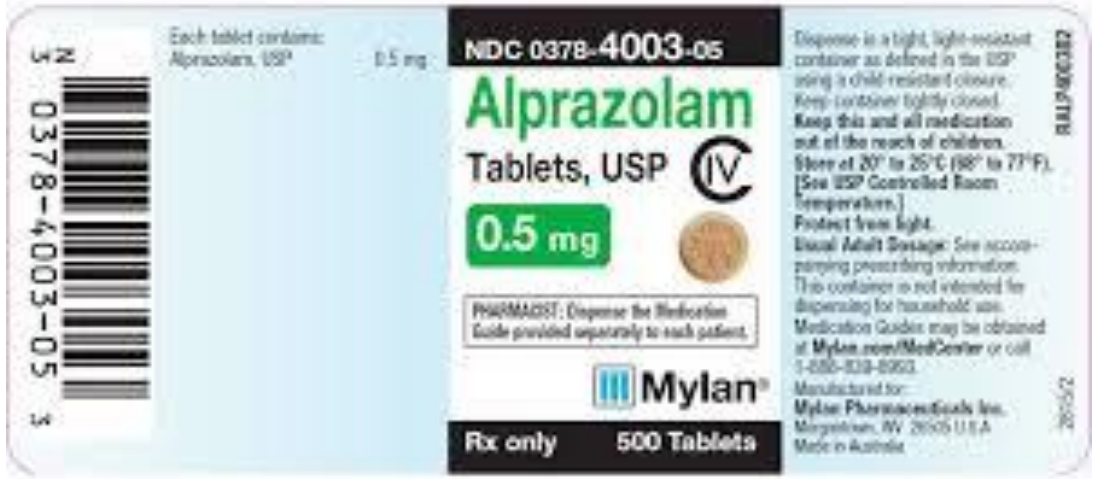
More from Hatch Waxman

- Patent term extension for half the time between IND and NDA submission.
- 5 year New Chemical Entity exclusivity.
- 3 year clinical study exclusivity (study essential for approval, prevents generic competition for that approval).
- 180 exclusivity for first generic applicant by challenging a listed patent (to allow generic completion). So called “paragraph IV” challenge.



Prescription Drug User Fee Act (PDUFA) of 1992

- Allowed FDA to collect user fees from drug and biologics manufacturers. In essence, firms are “buying” review chemists and clinicians to expedite product reviews.
- Collected for product applications, supplements, and other submissions
- Created FDA performance goals for review. Supposed to reduce FDA review times. Results? Depends on whom you ask.
- Renegotiated and reauthorized every 5 years.

Other Modern Legislation

- GDUFA (2012) – Puts generic drugs under a user fee structure. Some room for adjustment due to size of the firm.
- Biologics Price Competition and Innovation Act (2009) – sets framework for “biosimilar” and “interchangeable” products. In a small molecule drug, we can say “substance X provides the active effect”. In a biologic, this active affect can be from a complex matrix.

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Other Modern Legislation

- Drug Quality and Security Act 2013 -
- 2016 21st Century Cures Act – Acts to improve FDA review using “real world evidence”, establishes centers of excellence, breakthrough designation for devices.
- FDA Reauthorization Act of 2017 strengths the legal basis of the user fees. User fees for biosimilars and devices.
- CARES Act of 2020 – requires more firms to notify FDA of discontinuing operations, requires drug manufacturers, *including active ingredient manufacturers* to have detailed plans for dealing with supply interruptions, requires reporting of quantity of drugs produced.

Compounding Pharmacy Scandal

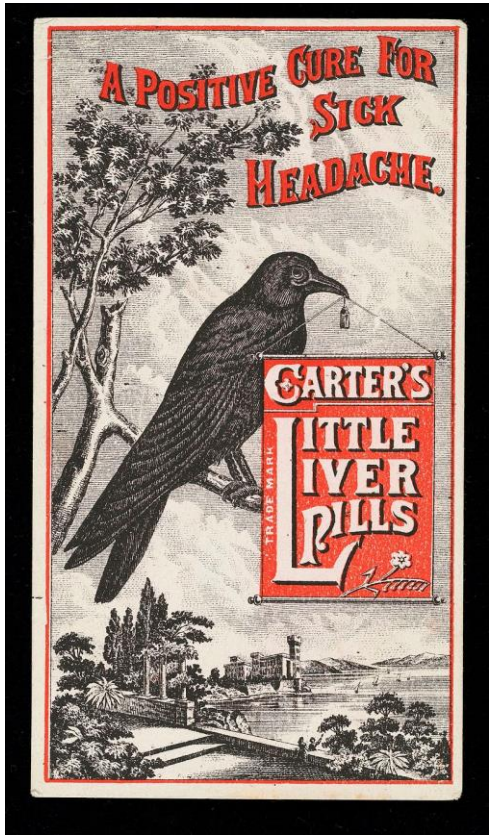
- Resulted in the Drug Quality and Security Act of 2013.
- A number of deaths and injuries resulted from poor quality control at compounding pharmacies.
- Congressional outrage at FDA muted by FDA's response that ***Congress*** had exempted compounding pharmacies from most regulation.
- Act tries to close loopholes.
- Many FDA inspectional actions since.

Other Scandals

- 2008 Heparin Adulteration Scandal – Nonspecific test in biological product led to replacement of material with cheaper alternative. Highlighted that API industry fled Western regulatory regimes to China and India.
- 2007 Medicine in Haiti for fever used contaminated glycerin. Glycerin contaminated with the ***same solvent*** as Elixir Sulfanilamide. Material passed through many hands. ***No one tested it.*** COA recopied.

Supreme Court Decisions

- 1911 – False claims about efficacy are not illegal, only false claims as to ingredients. Congress then made such claims illegal *if intended to defraud.*
- 1948 – FDA power extends to retail pharmacies.
- 1950 – Since a drug must state its intended purpose on the label, a “snake oil” cannot escape such regulation by not stating a purpose.
- 1952 – Cardiff decision. FDA’s inspectional authority in factories “too vague”. More impetus for written Good Manufacturing Practices (GMP).
- 1970 – Upjohn v Finch – Commercial success does not imply efficacy, it must be proven scientifically.



Sources of Legal and Regulatory Requirements

- Constitution
- Statues
- Regulations
- Guidance Documents
- Compliance Policy Guides
- Staff SOPs
- Enforcement Actions, Consent Decrees
- Warning Letters, FD 483s
- Industry practice!
- **REMEMBER the “c” in cGMP stands for current.**

The Constitution and Statutes

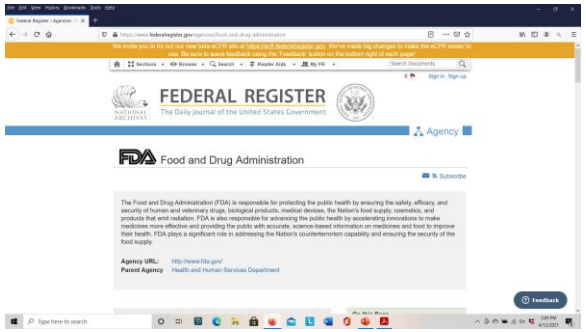
- Statutes rely on the interstate commerce clause and perhaps the “necessary and proper” clause of the constitution.
- FDA will try to establish jurisdiction during inspections by obtaining evidence of movement across state lines.
- Early drug laws emphasized the “rights” of the manufacturer over the safety of the consumer.

Regulations

- Detailed requirements intended to implement the FD&C Act and all other laws governing drug production. Often "rule" is used in its place.
- Codified in 21 Code of Federal Regulations.
- Very difficult to write and get approved.
- "Notice" and a comment period are required. These are published in the *Federal Register.* Analysis of comments usually published in the preamble to the regulation.

Federal Register Notices

- Published in paper form and online. Free online:



- https://www.federalregister.gov/agencies/food-and-drug-administration
- April 12, 2021 issue contains several notices for animal drug user fees. Several pages per day published.

Advisory Opinions

- Advisory opinions represent FDA's formal position regarding a specific matter.
- FDA may issue advisory opinion in response to request from interested person.
- Statements of policy or interpretation made…other than the text of proposed or final rules (e.g., preambles); or other documents specifically identified as advisory opinions.
- FDA may not recommend legal action against person or product for action taken in conformity with advisory opinion (safe harbor).
- “Go not to the Eldar for advice for they will say both “no” and “yes”.

Guidance Documents

- Currently the core of cGMP. FDA.gov contains hundreds of these documents.
- Do not establish enforceable rights like an advisory opinion.
- FDA even has a guidance document for the preparation of guidance documents.

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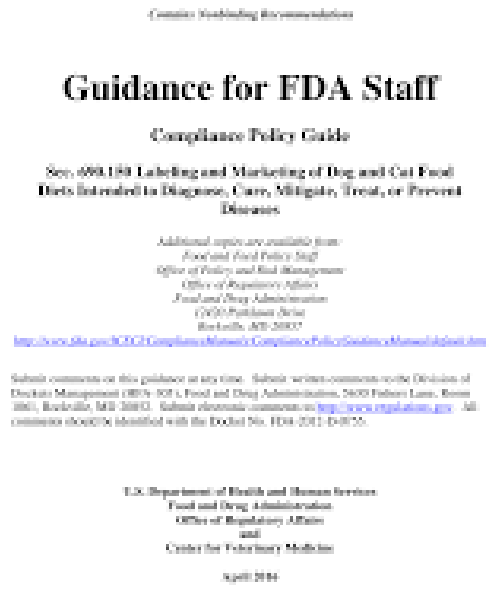
Compliance Policy Guides/Staff Manuals

- Explain FDA's policy on certain regulatory issues, mostly practical in nature.
- Mainly advise the center and field staff.
- Freedom of Information Act requests made them available to the public routinely. Published on FDA.gov.
- Staff manual guides (SMGs) describe FDA internal procedures.
- Cover organizations and functions, delegations of authority, administrative and program policies and Internal responsibilities



Guidance for FDA Staff

Compliance Policy Guide

Sec. 690.150 Labeling and Marketing of Dog and Cat Food Diets Intended to Diagnose, Cure, Mitigate, Treat, or Prevent Diseases

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Regulatory Affairs
and
Center for Veterinary Medicine

April 2014

Inspectional Guides

- Under “compliance programs”, intended to guide FDA personnel on proper procedures for evaluating industry compliance with the FD&C Act and other laws.
- Seem to be dormant. First put out internally, now subject to Freedom of Information Act.
- Many are approaching and over 30 years old, but still excellent sources for specific topics.

Enforcement Actions (in increasing order of “woe”.)

- Result of inspection or possibly examination of published materials (website, advertisements).
- Contained in the Establishment Inspection Report (EIR).
- Objectionable conditions discussed with management are informal observations that are minor in nature. Will be reviewed in the next inspection.

Enforcement Actions – FDA 483

- FDA 483 – by far the most common action.
- Always issued in conjunction with the inspection.
- Will detail an objectionable condition observed (and heavily documented) by the inspector.
- You have a chance to discuss the finding during the inspection. Maybe discuss possible solutions, though the inspector cannot commit.
- A failure to respond to a 483 may result in further sanctions.
- Usually, responses will be checked in the next inspection.


THE UNITED STATES OF AMERICA

FDA - NOTICE OF ACTION

Enforcement Actions – Warning and Untitled Letters

- Warning Letters – probably the most “dreaded” as they are relatively common and are made public.
- Issued for significant or repeated violations of regulations.
- Formatted in a similar way to a 483 and will follow the 483. Must respond in 15 days.
- Promised corrective actions will be checked. Best to continually update agency on progress.
- Untitled letters are less serious, not published.

TRANSMITTED BY FACSIMILE

WARNING LETTER

Enforcement Actions - Seizures

- Federal marshals can “seize” any materials deemed to present a danger to the public.
- FDA can order a recall. Generally, the firm itself agrees to a recall which simplifies the process.

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Debarment

- ***Debarment*** – a formal process where FDA will refuse to approve any application that has been aided by a person formally named. Conviction under the FD&C Act can lead to debarment by a different process. Debarment can be permanent or temporary.
- Firms will certify that no debarred person works for them in an application.
- ***https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/fda-debarment-list-drug-product-applications***

Consent Decree

- A firm that has committed serious continued violations of cGMP and other regulations may agree to a consent decree to avoid criminal prosecution.
- Firm agrees to outsource much of its Quality responsibilities to a third party.
- Substantial fines.
- Estimated costs of up to a billion dollars.

Criminal Trial

- Relatively rare, especially for firms. Generally, a civil agreement is reached.
- Repeated deliberate violations of the law and regulations precedes criminal prosecution, though this is not required.
- Employees prosecuted for lying to investigators.

Participating in FDA Policy Making

- These are in no particular order.
- Formal Meeting – within the approval process, meetings about trial strategy are common.
- FDA guidance is available on meetings.
- emails , phone calls and letters are possible, but will rarely lead to decisive actions.
- Public meetings solicit input and provide information to stakeholders.
- FDA allows speakers to address industry meetings.
- Advisory meetings with independent experts.

Citizen's Petition

- Citizen's Petition – for the purposes of policy, firm's are "citizens". A formal request to FDA to take an action or refuse an action. Often used in generic drug cases. Response is published. Other "citizens" may comment.
- Process is in 21 CFR 10.30, guidance documents are available. Tentative response within 180 days.
- Sham petitions are prosecuted by FTC.

Dispute Resolution

- Informal – scientific disputes may be resolved by experimentation. Or an agreement to change a procedure may be reached with the official reviewing the operation.
- Written requests can be submitted.
- Formal disputes resolved via 21 CFR 10.75. Up proper chain of command. A scientific dispute can be reviewed by independent investigators.
- User fee deadlines may apply.

Regulatory Hearings

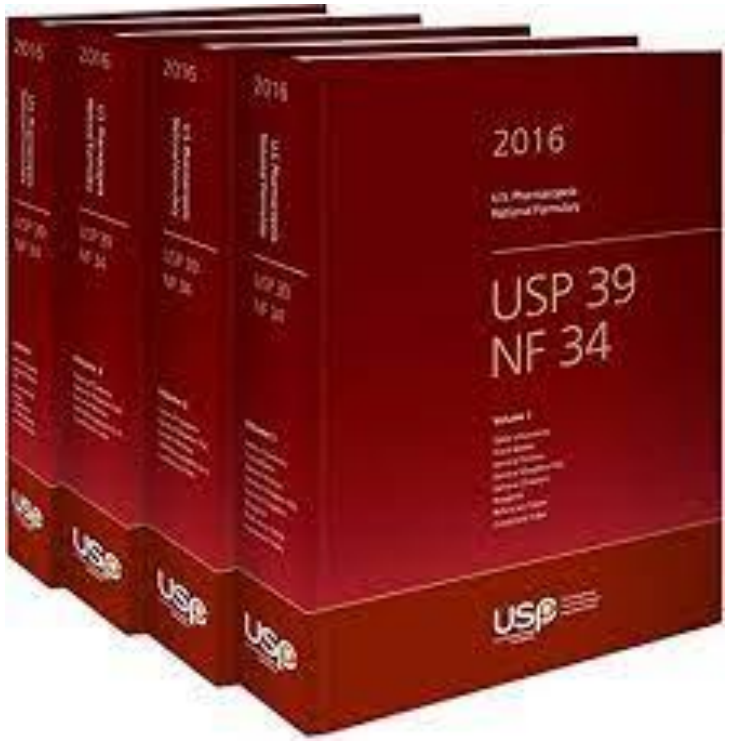
- FDA may decide or agree to offer the opportunity for regulatory hearings. They can there obtain information or discuss anticipated regulatory/legal actions.
- May be required by underlying statute.
- “Notice of opportunity for hearing” from FDA. Used in debarment cases. Only defense is an FDA mistake in identity.
- Generally public. May be presided over by administrative law judge.

Judicial Review

- Administrative Procedure Act provides for final judicial review of any final actions.
- FDA regulations note that affected persons can request judicial review. Judges will not grant review while civil processes still are possible.
- FD&C Act provides for direct judicial review of certain agency orders by adversely affected persons.

Other Sources of Requirements

- International Conference on Harmonisation (ICH). Formed in 1990. Attempt to standardize drug regulations among USA, EU and Japan. Other developed countries have observer status.
- Formally endorsed by FDA by publication as is in guidance documents.
- ISO International Standards Organization – ISO 9001 common for active ingredient precursors.
- United States Pharmacopeia, European Pharmacopœia and others. Often quote regulations. Offer safe harbors. USP tests are “final” where they exist but are often not enough to ensure quality.



FDA under the Biden Administration

- No commissioner appointed yet; older commissioner is in place as temporary appointment – Janet Woodcock.
- Generally, Democratic administrations allow tighter regulation of industry, Republicans avoid new regulation, but rollback is rare.
- Industry desires regulations as barriers to entry and they understand access to overseas markets relies on assurance of FDA oversight.

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Thank you