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)

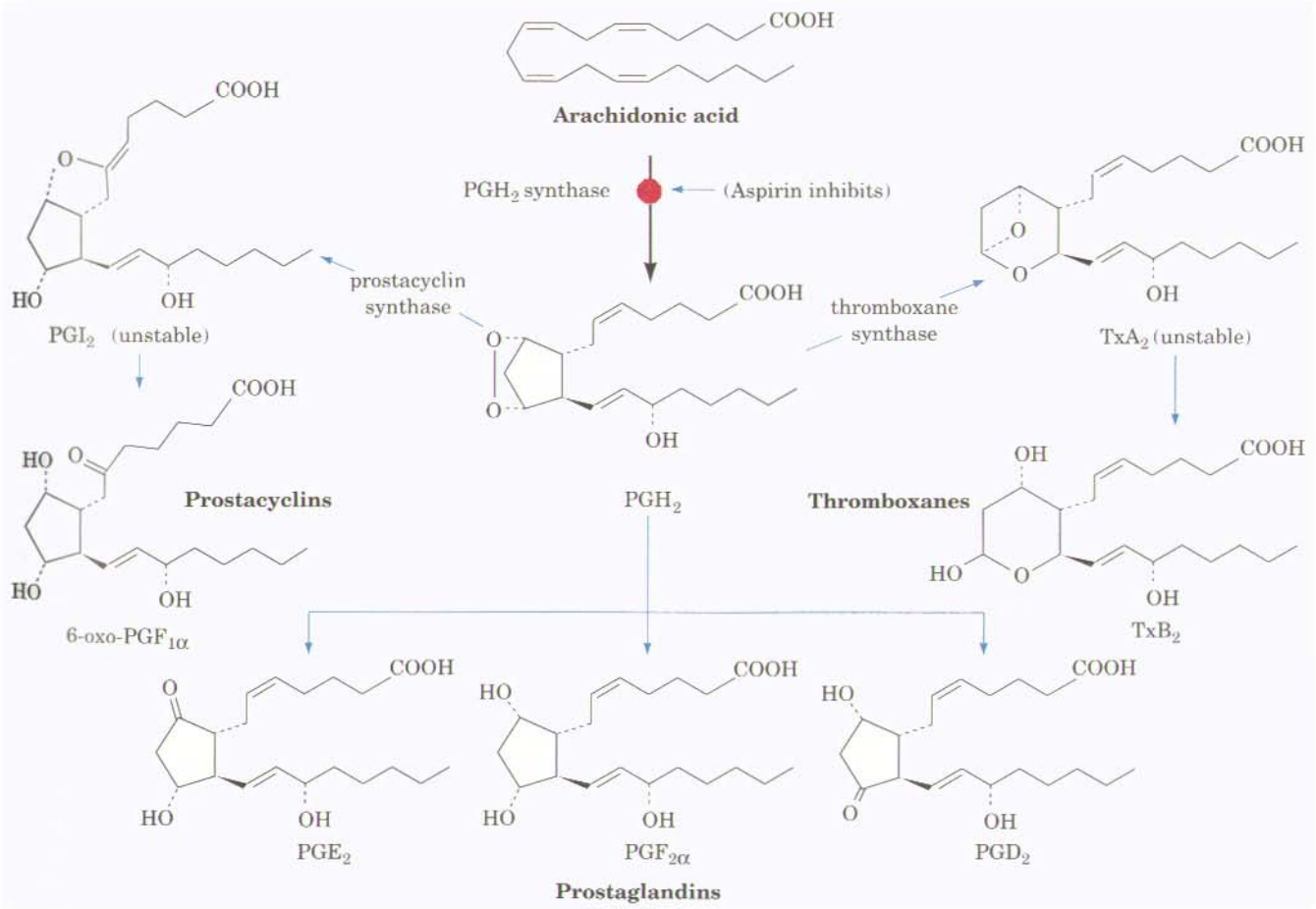
Association of American Physicians & Surgeons v. FDA

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)

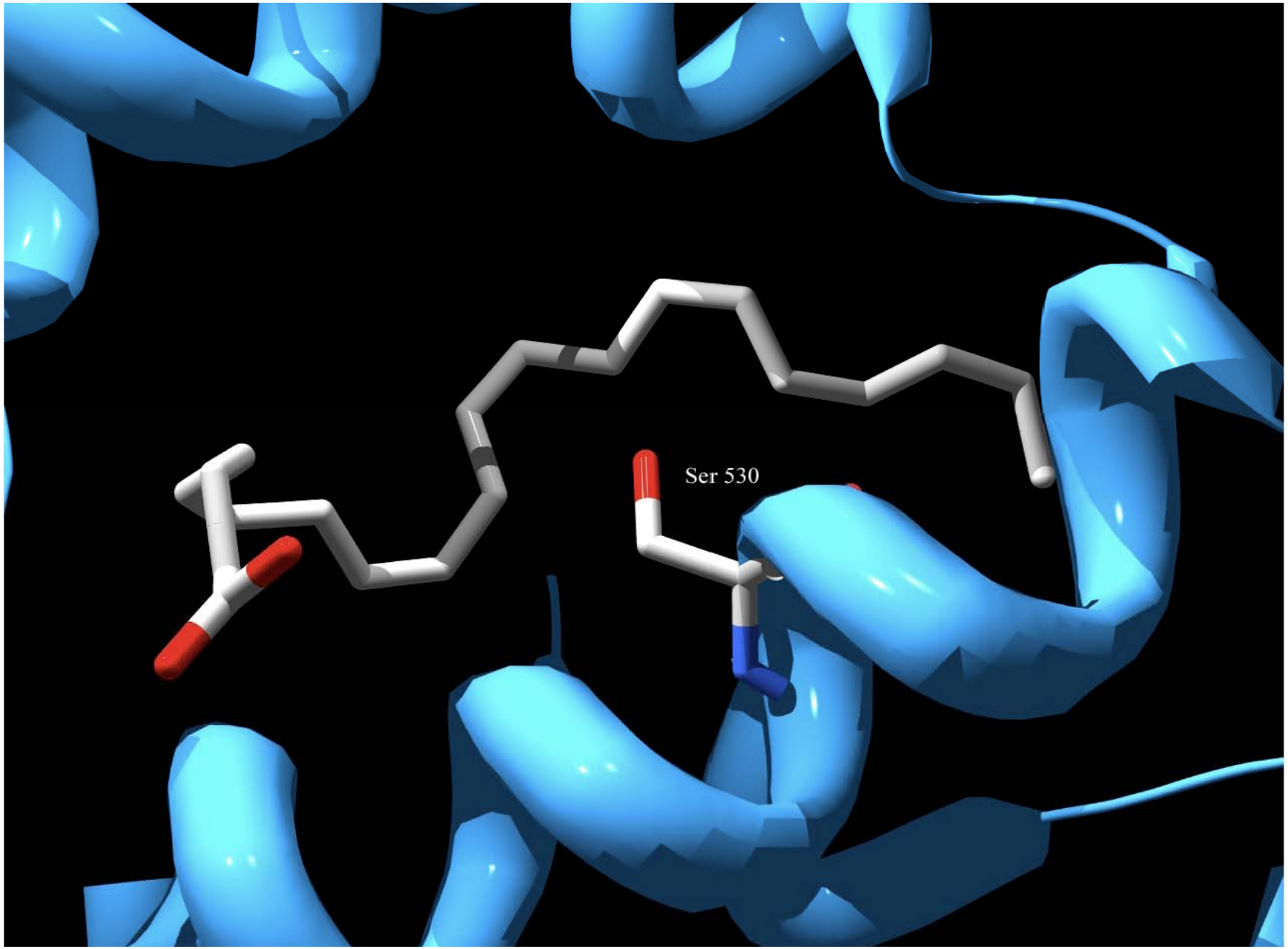
Arachidonic Acid Metabolism (Revisited): Thromboxanes and Prostacyclins



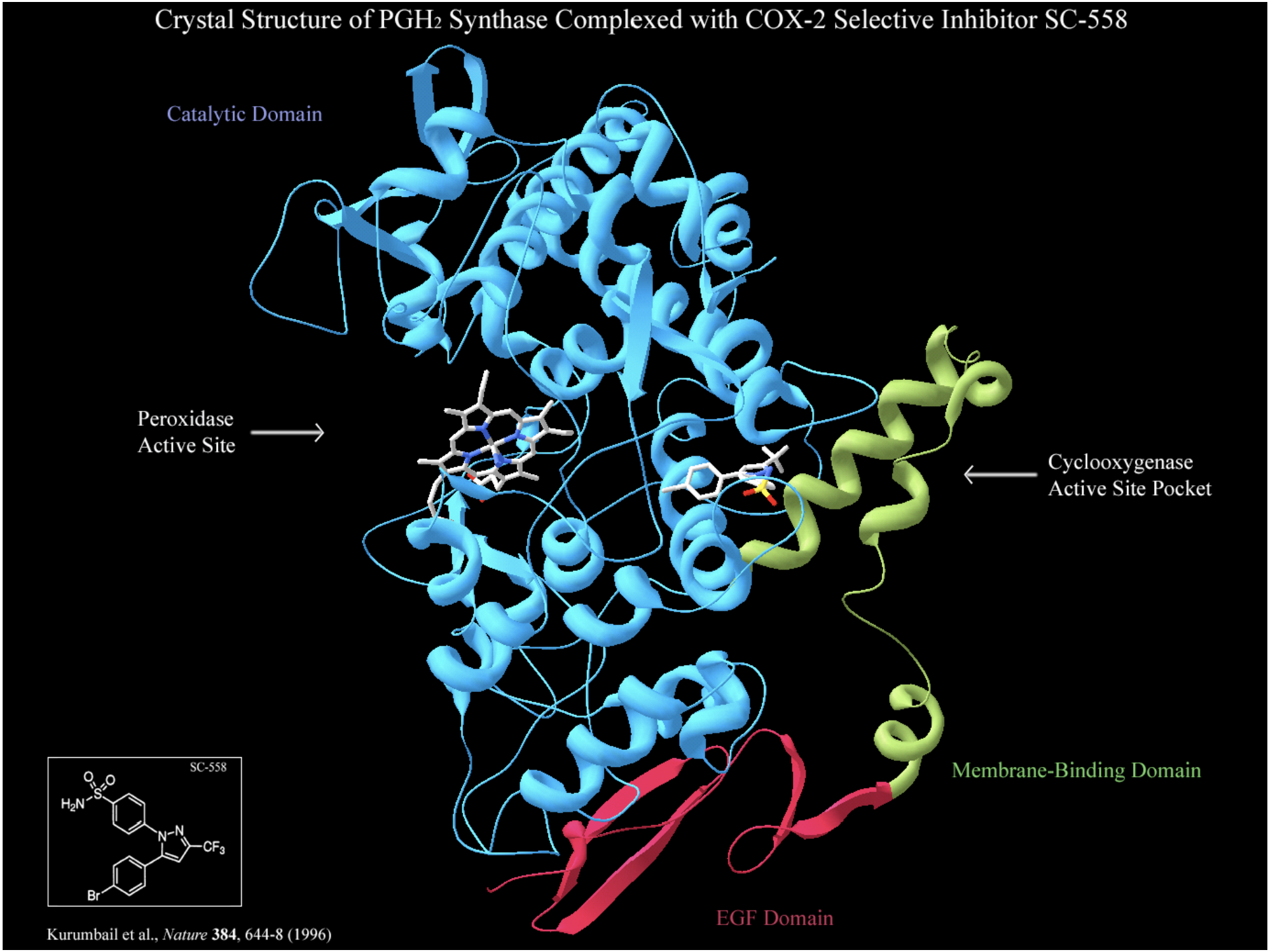
Molecule	Physiological Effect
TxA_2	Platelet Aggregation, Vasoconstriction
PGI_2	Inhibits Platelet Aggregation, Vasodilation

Reminder: Enzymes Targeted by Drugs

Aspirin Irreversibly Inhibits COX by Acetylating Serine 530



Crystal Structure of PGH_2 Synthase Complexed with COX-2 Selective Inhibitor SC-558



Kurumbail et al., *Nature* **384**, 644-8 (1996)

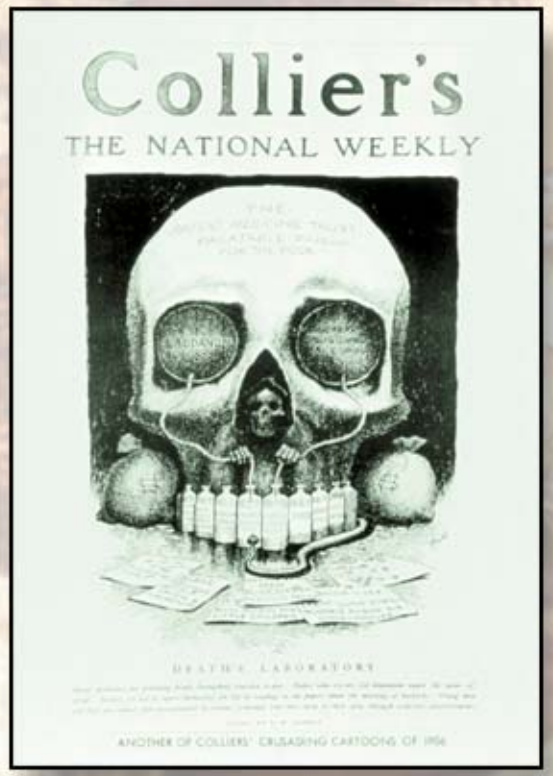
1906

LABELING DRUGS

- **Manufacturers continue to sell unsafe foods and drugs**
- **Drug advertising had no standards**

1906

LABELING DRUGS



- **Journalists expose abuses**
  - ***Collier's* magazine**
  - **Upton Sinclair's novel, *The Jungle***

1906

LABELING DRUGS

- **1906 Pure Food and Drugs Act**
  - **Prohibited interstate commerce of unsafe drugs**
  - **Required proper labeling**
  - **Identified official standards for drugs**

DRUG LABEL EVOLUTION I

- **Early labels decorative**
- **Drug labels today**
  - **Indications**
  - **Dosage**
  - **Possible interactions**
  - **Other information**

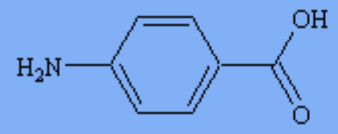
1938

DRUG SAFETY

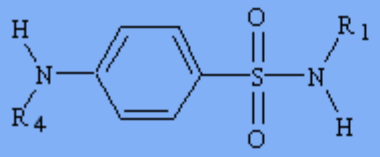
- **Shortcomings of the 1906 Act**
  - **Lack of inspections**
  - **Inability to control false claims**
- **Sulfanilamide disaster**

Sulfa Drugs and Folic Acid

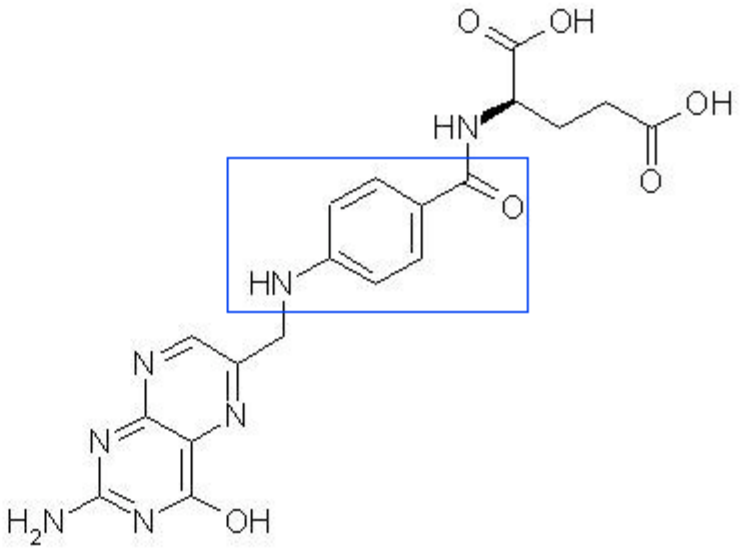
Sulfa Drugs



para-aminobenzoic acid
PABA



Sulfonamide base structure



1938

DRUG SAFETY

- **The Food, Drug, and Cosmetic Act of 1938**
  - **Required proof of safety**
  - **Authorized inspections**
  - **Outlawed false claims**

DRUG LABEL EVOLUTION II

- **Food, Drug, and Cosmetic Act of 1938**
  - **Complete list of ingredients**
  - **Directions for safe use**

1962

DRUG EFFICACY

- **Calls for revisions of the drug laws**
- **Thalidomide disaster**

1962

DRUG EFFICACY

- **Thalidomide approval stalled in U.S.**
- **Thousands were harmed worldwide**

1962

DRUG EFFICACY

- **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**

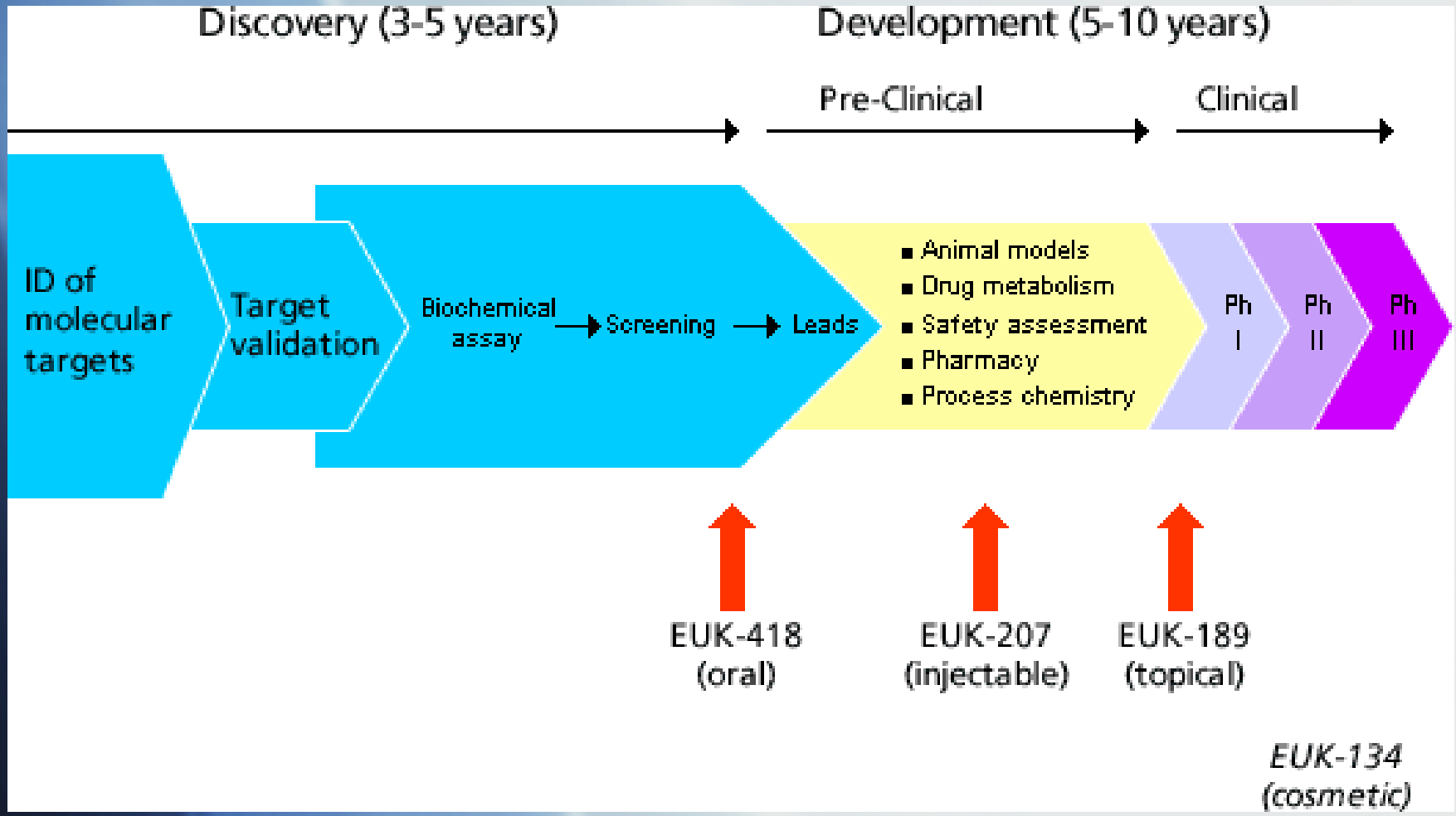
Implementing the 1962 Amendments

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


Discovery (3-5 years)
Development (5-10 years)
Pre-Clinical
Clinical
ID of molecular targets
Target validation
Biochemical assay
Screening
Leads
Animal models
Drug metabolism
Safety assessment
Pharmacy
Process chemistry
Ph I
Ph II
Ph III
EUK-418 (oral)
EUK-207 (injectable)
EUK-189 (topical)
EUK-134 (cosmetic)

Investigational New Drug Application (IND)

IND is not a marketing application

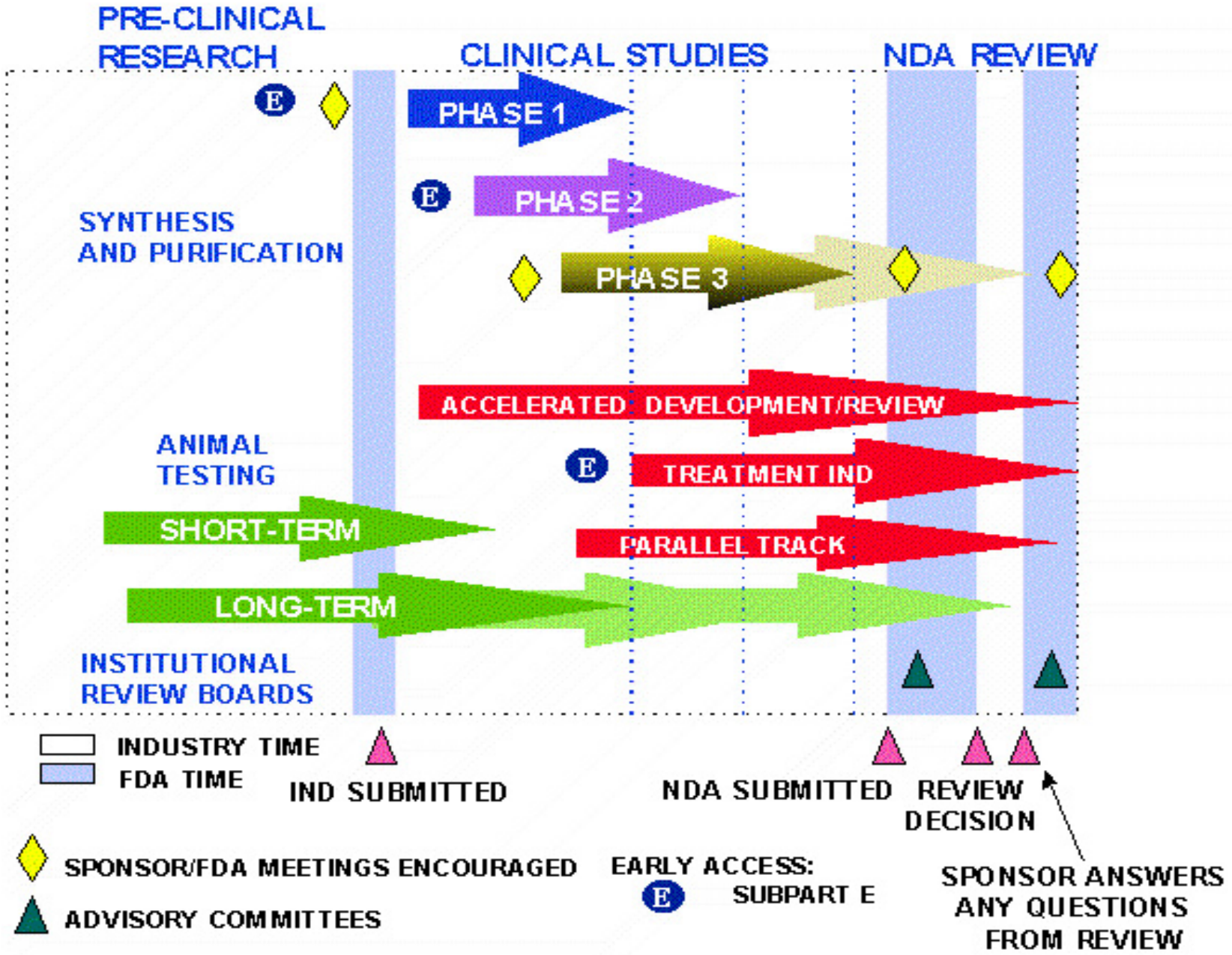
IND is a request for exemption from the federal statute which prohibits transport of unapproved drugs in interstate commerce

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


PRE-CLINICAL RESEARCH
CLINICAL STUDIES
NDA REVIEW
E
PHASE 1
E
PHASE 2
SYNTHESIS AND PURIFICATION
PHASE 3
ACCELERATED DEVELOPMENT/REVIEW
ANIMAL TESTING
E
TREATMENT IND
SHORT-TERM
PARALLEL TRACK
LONG-TERM
INSTITUTIONAL REVIEW BOARDS
INDUSTRY TIME
FDA TIME
IND SUBMITTED
NDA SUBMITTED
REVIEW DECISION
SPONSOR/FDA MEETINGS ENCOURAGED
EARLY ACCESS:
E
SUBPART E
SPONSOR ANSWERS ANY QUESTIONS FROM REVIEW
ADVISORY COMMITTEES

NDA Actions

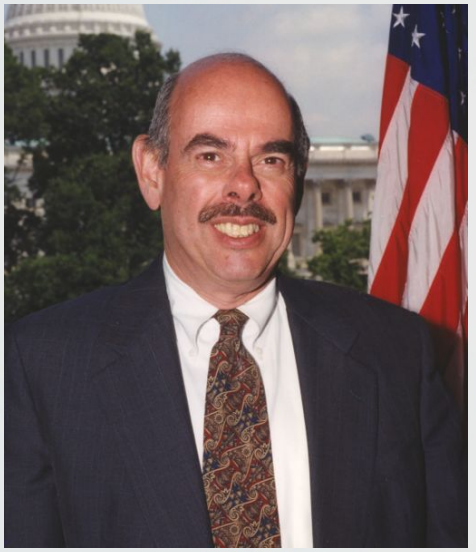
Approval Letter: States that the drug is approved and includes the label

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

1984



Hatch-Waxman virtually created the generics industry

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

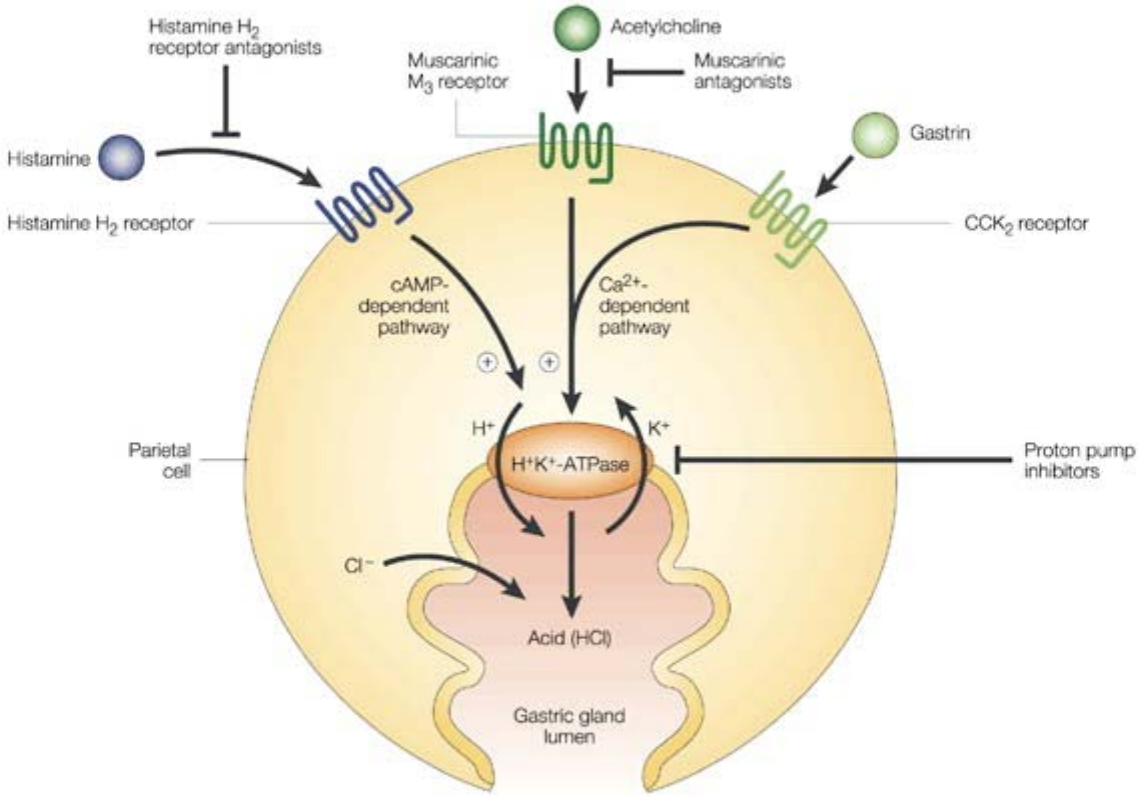
Nexium/Prilosec/Omeprazole

Fighting off the Generics

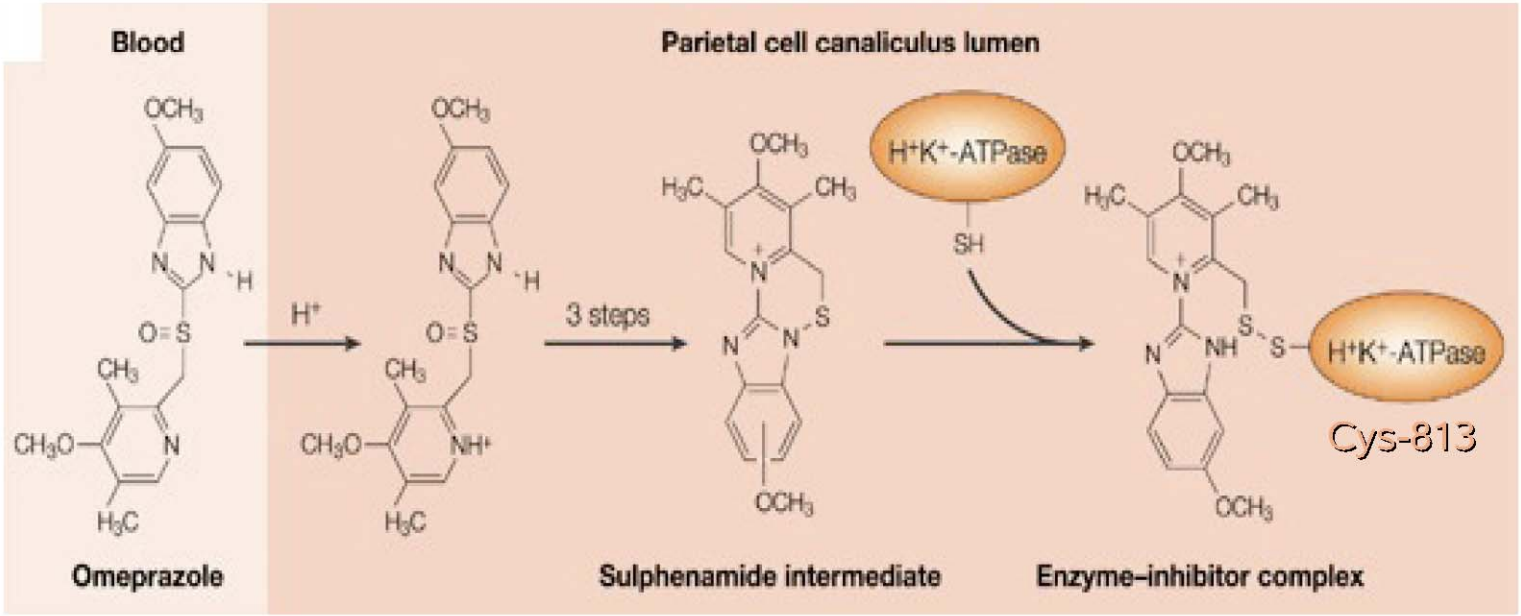
Malcolm Gladwell, “High Prices: How to think about prescription drugs”, The New Yorker, October 25, 2004, pp 86-90

Omeprazole: Therapeutic Hypothesis

The Proton Pump

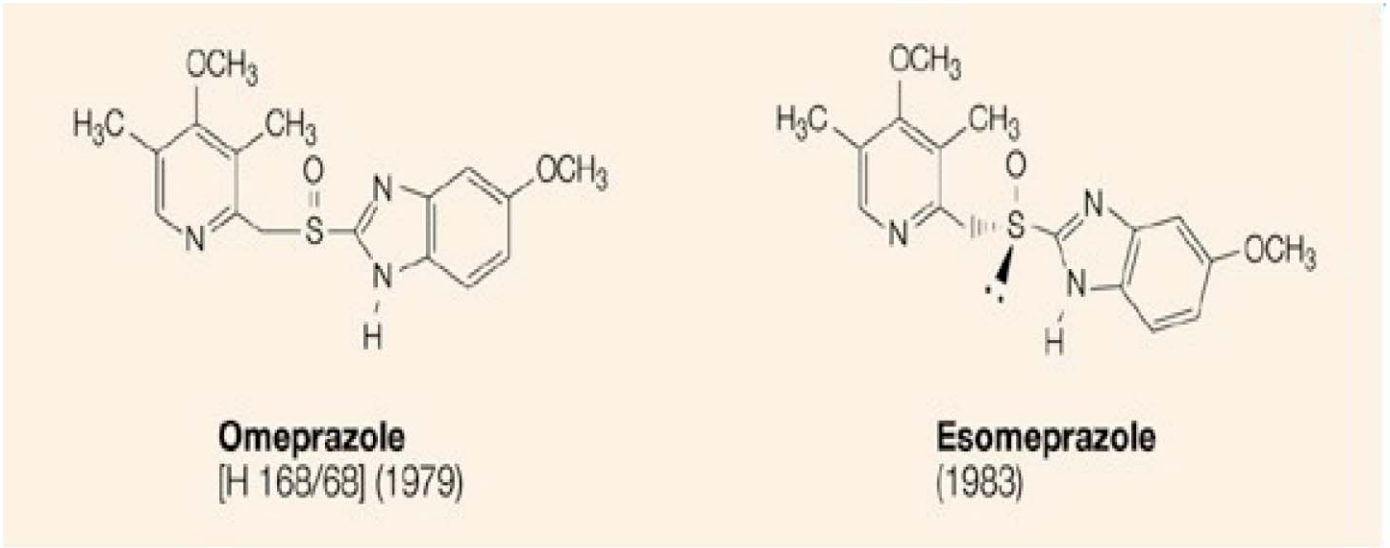


Omeprazole: Mechanistic Hypothesis



Study of Praying Hands, by Albrecht Dürer (1508)

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)

DRUG APPROVAL in the 1990's

- **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

Hammer-Breslow, L., Harvard J. Legislation 40:133-192(2003)

Post-Marketing Surveillence in Wake of VIOXX Recall

Phase IV

(voluntary)

Eric J. Topol, NEJM, Oct 21, 2004, 1707-1709

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