

Key Historical Moments for United States FDA

Lessons Learned, Unlearned, &
Re-learned

Methods & Outline

- Re-visit the circumstances at selected moments in FDA history to:
- Clarify the tensions between industry & regulators from their distinct missions & responsibilities (stockholders vs. public)
- Demonstrate the arc of the first & most important FDA mission (drug Safety) as power ebbs & flows between industry & regulators, to gain perspective on current events

Preamble

- “The Jungle” by Upton Sinclair – graphic description of adulteration in meat packing industry is published in 1900
- Refusal of food manufacturers when asked to document safety of preservatives used, citing mass public hysteria by book & concerns from overhead costs of testing
- Harvey Wiley forms Bureau of Chemistry-1902

Preamble (continued)

- Wiley forms “Poison Squad”- first systematic approach to PK, focusing on borax, salicylic & sulfuric acids, Na Benzoate, & formaldehyde
- Steadily increasing quantities of each preservative are placed in meals, ingested by volunteers-periodic physical examinations, PK testing of urine, feces, sweat for retrieval of preservatives

First Pillar of FDA

quality assurance of products &
truthful labeling of ingredients

Pure Food & Drug Act of 1906

- Theodore Roosevelt's fondness for reading (*The Jungle*: lack of toilet facilities for meat packing plant workers & ubiquitous rodents) while eating breakfast sausages provides final piece to solidify push toward legislation
- Expands Bureau of Chemistry oversight to include adulteration, misbranding, & mislabeling in addition to safety testing of preservatives: "truth in labeling" coined

Observations & Conclusions

- Refusal of request for self-regulation & misreading of intensity of public concern coupled with engaged governmental leadership creates a climate ripe for governmental regulatory oversight
- Such oversight leads to expansion of original reason behind outcry (food preservatives only) with over-reach by government (from industry viewpoint) lays framework for future interplay

1906-1937

- Establishes the continuity and ensures the longevity of first pillar: “truth in labeling”
- Continued focus on branding
- Policing function (retrospective & reactive), fosters climate of automatic antagonism between industry & Bureau of Chemistry
- Distinct from future regulatory role of future FDA (prospective, more collaborative)

“Elixir” Sulfonilamide (I)

- Quality assurance functions of marketed drugs focuses on policing infractions vs. prevention
- 1932: para-amino benzene sulfonamide (Prontosil®) discovered by Gerhard Domagk
- 1934: reports of diethylene glycol toxicity from inadvertent ingestion in industrial workers unknown to pharmaceutical chemists

“Elixir” Sulfonilamide (II)

- No requirements for companies to perform safety testing of either active drug or diluents
- Competition for market share of childhood Strep places pressure on chemists to formulate palatable liquid formulation
- 1937: distribution of preparation containing 72% diethylene glycol passes “control laboratory testing for appearance, flavor & fragrance”

“Elixir” Sulfanilamide (III)

- September, 1937: 240 gallons in 1304 shipments distributed across USA
- 105 deaths / 353 exposures
- FDA response limited, since 1906 statute only to protect from adulterated food, misbranded drugs: thus only infraction was no ethanol
- Massengill fined \$26,000 & chemist Watkins commits suicide, Domagk awarded Nobel

Second Pillar of FDA

1938 Food, Drug, & Cosmetic Act
requires toxicity testing prior to
release of a new drug

Conclusions from First ½ Century

- Central theme for public benefit is that catastrophes must prompt policy change
- Outcome is an extension of safety focus & Bureau of Chemistry becomes FDA & is given a regulatory mandate into law
- Overhead costs & price per share drive desire to influence de-regulation by manufacturers
- Remaining issues: no efficacy requirements, no standardization & no FDA review of clinical trials with manufacturer in control of testing

European Continent without “Elixir” Sulfanilamide Disaster

- No focus on government-sponsored oversight of premarketing drug development processes
- Maintain reliance on guilds and professional societies for drug safety
- Disaster in USA causes a divergent response to enact laws requiring pre-marketing safety testing designed to delay or prevent drug approvals has no European equivalent

Thalidomide

- Top-selling sedative in Germany in 1960 with 700,000 chronic users followed aggressive marketing campaign emphasizing safety
- US License obtained in 1958, but marketing was delayed for 20 months by clinical trial safety testing
- Thus, phocomelia reports in 1960-1962: 4000 cases in Germany, 17 in USA

Linking Safety with Efficacy

vignettes leading to pre-marketing
efficacy regulations

Hepasyn ® (arginase)

- Rationale: in vitro observations that certain solid tumors over-express arginine that appears to accelerate cell division
- “Clinical trials” in 1950s contain anecdote & slipshod record keeping out of proportion to extraordinary claims of efficacy
- FDA review concludes: “without measure of activity, cannot establish effective dose & therefore cannot establish a safe dose”

Altafur ® (furaltadone)

- Forerunner of nitrofurantoin
- Within 6 months of marketing in 1959, 30 reports received by manufacturer of circulatory & neurological toxicity
- Manufacturer “Dear Doctor” letters alert to toxicity, but emphasis on “impressive therapeutic results” prompts FDA involvement
- FDA review fails to show evidence of efficacy, but no ability to regulate

Third Pillar of FDA

1962 Kefauver-Harris amendment
requires premarket efficacy testing

Caveat Emptor

- Shift over time from buyer beware to clarify and define role of emerging FDA, first as function of protection from harm then efficacy
- Shift from buyer (consumer) to watchdog for both purposes creates framework for modern day tension and lays groundwork for all future power balances between industry and FDA

Practolol & the Drug-lag

- Little impact of thalidomide in UK on policy change, continued “guild-model” of Germany
- First beta-1 selective beta blocker associated with 1130 cases of blindness & 1250 skin reactions “oculomucocutaneous syndrome”
- Post-1962 regulations empower FDA to withdraw products unsafe or ineffective & to require substantial evidence of efficacy before marketing prevents toxicity in USA & delay reinforces benefits of regulatory approach

Lessons from Regulatory Response

- Pattern emerging of the relationship in balance of power between regulators and industry
- Regulation beginning to appear intrusive when pejorative terms enter lexicon in 1970s (drug – lag) in aftermath of practolol
- Industry makes continued attempts to influence deregulation to detriment of safety

Lessons Unlearned

- Balance of power begins to shift to favor de-regulation coincident with 1982 legislation that markedly reduced government funding for FDA & allowed donations from industry directly to FDA
- This allows for a goal-alignment between manufacturers & regulators to streamline drug-approval with less power & resources given to phase 4 (pharmacovigilance)

Pillars Attacked & Damaged

- Practical outcomes of new alignment: acceleration of NDAs for “me-too” Rx
- “I think you can repeal the efficacy requirement altogether & let the market determine efficacy, since doctors are not going to prescribe drugs that do not work”: Rep. Joe Barton, Chair of House Commerce, 1996
- Rezulin ® removed in UK for hepatic failure in 1998, then allowed on US market in 1999

Ideology over Science (2000-present)

- Market forces as a panacea allows for coxib debacle & provides backdrop for unfolding saga of rosiglitazone & untoward cardiovascular outcomes
- Ideology informs policy in other arenas: marketing of “morning after” contraception (Plan B ®) delayed; line between industry & regulation blurs to extent that FDA Commissioner resigns due to continued financial interests in regulated companies

Lessons relearned?

Historical Imperatives to Move
Forward

Summary (I)

- Differential national impacts of thalidomide & practolol disasters underscores superiority of regulatory oversight codified by government
- Peer-pressure oversight by professional societies, even if driven by data, insufficient protector of public safety “guild” or “market” approaches are ineffective
- Conflict of interest must be actively prevented by aggressive separation of stakeholders

Summary (II)

- Current lessons to be relearned is the return to the safety focus of the second pillar, updated by infusing of resources and enactment of laws that de-link pharmacovigilance with Phase I-III
- These resources need to be used for development of national / international databases that make it easier for reporting and tracking