A Brief History of US Drug Law

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A BRIEF HISTORY OF US DRUG LAW

US drug law has evolved slowly since 1902, against fierce resistance, usually in response to horrific events that stimulated the public to demand congressional action.

The *Biologics Control Act of 1902*

- First federal regulation of biological products.
- In response to the deaths of 22 children who had contracted tetanus from contaminated horse serum. (Serum had been collected from a horse known to have tetanus).

The Pure Food and Drug Act (Wiley Act) 1906

- Main purpose was to ban foreign and interstate traffic in adulterated or mislabeled food and drug products.
- Required that active ingredients be placed on the label of a drug's packaging and that drugs could not fall below purity levels established by the USP or the NF.
- Response to Sinclair's *The Jungle*

Federal Food, Drug and Cosmetic Act (Copeland Act) 1938.

- Created the U.S. Food and Drug Administration (FDA)
- Authorized FDA to oversee the safety of food, drugs, medical devices, and cosmetics.
- Required that drugs be labeled with adequate directions for *safe* use.

1938 Act (Continued)

- Required pre-market approval of all new drugs based on proof of *safety (not efficacy)*.
- Prohibited false therapeutic claims for drugs. (Federal Trade Commission jurisdiction over drug advertising).
- Authorized factory inspections, and injunctions (seizures) as an enforcement tool.

1938 Act (Continued)

- Stimulated by Elixir of Sulfanilamide and the "American chamber of horrors" Lash Lure, Koremlu, Radithor, and the Wilhide Exhaler, which falsely promised to cure tuberculosis and other pulmonary diseases.

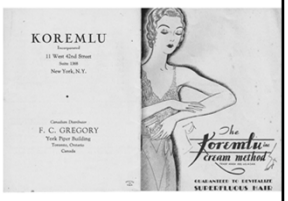
"Chamber of Horrors"

Elixir of Sulfanilamide caused the death of more than 100 people from kidney damage. Diethylene glycol was used to dissolve the drug. Manufacturer desired a liquid for marketing (not medical) purposes. No testing or research into solvent

"**Chamber of Horrors**"

Koremlu, a depilatory, contained thalium acetate. Widely marketed in the 1930s. It sold at $10 a jar, ($150 today). It caused baldness, pain and paralysis.

Thallium was a rat poison. Now banned in the US as too toxic. Koremlu didn't qualify as a drug and the FDA did not yet have power to regulate cosmetics.



"Chamber of Horrors"

Radithor advertised as "A Cure for the Living Dead"claimed to cure impotence, among other ills.

Eben Byers, American athlete and industrialist died from Radithor radium poisoning in 1932. He was buried in a lead-lined coffin; in 1965 his remains were still highly radioactive.

A 1990 *WSJ* article describing the Byers incident was titled "The Radium Water Worked Fine Until His Jaw Came Off"

Brief History of US Drug Law (6)

- ***Durham-Humphrey Amendment 1951.*** Defined/distinguished prescription and over-the-counter drugs.
- ***Kefauver-Harris Amendments 1962.*** Required proof of ***efficacy*** as well as safety before a new drug could be marketed, (retroactive to all drugs introduced after 1938)

1962 act (Continued)

- Gave FDA strict control over drug trials (required informed consent by subjects),
- Transferred regulation of *prescription* drug advertising from the FTC to the FDA,

1962 act (Continued)

- Established Good Manufacturing Practices (GMP) to be followed by pharmaceutical industry
- Increased FDA authority to access company production and control records to verify GMP was followed.
- Stimulated by the worldwide thalidomide disaster (narrowly averted in the USA).

Drug Efficacy Study Implementation (DESI)

- Response to the Kefauver-Harris requirement that all drugs be efficacious as well as safe.
- Classified pre-1962 drugs (already on the market) as either effective, ineffective, or needing further study.
- By 1984, final action taken on 3,443 products; of these, 2,225 were found to be effective, 1,051 were found not effective, and 167 were pending

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

- Outlined process for pharm mfg to file an Abbreviated New Drug Application (ANDA) for FDA approval of a generic drug
- Five-year period of market exclusivity awarded when the FDA approves an NDA for new chemical entity; during that period the FDA cannot approve a generic version of the drug.

Hatch-Waxman 1984 (continued)

- Extends patent life covering a drug by a portion of the time the drug is under regulatory review by the FDA, ensuring innovator companies that regulatory review will not unduly consume patent life
- Limits FDA evaluation of ANDA to (1) how generic applicant it is going to manufacture the drug and assure its quality and (2) a study showing that the drug they manufacture is bioequivalent.
- Stimulated by very few generics coming to market.

Generic Drug Enforcement Act (1992)

Authorized FDA to withdraw any application containing false data or to debar corrupt companies entirely, if need be.

User Fees Permitted

- **The Prescription Drug User Fee Act (PDUFA)** (1992) allows the FDA to collect a substantial fee from a drug manufacturer to fund the new drug approval process at the time a New Drug Application (NDA) In order to continue collecting such fees, the FDA must meet performance benchmarks, primarily related to the speed of the NDA review process.
- **Generic Drug User Fee Amendments (GDUFA)** (2012) enables FDA to assess industry user fees to bring greater predictability and timeliness to the review of generic drug applications.

FDA Documentation

- **FDA Drug Safety Communications**
- https://www.fda.gov/drugs/drug-safety-and-availabilit**y**
- **Enforcement Reports**
- https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/enforcement-reports https://www.accessdata.fda.gov/scripts/ires/index.cfm#tabNav_advancedSearch

FDA Documentation

- **Warning Letters**
- https://www.fda.gov/drugs/warning-letters-and-notice-violation-letters-pharmaceutical-companies/warning-letters-2019#OPDP

FDA Warning Letter to ZHP

"Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B)."

FDA Documentation

- **Inspection Citation** https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-citation
- Inspection (Form 483) Database https://www.fda.gov/media/107480/download

Conclusion(1) Bad Advice from President Reagan

January 20, 1981: From Reagan's Inaugural Address

Conclusion (2)

- The facts show that there are still many pharmaceutical manufacturers here and abroad who will put their own interests ($) ahead of public safety and the needs of sick people.
- Some will commit any kind of fraud to get or to keep their drugs on the market
- This may be due to greed or incompetence, but the result is the same -- unsafe and ineffective drugs

Conclusion (3)

- 80% of API & 40% of finished drugs come from India or China
- This proportion may increase as originator and generic manufacturers respond to governmental and market pressure to lower prices
- The FDA is unable to maintain proper (complete) and regular inspections even of US plants

Conclusion (4)

- The FDA is our only defense against unsafe and ineffective drugs.
- Some people want to weaken the FDA to prevent it from doing its job
- It is in our interest to support the FDA's role in protecting us.

Better advice from Reagan:

"Trust but verify"

comment after the signing of the INF Treaty with Mikhail Gorbachev in December 1987