

Government 1521  
Bureaucratic Politics:  
Government, Military,  
Social and Economic Organizations

D. Carpenter

Lecture 15: Reputation and U.S.  
Pharmaceutical Regulation

---

---

---

---

---

---

---

---

The Power of the FDA  
over Pharmaceuticals

Patients are two removes from drugs: physician and FDA.  
Gatekeeping power – “veto” over product development –  
is life-and-death say over careers, companies, products,  
ads, labeling, even patients.

FDA regulates all clinical research with new  
pharmaceuticals, devices, vaccines, any new product  
claim (indication).

FDA is primary author and enforcer of human subjects  
protections in U.S.

---

---

---

---

---

---

---

---

Today

How did we get here?

How is FDA authority exercised? How can we  
best understand FDA decisions, rulemaking?

How do these Qs shed light on contemporary  
issues (Vioxx), others?

---

---

---

---

---

---

---

---

An original 1-gallon bottle of Elixir Sulfanilamide



Wax, P. M.  
Ann Intern Med 1995;122:456-461

Annals of Internal Medicine

---

---

---

---

---

---

---

---

## FDA Pharmaceutical Regulation

1. Origins in 1906 Pure Food and Drug Act: Regulation of patent medicines.

- Regulation of pharmaceutical advertising
- Aimed mainly at food (Upton Sinclair's *The Jungle*)
- precedent for govt ability to remove unsafe products from interstate commerce

2. KEY Leg: Food Drug and Cosmetic Act of 1938:

- (a) Follows sulfanilamide scandal of 1937 (>120 deaths)
- (b) Establishes FDA as market gatekeeper.
- (c) MANDATORY PRESCRIPTIONS (separate but related legislation): Establishes doctor as conduit for prescription drugs (death blow to patent medicine industry). Contemporary analog: vitamin and nutritional supplement industry ("Have you had your ginkgo biloba today?").

---

---

---

---

---

---

---

---

The Usual Story:  
Before Thalidomide and After Kelsey



---

---

---

---

---

---

---

---

## FDA Pharmaceutical Regulation

1. 1962 Amendments to 1938 Act:
  - Follows thalidomide scandal of 1959-1960 (FDA's Frances Kelsey keeps it out of U.S.)
  - Adds efficacy review to safety review
  - FDA drug regulations create modern clinical trial system
2. Basics of drug development:
  - (a) IND (Investigational New Drug) Stage: comprised of Phase I (safety), Phase II (safety and efficacy) and Phase III trials (verification of safety and efficacy, plus adverse reaction monitoring). Avg: 6 years (↑ing recently).
  - (b) NDA (New Drug Application) Review: drug assigned to review team (chem, pharm, mol-bio, stat, MDs), overseen by FDA division head. Avg: 1-1.5 years (↓ing recently).

---

---

---

---

---

---

---

---

## A Different Story

Big changes in medicine, pharmacology, and FDA's Bureau of Medicine in 1950s

Arrival of pharmacologists to FDA. F. O. Kelsey the latest.

Organizational Learning: Chloromycetin, MER-29, others.

Efficacy: Need something to balance safety. Regulations and drug approvals explicitly and implicitly incorporate efficacy **7-10 years** before '62 legislation

---

---

---

---

---

---

---

---

## A Different Story

FDA officials (Ralph Smith, Kelsey, others) speak out in favor of (1) more and regulated pre-market clinical testing, (2) advertising regulation, (3) efficacy standard.

AMA bodies opposed, but specialty medical societies (Am. Psych Association) in favor.

Thalidomide confirms (1) internal FDA beliefs, (2) external FDA reputation.

1963 IND regs underway at least 5 years before thalidomide.

---

---

---

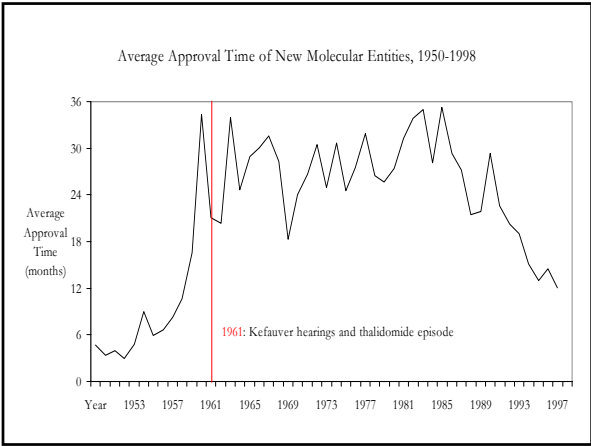
---

---

---

---

---




---

---

---

---

---

---

---

---

**Theme: Reputation**

FDA exercises unique social, political, scientific and economic power because of its **organizational reputation** (scientific accuracy and consumer protection).

REPUTATION: Beliefs embedded in audiences.  
 What makes an organization unique, effective?

Analogy: Medicine, university, church, military.

Audiences: general ("the public," students) and specific (cardiologists, physicists, bishops)

---

---

---

---

---

---

---

---

**FDA's Reputation**

Belief: "They keep us safe. They generally get it right. They're tough, rigorous."

Belief not necessarily the truth, for any org.

Audiences: Public, scientific/medical, political (patient advocacy groups), functional (firms).

FDA's aim is to enhance and preserve this reputation.

So, how did we get here....?

---

---

---

---

---

---

---

---

## Folk Wisdom

First sulfanilamide (1937)

Then safety (1938)

Then thalidomide (1959-1961)

Then efficacy (1962, 1963)

Not quite

---

---

---

---

---

---

---

---

## Reduction of Visible Error

**Type I** (“commission”): Approve a bad drug.

- See approval as irreversible
- Less attention to Phase IV and post-marketing surveillance
- More attention to pre-approval

**Type II** (“omission”): Reject or delay a good drug.

- Type II errors not publicized unless an audience is there to publicize them.
- Not firms, but patient advocacy groups

---

---

---

---

---

---

---

---

## Procedural Conservatism

Drug approval viewed as irreversible. Can withdraw the drug, not the mistake.

FDA unlikely to approve drugs quickly, likely to ask for more studies.

If constrained on NDA (approval) end, CDER may ask for more studies at IND end.

Drug approval often slows (stringency rises) in response to visible error.

---

---

---

---

---

---

---

---

## Inherent Uncertainty

Because no pharmacologically active drug substance is entirely free of risk, the conclusion that a drug has been shown to be “safe for use,” is actually no more than an opinion...

Accordingly, risk to benefit assessments are inherently arguable, all the more so because each turns not only on personal sentiments about the nature of risks and benefits of a drug, but upon incomplete and imperfect information concerning the drug’s risks.<sup>[1]</sup>

[1] Memorandum from Paul Leber, M.D., to Robert Temple, M.D., Director, Office of New Drug Evaluation I, Subject “NDA 20-658, *Requip*™ [ropinerole HCl tablets],” pp. 6-7. Public File for NDA 20-658; Center for Drug Evaluation and Research, U.S. Food and Drug Administration.

---

---

---

---

---

---

---

---

## Inherent Uncertainty and Flags

...in our safety review of NDA study we usually do not get definitive answers based on unequivocal data but are forced to interpret “flagging” events. We think that in the case of bromfenac, we have seen a “liver flag” that can be only fully explored through responsible marketing of the drug.<sup>[1]</sup>

[1] Rudolph Widmark, M.O., “Memo regarding hepatotoxicity of bromfenac,” undated [December 1995], p. 3; NDA File 20-535, Center for Drug Evaluation and Research, U.S. Food and Drug Administration. See also “Wyeth-Ayerst *Duract* Hepatotoxicity Warning was Suggested during NDA Review,” *Pharmaceutical Approvals Monthly* (F-D-C Reports) (April 1998), p. 34.

---

---

---

---

---

---

---

---

## Effect of Media Coverage of Disease

**Measure:** Annual story counts on diseases in LEXIS-NEXIS, *Washington Post*, and Vanderbilt TV news archive, 1969-1998

**Finding:** Controlling for disease severity (mortality, hospitalization costs), prevalence, age profiles, and disease-specific effects, & diz organization, increased disease coverage in media yields shorter approval times.

**Sample effect:** One std. dev. ↑ in *Post* stories on a disease (= 126) in 3 yrs *before* submission yields a 2.6- to-3.4-month ↓ in review time.

---

---

---

---

---

---

---

---



## Patient Politics Dominates

First few drugs are potential Type II (rejection) errors, and visible.

Implications: (1) Early “entrants” to a given disease market receive most favorable regulatory treatment, but has nothing to do with “rent-seeking” or “capture.”

(2) Firms target indications for which there are few alternatives, add (more profitable) supplemental indications later.

---

---

---

---

---

---

---

---

## Why the Acceleration?

Many factors, but several are crucial:

- (1) Staff (Congress, and user fees)
- (2) Patient organization and visibility of disease
  - Examples: AIDS advocates, NAMI, combined cancer lobbies.
  - Health-conscious society.

---

---

---

---

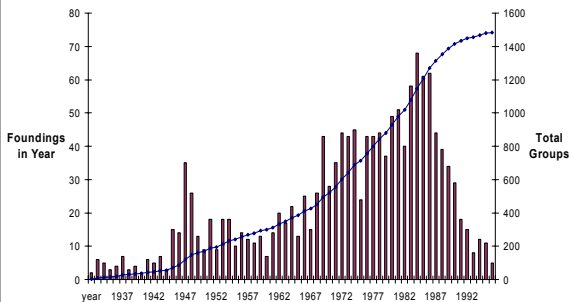
---

---

---

---

Figure 1:  
Growth of Disease-Advocacy Groups, 1993-1997  
(foundings for 1996 likely underestimated)



---

---

---

---

---

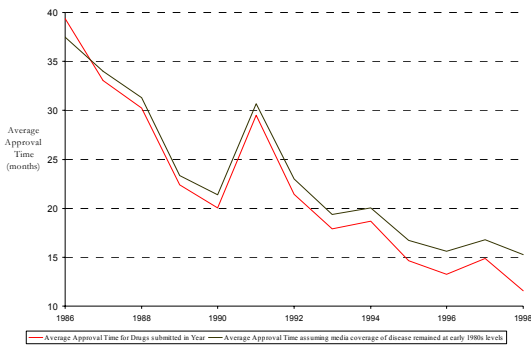
---

---

---



Figure 3: Reduction in Average Review Time, with and w/o controls for increasing public salience of disease




---

---

---

---

---

---

---

---

---

---

### SUM: Reputation can slow, accelerate CDER

**Slow:** For diseases with many treatments, poor visibility, generally slow approval and regulatory stringency

**Fast:** For diseases with no or few existing treatments, and that have well-organized and visible sufferers and advocates, can see less regulatory stringency, quicker decisions.

---

---

---

---

---

---

---

---

---

---

### Pre-Market or Post-Market?

#### The Logic of Reputation Protection

Decreased emphasis on post-marketing surveillance

Less reliance upon recall than you might guess (recall = publication of error)

Less reliance on "Phase IV" trials.

Generally: More reliance upon pre-market review, less reliance on post-approval learning.

---

---

---

---

---

---

---

---

---

---

## Reputation and the Logic of Product Recall

September 30, 2004: Merck's Vioxx (rofecoxib)  
voluntarily withdrawn.

FDA induces firms to recall, even when the FDA  
shares responsibility for faulty approval.

But how does the public observe this event?

---

---

---

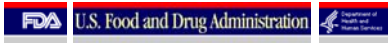
---

---

---

---

---



[FDA Home Page](#) | [Search FDA Site](#) | [FDA A-Z Index](#) | [Contact FDA](#)

### FDA News

#### FDA Issues Public Health Advisory on Vioxx as its Manufacturer Voluntarily Withdraws the Product

The Food and Drug Administration (FDA) today acknowledged the voluntary withdrawal from the market of Vioxx (chemical name rofecoxib), a non-steroidal anti-inflammatory drug (NSAID) manufactured by Merck & Co. FDA today also issued a Public Health Advisory to inform patients of this action and to advise them to consult with a physician about alternative medications.

Merck is withdrawing Vioxx from the market after the data safety monitoring board overseeing a long-term study of the drug recommended that the study be halted because of an increased risk of serious cardiovascular events, including heart attacks and strokes, among study patients taking Vioxx compared to patients receiving placebo. The study was being done in patients at risk of developing recurrent colon polyps.

"Merck did the right thing by promptly reporting these findings to FDA and voluntarily withdrawing the product from the market," said Acting FDA Commissioner Dr. Lester M. Crawford. "Although the risk that an individual patient would have a heart attack or stroke related to Vioxx is very small, the study that was halted suggests that, overall, patients taking the drug chronically face twice the risk of a heart attack compared to patients receiving a placebo."

Dr. Crawford added that FDA will closely monitor other drugs in this class for similar side effects. "All of the NSAID drugs have risks when taken chronically, especially of gastrointestinal bleeding, but also liver and kidney toxicity. They should only be used continuously under the supervision of a physician."

---

---

---

---

---

---

---

---

## Why Vioxx?

Remember the arthritis effect. Vioxx got priority  
NDA review (< 6 months).

Also, the "Merck effect": Merck has "good" org  
reputation at the FDA, in industry.

This may be "favoritism," may be rational.

Recall good for Merck, both to limit legal liability,  
and to preserve credibility with FDA.

---

---

---

---

---

---

---

---

## Will the FDA take a hit?

Maybe: Evidence that David Graham and others were not believed, perhaps squelched, re Vioxx.

Maybe not: FDA epidemiology wins public and scientific victories.

- Graham and Kaiser study of Vioxx.
- Mosholder and study of adolescent/teenage suicidality with SSRIs (esp Paxil). Columbia Univ "confirmation" of his results.
- This morning: FDA had flagged Chiron vaccine plant in June 2003

SUM: Scientific (career) officials at FDA seem to have been getting it right.

---

---

---

---

---

---

---

---

## Policy Lessons

Cynical? Yes, to some degree. But all organizations have motivations and incentives. All pay attention to their reputation.

Proper Q: Does reputation-seeking serve us well compared to other goals that might drive such an agency (turf)?

Answer: Depends. Perhaps proper balance between pre- and post-market regulation is thrown off. However, more scientifically-guided R&D process in pharmaceuticals than ever before, and this has been led by FDA.

---

---

---

---

---

---

---

---