

# Adverse Drug Reactions: A Perspective

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# Presentation Outline

- From the Headlines!
- What is an adverse drug reaction (ADR)
- Types and Classification of ADRs
- Risk Factors for ADRs and Examples
- Regulations and the FDA: History, Background, and Postmarketing Surveillance
- Specific ADR Cases
- Future/Conclusions

From The Headlines!!

**The New York Times**  
ON THE WEB

*Vioxx™ Recall May .....*

Los Angeles Times  
**latimes.com**®

**Report: .....Held Back on  
Drug Dangers**

# From The Headlines!!



**FDA Officer Suggests Strict  
Curbs on 5 Drugs**  
**Makers Dispute Claims About Health  
Risks**

# The Perceptions and Implications.....

- Adverse drug reactions have had significant media exposure, with the resulting impact on the public at large.
- Pharmaceutical companies have felt the pinch of mismanagement of high-profile ADR reports that have effected the industry.
- Patient care may suffer or they may lose confidence in a drug (especially in the case of recall).

# The Reports and Findings.....

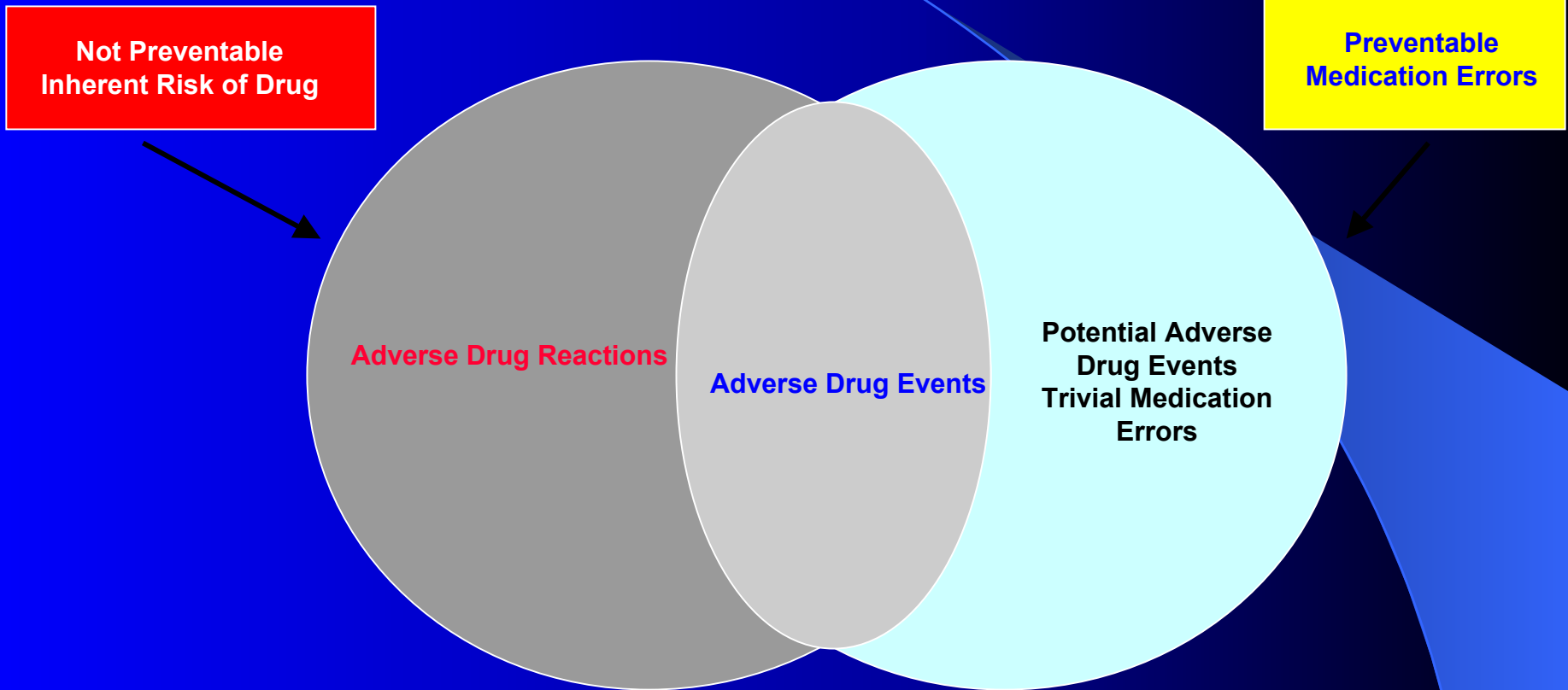
- A meta-analysis of 39 studies found an inhospital incidence of ADRs of 6.7%, and an incidence of fatal ADRs of 0.3%.
- This makes fatal ADRs amongst the top six leading causes of death in the United States
- 30% to 60% are preventable
- ADRs may lead to an additional \$1.56 to \$4 billion in direct hospital costs per year in the United States

Reference: Lazarou j, Pomeranz BH, Corey PN., JAMA, 1998; 279: 1200-5

# Adverse Drug Reactions: What are they?

- **An injury resulting from medical intervention related to a drug**
- **Any noxious and unintended effect of drug that occurs at doses used in human for prophylaxis, diagnosis, or treatment**
  - **WHO definition**
- **Excludes therapeutic failures, overdose, drug abuse, noncompliance, and medication errors**
- **Majority of ADRs are caused by predictable, nonimmunologic effects (75 to 80 percent)**

# Relationship Between ADEs and ADRs



Adapted From: <http://www.annals.org/cgi/content/full/142/1/77>



# Adverse Drug Reactions: How do we learn about them?

- **Most common adverse reactions are detected in premarketing clinical trials (reported in prescribing information)**
- **However, most clinical trials are of short duration, and patient numbers in trials are low compared to population**
  - **Latent ADRs often missed**
  - **3000 patients at risk needed to detect with an incidence rate of 1/1000 with 95% certainty**
- **Most trials also exclude the very young and old, pregnant women, patients with multiple diseases, and any potentially interacting medications**
- **Additional ADRs are discovered once a drug enters the marketplace**

References: Ahmad S.R., J Gen Intern Med, 2003; 18:57-60  
[www.cc.nih.gov/researchers/training/ppt/calis\\_slides\\_2002-2003.ppt](http://www.cc.nih.gov/researchers/training/ppt/calis_slides_2002-2003.ppt)

# Types of Drug Reactions: Nonimmunologic

## Nonimmunologic

### Predictable

Pharmacologic side effect	Dry mouth from antihistamines
Secondary pharmacologic side effect	Thrush while taking antibiotics
Drug toxicity	Hepatotoxicity from methotrexate
Drug-drug interactions	Seizure from theophylline while taking erythromycin
Drug overdose	Seizure from excessive lidocaine (Xylocaine)

### Unpredictable

Pseudoallergic	Anaphylactoid reaction after radiocontrast media
Idiosyncratic	Hemolytic anemia in a patient with G6PD deficiency after primaquine therapy
Intolerance	Tinnitus after a single, small dose of aspirin

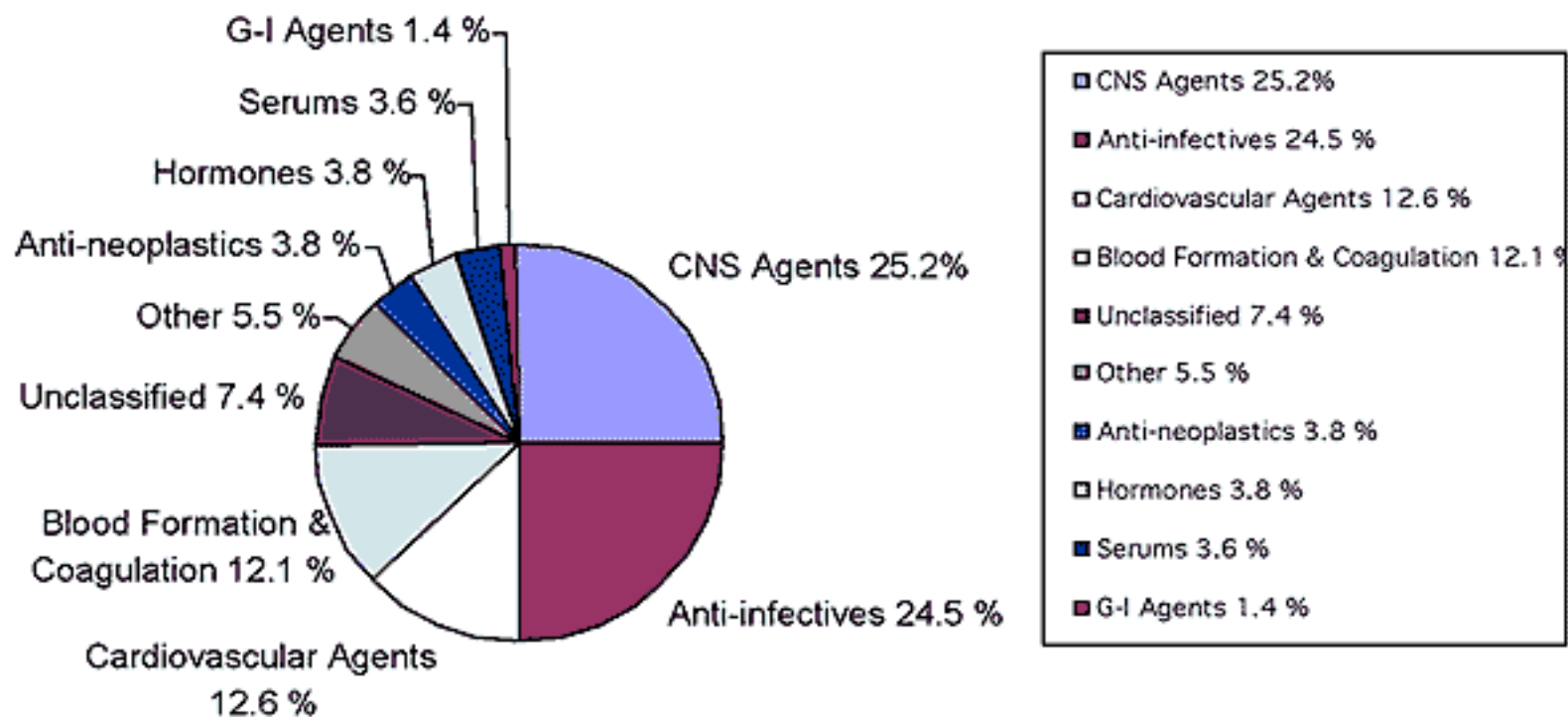
G6PD = glucose-6-phosphate dehydrogenase.

# Types of Drug Reactions: Immunologic

Type I reaction (IgE-mediated)	Anaphylaxis from b-lactam antibiotic
Type II reaction (cytotoxic)	Hemolytic anemia from penicillin
Type III reaction (immune complex)	Serum sickness from anti-thymocyte globulin
Type IV reaction (delayed, cell-mediated)	Contact dermatitis from topical antihistamine
Specific T-cell activation	Morbilliform rash from sulfonamides
Fas/Fas ligand-induced apoptosis	Stevens-Johnson syndrome Toxic epidermal necrolysis
Other	Drug-induced, lupus-like syndrome Anticonvulsant hypersensitivity syndrome

Adapted From: <http://www.aafp.org/afp/20031101/1781.html>

# ADRs by Drug Class



Adapted From: <http://www.vh.org/adult/provider/pharmacyservices/PTNews/2003/may.html>

# Body Systems Commonly Involved

- Central Nervous System
- Hematologic
- Cardiovascular
- Renal/Genitourinary
- Sensory
  - Neuropathy
  - Auditory
- Dermatologic
  - especially visible lesions or eruptions
- Gastrointestinal
- Metabolic

# ADR Effects (Erythema Multiforme)



Used with permission from Michelle Ehrlich, MD and eMedicine.com, Inc., 2005

# ADR Effects (Gingival Enlargement due to Ca<sup>2+</sup>-Channel Blockers)



Used with permission from Carl Allen, DDS and eMedicine.com, Inc., 2005

# ADR Effects (Coumadin Necrosis of the Leg)



Used with permission from Michelle Ehrlich, MD and eMedicine.com, Inc., 2005



# Risk Factors for Adverse Drug Reactions

- Simultaneous use of several different drugs
  - Drug-drug interactions
- Very young, or very old in age
- Pregnancy
- Breast Feeding
- Hereditary Factors
- Disease states which may effect drug absorption, metabolism, and/or elimination

Reference: <http://www.merck.com/mmhe/sec02/ch015/ch015e.html>

# Risk Factors Examples: Simultaneous Drug Use or Drug-Drug Interactions

- Cerivastatin-Gemfibrozil interactions in hypercholesterolemia patients (rhabdomyolysis)
- Coumadin-NSAID interactions (increased inhibition of platelet aggregation)
- Venlafaxine-indinavir interactions in depressed HIV-infected patients (decreased indinavir concentrations)

References: Psaty BM, et al, JAMA, 2004 Dec 1; 292 (21), 2622-31  
Van Dijk KN, et al, Thromb Haemost, 2004 Jan; 91(1), 95-101  
Levin, GM, et al, Psychopharmacol Bull, 2001 Spring, 35 (2) 62-71

# Risk Factors Examples: Age Related Issues

- Children are often at risk because their capacity to metabolize drugs is usually not fully developed
  - Newborns cannot metabolize or eliminate chloramphenicol, an antibiotic
  - Children younger than 18 may be at risk of developing Reye's syndrome if given acetylsalicylic acid (aspirin) while infected with chickenpox or influenza
  - Central nervous system effects of topiramate in children (seizures, tremor, and dizziness)

## References:

<http://www.merck.com/mmhe/sec02/ch015/ch015e.html>  
Shechter T, et al, Pharmacoepidemiol Drug Saf. 2004 Nov 1

# Risk Factors Examples: Age Related Issues

- ADRs, including drug interactions, are a common cause of admission to hospitals in the elderly
- Reasons for ADRs in the elderly:
  - Concomitant use of several medications
  - Disease states leading to drug ADME changes
  - Decreased drug ADME activity due to age
- These conditions are exacerbated by malnutrition and dehydration, common in the elderly

Reference: Routledge P.A., O'Mahoney, M.S., *Brit. Journ of Clinical Pharmacology*, 2003, 57 (2), 121-126

# Risk Factors Examples: Pregnancy

- Use of sulfonamides (antibiotic) can lead to jaundice and brain damage in the fetus
- Warfarin use for anticoagulation can lead to birth defects, and increased risk of bleeding problems in newborns and mothers
- Lithium, for bipolar disorder, can lead to defects of the heart, lethargy, reduced muscle tone, and underactivity of the thyroid gland

Reference: [http://www.merck.com/mmhe/sec22/ch259/ch259a.html#tb259\\_1](http://www.merck.com/mmhe/sec22/ch259/ch259a.html#tb259_1)

# Risk Factors Examples: Breastfeeding

- Similar concerns, as for other children with underdeveloped capability to metabolize or excrete xenobiotics
- Many drugs can be passed from mother to infant via breast milk
  - Amantadine (antiviral)
  - Cyclophosphamide (antineoplastic)
  - Cocaine (Schedule 2 FDA drug)
  - Carisoprodol (skeletal muscle relaxant)

# Risk Factors Examples: Hereditary Factors

- Genetic polymorphisms may play a role
  - Evident in CYP2C9 and 2C19, especially in the Asian population (phenytoin)
  - May lead to impaired metabolism in mutation of enzymes
- Higher risk of hemolysis in some populations, such as African, Middle Eastern, and South East Asian races
  - Quinolones
  - Antimalarials

Reference: [http://www.cppe.man.ac.uk/openlearning/e\\_adr/section2.asp](http://www.cppe.man.ac.uk/openlearning/e_adr/section2.asp)  
Odani A, et al., Clin Pharmacol Ther, 1997 Sep;62(3):287-92

# Risk Factors Examples: Disease States

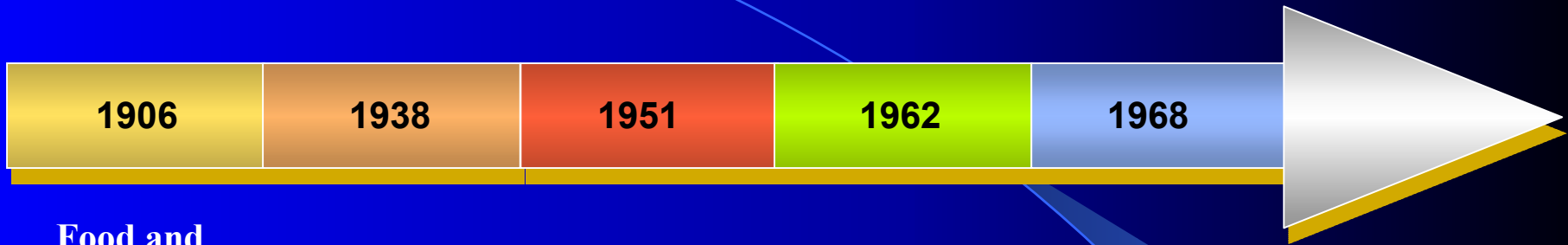
- Metabolism (Phase I or II) may be impaired with hepatic disease
  - Cirrhosis
  - Hepatic Carcinoma
- Renal Insufficiency
  - Acute or Chronic Renal Failure
  - Decreased glomerular filtration rate (GFR)
- Drug levels may become toxic if too high, so dosing modifications may be indicated



The background is a dark blue gradient. A thin, light blue curved line starts from the top left and curves towards the bottom right. A larger, lighter blue curved shape is positioned in the lower right quadrant, partially overlapping the dark blue background.

# **Regulations and the FDA: History, Background and Postmarketing Surveillance**

# FDA Historical Milestones



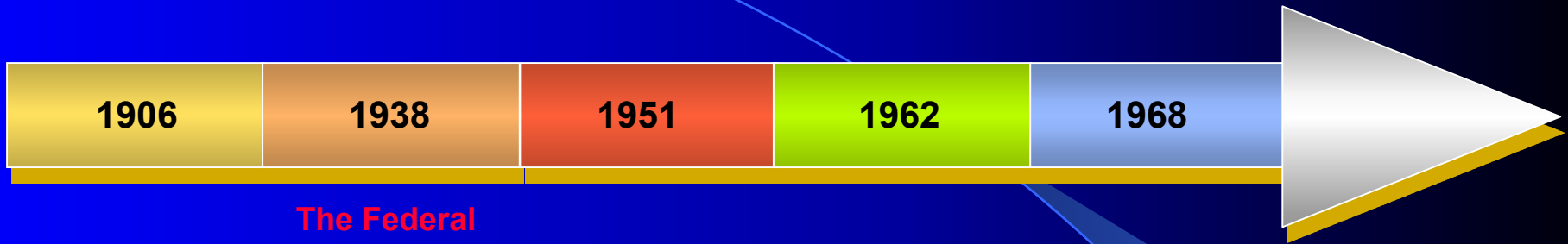
**Food and  
Drugs Act is  
Passed.**

**Signed by  
President  
Theodore  
Roosevelt.**

**It prohibits  
interstate  
commerce in  
misbranded  
&  
adulterated  
foods, drinks,  
and drugs.**

Reference: <http://www.fda.gov/opacom/backgrounders/miles.html>

# FDA Historical Milestones



1906

1938

1951

1962

1968

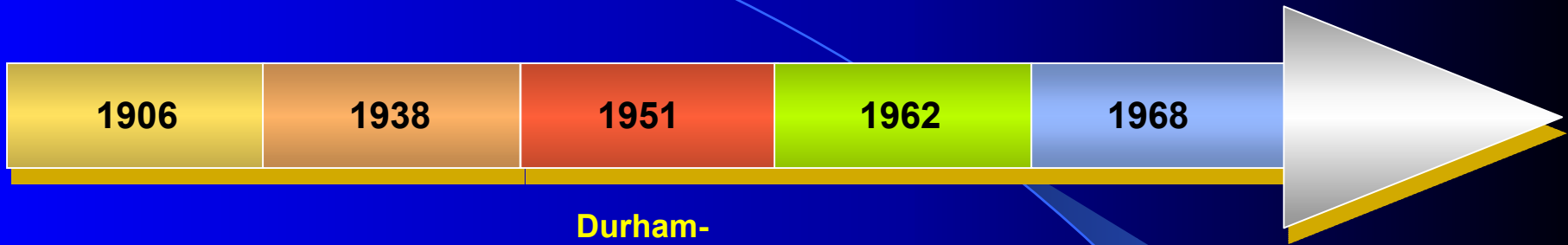
**The Federal  
Food, Drug, and  
Cosmetic (FDC)  
Act is passed.**

**Passed by  
Congress.**

Many provisions,  
one of which  
required  
manufacturer  
prove the safety  
of a drug before  
it can be  
marketed.

Reference: <http://www.fda.gov/opacom/backgrounders/miles.html>

# FDA Historical Milestones

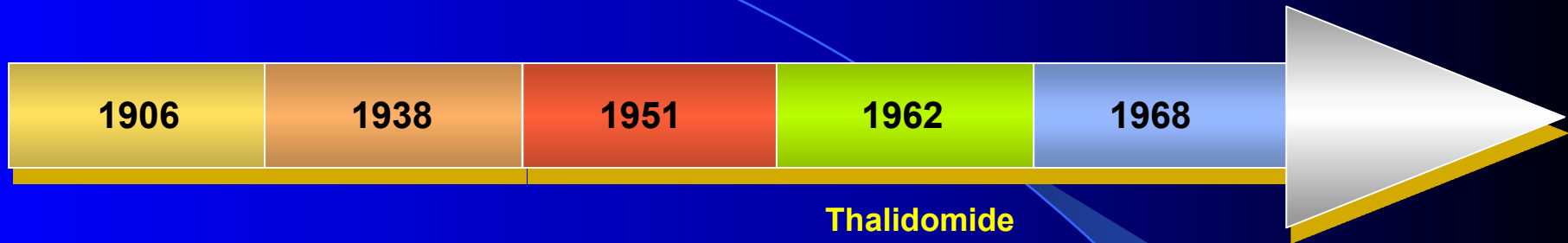


## **Durham-Humphrey Amendment**

**Defined prescription drugs as those unsafe for self-medication and which should be used only under a doctor's supervision**

Reference: <http://www.fda.gov/opacom/backgrounders/miles.html>

# FDA Historical Milestones



**Thalidomide**

**Kefauver-Harris Drug  
Amendments**

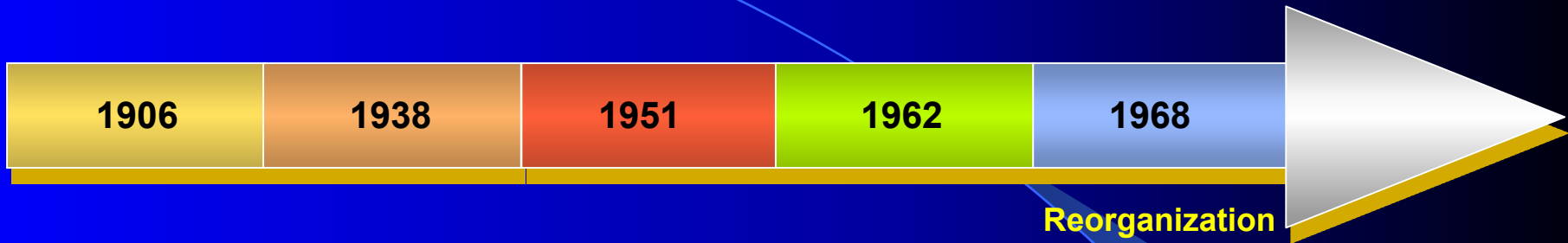
**Consumer Bill of  
Rights**

**Drug manufacturers  
were required to  
prove to FDA the  
safety and  
effectiveness of their  
products before  
marketing them.**

**Consumer Bill of  
Rights (informed  
consent)**

Reference: <http://www.fda.gov/opacom/backgrounders/miles.html>

# FDA Historical Milestones

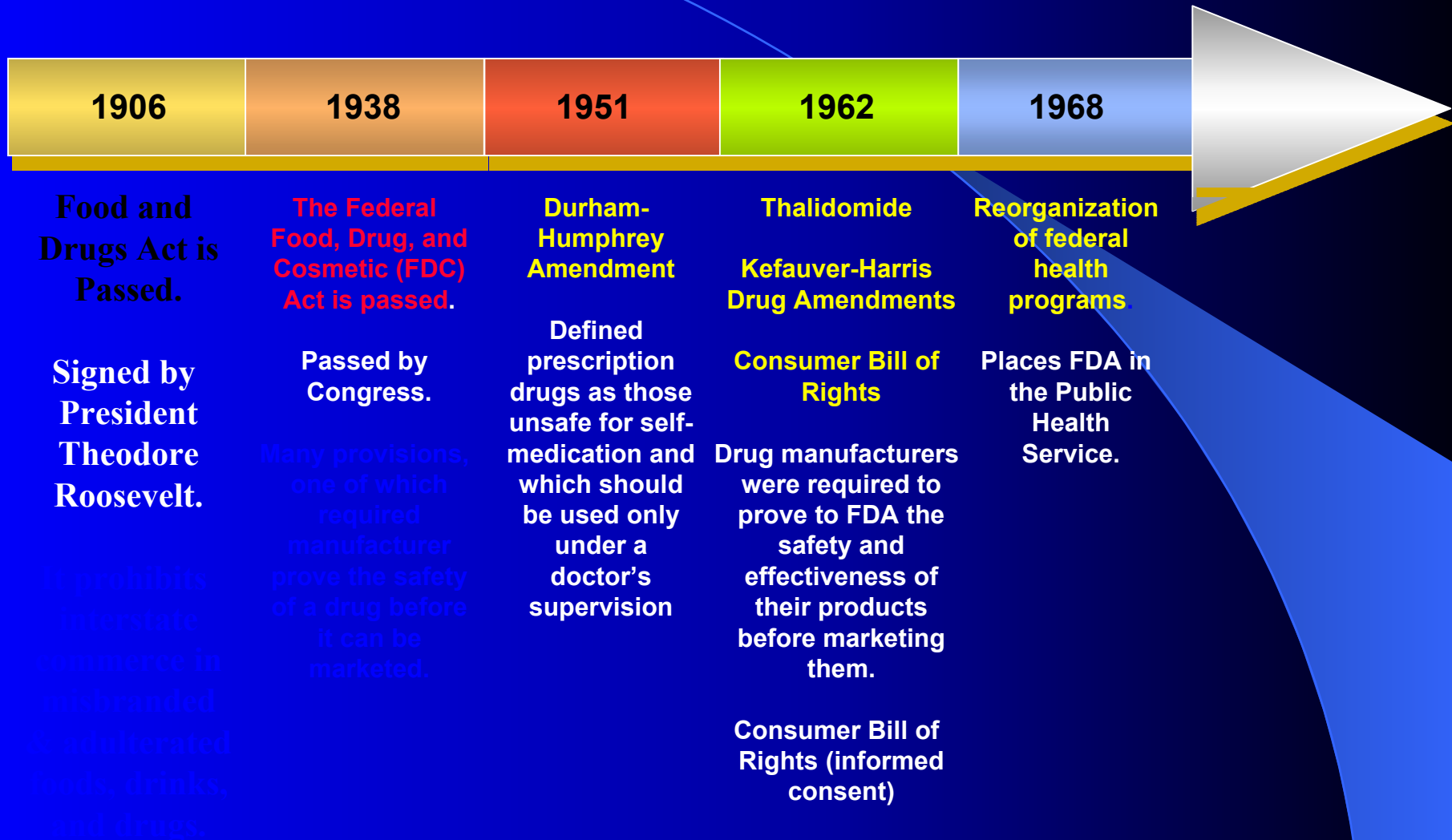


**Reorganization  
of federal  
health  
programs.**

**Places FDA in  
the Public  
Health  
Service.**

Reference: <http://www.fda.gov/opacom/backgrounders/miles.html>

# FDA Historical Milestones



Reference: <http://www.fda.gov/opacom/backgrounders/miles.html>

# The Role of the FDA

- Responsible not only for drug approval, but for monitoring drug safety after they reach the market
  - Pharma companies report ADEs to FDA in the NDA or aNDA (data from clinical trials)
- FDA's Office of Drug Safety carries out this role
  - Adverse Event Reporting System (AERS)
- AERS receives reports from two sources:
  - Mandatory reports from Pharma companies
  - Adverse event reports from HCPs

Reference: Ahmad S.R., J Gen Intern Med, 2003; 18:57-60



# FDA Adverse Event Reporting System

**U.S. Food and Drug Administration**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

<http://www.fda.gov/cder/aers/default.htm>

# The Role of the FDA and the AERS

- Majority of reports come from pharma companies
- Late or non-reporting of ADRs are major problems
  - Benoxaprofen (Oraflex)
  - Ticrynafen (Selacryn)
  - Nomifensine (Merital)
- Criminal prosecutions have occurred
- Warning letters can be sent in some cases of late reporting of ADEs

Reference: Ahmad S.R., J Gen Intern Med, 2003; 18:57-60

# Labeling Changes due to Post-Marketing Surveillance

- **Many requested label changes have occurred due to adverse drug events *post-marketing***
  - Many companies proactively update drug labels based on information received in the postmarketing setting
- **Examples:**
  - Protease Inhibitors – Increases in blood sugar levels in HIV patients
  - Loratadine/pseudoephedrine – Upper GI tract narrowing and decreased esophageal peristalsis
- **Black Box Warnings now used for products with potential for life-threatening ADRs**
  - Letters go out to physicians, and close monitoring is called for

Reference: <http://www.vh.org/adult/provider/pharmacyservices/PTNews/1997/1297PNT.html>

# Black Box Warning Example

Cases of life-threatening hepatic failure have been reported in patients treated with SERZONE.

The reported rate in the United States is about 1 case of liver failure resulting in death or transplant per 250,000 – 300,000 patient-years of SERZONE treatment. The total patient-years is a summation of each patient's duration of exposure expressed in years. For example, 1 patient-year is equal to 2 patients each treated for 6 months, 3 patients each treated for 4 months, etc. (See WARNINGS).

Ordinarily, treatment with SERZONE should not be initiated in individuals with active liver disease or with elevated baseline serum transaminases. There is no evidence that pre-existing liver disease increases the likelihood of developing liver failure, however baseline abnormalities can complicate patient monitoring.

Patients should be advised to be alert for signs and symptoms of liver dysfunction (jaundice, anorexia, gastrointestinal complaints, malaise, etc.) and to report them to their doctor immediately if they occur.

SERZONE should be discontinued if clinical signs or symptoms suggest liver failure (see PRECAUTIONS: Information for Patients). Patients who develop evidence of hepatocellular injury such as increased serum AST or serum ALT levels  $\geq 3$  times the upper limit of NORMAL, while on SERZONE should be withdrawn from the drug. These patients should be presumed to be at increased risk for liver injury if SERZONE is reintroduced. Accordingly, such patients should not be considered for re-treatment.

- Serzone is an antidepressant
- Patients were at an increased risk of liver failure and/or toxicities
- Serzone no longer manufactured or marketed in the U.S.

# Specific ADR Cases

# Mibefradil (Posicor™)

- Indication: Ca<sup>2+</sup>-channel blocker for hypertension
- ADR Problem: Potent *inhibitor* of CYP3A4
  - Drug-drug interactions noted in patients
- Withdrawn: Posicor™ withdrawn from market in June 1998

References: Mullins ME, et al, JAMA, July 8, 1998, 280(2), 157-158  
Ahmad S.R., J Gen Intern Med, 2003; 18:57-60

# Troglitazone (Rezulin™)

- Indication: Antidiabetic agent used in combination with insulin or sulfonylurea for Type II diabetes
- ADR Problem: Hepatotoxicity
  - Indicated by increased liver transaminase levels
  - Some cases of liver transplantation, and a few deaths reported
- Withdrawn: Rezulin™ recalled from market in 2000

References: <http://www.fda.gov/bbs/topics/ANSWERS/ANS00831.html>  
Ahmad S.R., J Gen Intern Med, 2003; 18:57-60

# Grepafloracin (Raxar™)

- Indication: Oral fluoroquinolone antibiotic
- ADR Problem: Linked to prolongation of the heart's QT interval, leading to ventricular arrhythmia
- Withdrawn: Raxar™ removed from the market in 1999

References: <http://www.who.int/medicines/organization/gsm/activities/drugsafety/orggsmalerts.shtml>

Ahmad S.R., J Gen Intern Med, 2003; 18:57-60



# Cerivastatin (Baycol™)

- Indication: Oral statin to lower cholesterol
- ADR Problem: Rhabdomyolysis (injury to skeletal muscle)
  - Muscle weakness and myalgia very common
  - Many cases seen in combination with gemfibrazil
  - Deaths reported with cerivastatin, although no definitive link
- Withdrawn: Baycol™ removed from the market in 2001

References: Psaty BM, et al, JAMA, 2004 Dec 1; 292 (21), 2622-31  
Ahmad S.R., J Gen Intern Med, 2003; 18:57-60

# Conclusions/Future

- Adverse drug reactions have implications not only for the patient, but for the entire health care system
- Reporting of ADRs and ADEs provides clinicians and health care companies valuable insight into the toxicity profile of an agent
- Many ADRs and ADEs are preventable, although some effects cannot be avoided (e.g. nausea in chemo treatment for cancer)
- Better research and greater understanding of disease processes will lead to more effective, and hopefully, safer drug products

The background is a dark blue gradient. A thin, light blue curved line starts from the left edge and curves downwards towards the center. A larger, light blue shape, resembling a sector of a circle or a lens, is positioned in the lower right quadrant, overlapping the main blue background.

Questions??