Regulating the Pharmaceutical Industry

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General Remarks about the Pharmaceutical Industry

History, Pricing, Drug Pipeline, Blockbuster Drugs, Legislative Trends, Federal Courts
FDA: important legislative events

1906: Food, Drug & Cosmetics Act (‘label’) -- Upton Sinclair’s *The Jungle*

1938: FDC Amendments (‘safety’) -- *the Elixir of Sulfanilamide*

1962: Harris-Kefauver Bill (‘efficacy’) -- *the Thalidomide Disaster*

1984: Hatch-Waxman Bill (‘price’) -- *created the generic drug industry*
Role of the Federal Courts

U.S. v. Johnson (1911)
The Shirley Amendment (1912)

Roche v. Bolar (1970)
Drug Price Competition & Patent Term Restoration Act (‘Hatch-Waxman’)

‘Final Pediatric Rule’ (1998)
Association of American Physicians & Surgeons v. FDA
Best Pharmaceuticals for Children Act (2002)
Why Drug Discovery is Difficult

- Must discover a key enzyme ‘target’

- Must have a clear ‘therapeutic hypothesis’

- ADME - absorption (get to target site), distribution (not somewhere else with side effects), metabolism (survive liver enzymes), excretion (must be cleared)
Arachidonic Acid Metabolism (Revisited): Thromboxanes and Prostacyclin

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Physiological Effect</th>
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<tbody>
<tr>
<td>$\text{TxA}_2$</td>
<td>Platelet Aggregation, Vasoconstriction</td>
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<tr>
<td>$\text{PGI}_2$</td>
<td>Inhibits Platelet Aggregation, Vasodilation</td>
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Reminder: Enzymes Targeted by Drugs

Aspirin Irreversibly Inhibits COX by Acetyling Serine 530
Crystal Structure of PGH₂ Synthase Complexed with COX-2 Selective Inhibitor SC-558

Catalytic Domain

Peroxidase Active Site

Cyclooxygenase Active Site Pocket

Membrane-Binding Domain

EGF Domain

• Manufacturers continue to sell unsafe foods and drugs

• Drug advertising had no standards
• Journalists expose abuses
  ° Collier’s magazine
  ° Upton Sinclair’s novel, *The Jungle*
1906 Pure Food and Drugs Act
- Prohibited interstate commerce of unsafe drugs
- Required proper labeling
- Identified official standards for drugs
• Early labels decorative

• Drug labels today
  ° Indications
  ° Dosage
  ° Possible interactions
  ° Other information
• Shortcomings of the 1906 Act
  ° Lack of inspections
  ° Inability to control false claims

• Sulfanilamide disaster
Sulfa Drugs and Folic Acid

Sulfa Drugs

para-aminobenzoic acid (PABA)

Sulfonamide base structure

[Chemical structure of sulfa drugs and folic acid]
The Food, Drug, and Cosmetic Act of 1938
- Required proof of safety
- Authorized inspections
- Outlawed false claims
• Food, Drug, and Cosmetic Act of 1938
  ° Complete list of ingredients
  ° Directions for safe use
• Calls for revisions of the drug laws
• Thalidomide disaster
Thalidomide approval stalled in U.S.

Thousands were harmed worldwide
• The Kefauver-Harris Amendments of 1962
  ° Required proof of effectiveness
  ° Gave FDA control over investigations
  ° Gave FDA authority to regulate advertising of prescription drugs
  ° Established good manufacturing practices
Implementing the 1962 Amendments

Upjohn & FDA
The case of Panalba (1970)

J. Scott Armstrong, “Social irresponsibility in management”
J. of Business Research, Sept 1977, 185-213

Science, August 29, 1969
Investigational New Drug Application (IND)

IND is not a marketing application

IND is a request for exemption from the federal statute which prohibits transport of unapproved drugs in interstate commerce
New Drug Application (NDA)

NDA is an application for marketing

NDAs are submitted for:

- New molecular entity (NME)
- New formulation of previously approved drug
- New combination of two or more drugs
- New indication (claim) for already marketed drug
NDA Actions

**Approval Letter**: States that the drug is approved and includes the label

**Approvable Letter**: Signals that the drug can be approved, after correction of deficiencies, sometimes limited to labeling

**Not Approvable Letter**: Lists the deficiencies and explains reasons for non-approval
Drug Price Competition & Patent Term Restoration Act

Hatch-Waxman virtually created the generics industry

1984
The Hatch-Waxman Compromise (Generics)

- Can conduct research during the patent life of product (removing *de facto* patent extension)
- Not required to prove safety and efficacy, only bioequivalence (*saving money*)
- First to file an abbreviated NDA obtains six months market exclusivity (paragraph IV certification)
The Hatch-Waxman Compromise
(Brand-Name Company)

• Granted extended patent life in compensation for long approval times (six months/year of waiting for approval)

• After ANDA is filed by a generic company, brand-name company gets 30 month stay if they sue the generic within 45 days (lifted if patent expires or declared invalid)

(Remember: each year of sales on a ‘blockbuster’ drug is worth billions of dollars in profits)
‘Gaming the System’

“Generic Drug Entry Prior to Patent Expiration: An FTC Study” July 2002
Nexium/Prilosec/Omeprazole

Fighting off the Generics

Omeprazole: Therapeutic Hypothesis
The Proton Pump
Omeprazole: Mechanistic Hypothesis

Omeprazole

Blood

Parietal cell canaliculus lumen

Sulphenamide intermediate

Enzyme-inhibitor complex

Cys-813

H^+K^+-ATPase

3 steps
Structures of Omeprazole and Esomeprazole
Other Important Legislative Acts

1980 - Bayh-Dole Act - Universities can obtain patents from NIH-funded research

1983 - Orphan Drug Act - incentives (7yr market exclusivity) to develop drugs for rare conditions (Gleevec)
The Prescription Drug User Fee Act of 1992
- FDA allowed to collect fees from industry
- FDA required to reduce review time
The Best Pharmaceuticals for Children Act of 2002

Off-label prescriptions, six months market exclusivity, clinical trials, legislative history

Post-Marketing Surveillance in Wake of VIOXX Recall

Phase IV
(voluntary)

An Example of Post-Marketing Action

Terfenadine (SELDANE®) Antihistamine

“NME” or New Molecular Entity

US Approval (1985)

Safety and efficacy data from clinical trials including several thousand patients (4 yrs European experience)

2nd generation: “Nonsedating” claim was novel
SIGNALS

1983--First non-US cases of cardiac rhythm disturbances reported

1987--First US cases reported

Rhythm “torsades-de-pointes” was unusual

“Typical” patient was young (mid-30’s), female, and otherwise healthy

1989--Contribution of co-administered drugs (drug-drug interactions)
ACTIONS - I

1987 Label changed to include cardiac arrhythmia (irregular heart beat), syncope (loss of consciousness), and hypotension (low blood pressure) under Adverse Events.

1989 More label changes to include potential drug interactions under Warnings.

1990 & 1996 Manufacturer required to send “Dear Doctor” letter to all potential prescribers.

1992 “Black Box” Warning added to label.
ACTIONS - II

1996--Survey commissioned by Agency showed continued co-prescription of contra-indicated medications (drug-drug interactions)

1998--Seldane voluntarily withdrawn from the Market
Concluding Remarks