“All things are pions, for there is nothing without poisonous qualities. It is only the dose which makes a thing poison” - Paracelsus

Based on Federal Food, Drug and Cosmetics Act (1938) the FDA is responsible for pre-market review of safety of all new drugs. FDA is also responsible for monitoring and enforcing post-marketing recalls of ineffective or harmful drugs.

In EU similar function has European Medicinal Agency (EMA).

MedWatch (founded in 1993) is FDA’s Safety Events and Adverse Effects Reporting Program

**FDA Drug Recall Procedure:**

- After receiving feedback from MedWatch regarding adverse effect, a health hazard evaluation is conducted which categorizes drug's risk by class:
  - **Class I** - a dangerous and defective product that can cause severe health complications, or even death
  - **Class II** - a product with the potential to cause a temporary or serious health problem
  - **Class III** - a product that is unlikely to result in any adverse health reaction, but that violates an FDA labeling or manufacturing law

Recalled drugs in years 2012-2021: **Class I** (10.3%), **Class II** (79.5%), **Class III** (10.2%)

- After completed health hazard evaluation FDA may request pharmaceutical company to:
  - A) issue a safety communication to public or healthcare providers;
  - B) issue addition of an incremental boxed warning (black box warnings);
  - C) withdraw the product from market due to safety concerns

- FDA is responsible for monitoring of the recall process. Status of the recall is updated on the FDA web page

**Ongoing Recall** - a recall that is in process of taking the necessary safety precautions advised by the FDA

**Completed Recall** - a recall which reaches the point at which the company has retrieved and captured all outstanding product that could reasonably be expected to be recovered, or has completed all product corrections advised by FDA

**Terminated Recall** - a recall where the FDA has determined that all reasonable efforts have been made to remove or correct violative product to the best of their ability

- After providing compelling information to FDA (i.e. additional clinical studies) the company may request re-approval or approval of the drug for different purpose

**Most common reasons for drug recall**

- Contamination (50%)
- Adverse reaction (10%)
- Mislabelling (22%)
- Defective product (7%)
- Incorrect potency (6%)
- Other (5%)

Source: AJHP 2016, 73, 235

**New England Compounding Center incident** (2012): three lots of injectable corticosteroids (betheamethasone and triamcinolone) were contaminated with fungal strains resulting in 750 reports of fungal meningitis and 64 deaths

**Proportion of 2001-2010 FDA approved drugs with serious postmarketing safety events by therapeutic area**

- Psychiatry (22%)
- Neurology (15%)
- Autoimmune (16%)
- Hematologic (13%)
- Cardiovascular (10%)
- Infectious disease (10%)
- Cancer (8%)
- Other (11%)
- Genitourinary (9%)

Source: JAMA 2017, 317, 1854

**Useful resources:**

- List of significant drug withdrawals: https://en.wikipedia.org/wiki/List_of_withdrawn_drugs
  - Chemotherapy 2001, 47, 3
- Books: The Practice of Medicinal Chemistry (4th ed.) 2015

**Previous GMs on related topics:**

- Opioids: Natural and Synthetic, Harwood (2019); Morphine/Codeine, Li (2005)
Thalidomide scandal timeline

1952
First synthesis by CIBA

April 1954
Improved synthesis patented by Chemie Grünenthal

October 1957
Contergan® released in Western Germany

1958
Drug released in Western Europe and Australia; in US SFK (now GSK) declines to commercialize drug after internal clinical trials

Late 1958
First reports of potential teratogenic effects (dismissed)

1959
Production in Germany reaches 1 t/month
> 1 million consumers

Early 1960
Australian physician William McBride raises concerns about thalidomide

September 1960
Richardson-Merrell applies for US approval to FDA; application is denied 6 times over the next year

November 1961
German physician Widukind Lenz proves teratogenic effects of Thalidomide

March 1962
Contergan® withdrawn from market worldwide

August 1962
President's Award for not allowing thalidomide to be approved for sale in the US

May 1968
Contergan® public criminal trial starts in Germany

December 1970
Trial ends with settlement - Grünenthal pays 110 million DM (~$27M) to victims

Mechanism of action and toxicology
- Detailed mechanism of action and all potential teratogenic pathways are still unknown
- Thalidomide is substrate for cereblon (CRBN) - which in form of the E3 ubiquitin ligase complex is responsible for ubiquitination of multiple proteins
- Thalidomide can act both as agonist or antagonist of E3 ubiquitin ligase complex (depending on protein)

Recent FDA approvals
- Approved in 1998 for treatment of leprosy (Celgene, Thalomid®)
- Approved in 2006 as an orphan drug for treatment of multiple myeloma cancer (Celgene)

Promoted as a drug for anxiety, trouble sleeping, and morning sickness
- No clinical studies on pregnant women were conducted
- Withdrawn due to embryo-toxic and teratogenic effect
- Most dangerous before third trimester
- Single 50 mg dose is enough to cause teratogenic effect
- ~40% died after birth
- Not approved by FDA at that time, in US only 17 cases of thalidomide victims

Thalidomide isomer R
- desired sedative effect

Thalidomide isomer S
- teratogenic, embryo-toxic

Myth: Thalidomide disaster could be avoided if pure isomer R was marketed
Fact: Both isomers epimerise rapidly in vivo for both oral and IV dosing

Process route: Chemie Grünenthal (1955)

L-glutamic acid
pyridine/reflux
85%

CO\_2
H\_2
O

Patent no. GB768821 (1955)

urea

reflux
92%

CDI, DMAP

OPRD 1999, 3, 139


1) L-glutamine
Na\_2CO\_3, H\_2O
69%

2) 4 M HCl

THF, reflux
91%

Frances Oldham Kelsey

Widukind Lenz


Infamous Drugs Recalled from the Market

- Charcot-Leyden Crystal
- Thalidomide
- Valium®
- Plaster of Paris
Mechanism of action:
- RadioChem route
- Corey's hypothesis

Toxicology:
- All COX-2 selective inhibitors have potential to facilitate thrombosis, leading to CV events
- Rofecoxib inhibits production of prostaglandin \( \text{I}_2 \) responsible for the inhibition of platelet aggregation and prevention of vascular smooth muscle cell proliferation

In 2007 Merck agreed on a mass settlement of $4.85 billion to end ~27,000 lawsuits over Vioxx®

In 2017 FDA granted rofecoxib orphan designation for treatment of hemophilic arthropathy

Fenfluramine

- marketed as treatment for obesity
- popular from 1996 as a combination with phentermine (Fen-Phen®)
- based on multiple reports FDA requested health care professionals to report cases of CV events associated with fenfluramine

Valdecoxib

- marketed as treatment for osteoarthritis, rheumatoid arthritis and painful menstruation
- less selective for COX-2 than rofecoxib (COX-2/COX-1 = 60) - higher chance of developing gastric ulcers
- following Vioxx® case the American Heart Association presented to FDA report indicating that valdecoxib is ~2 times more likely to cause heart attack than other NSAIDs
- FDA requested Pfizer to withdraw Bextra® from market based on potential increased risk of serious CV adverse events
- from 2002 to 2005 Pharmacia & Upjohn (Pfizer subsidiary) was marketing Bextra® for “off-label” uses not approved by FDA
- in 2009 Pfizer was fined $2.9 billion for marketing Bextra® “with the intent to defraud or mislead”
Infamous Drugs Recalled from the Market

Mechanism of action:
- HMG-CoA reductase inhibitor; IC_{50} = 1.1 nM (for Lipitor® IC_{50} = 390 nM)
- HMG-CoA reductase takes part in the rate-limiting step of cholesterol biosynthesis

Toxicology:
- All HMG-CoA reductases are associated with adverse effects on skeletal muscles but the exact mechanism is unknown
- Cerivastatin was found to lower the level of ubiquinone (which takes part in mitochondrial electron transfer chain) in muscle and blood cells leading to apoptosis

MedChem Route:
- 1) LAH, THF reflux
- 2) PCC, DCM reflux
- 3) NaOH, EtOH, reflux
- 4) HCl, water

Mechanism of action:
- Reversible inhibitor of NKCC2 symporter in kidney
- Binds to Cl⁻ binding site
- Inhibits Na, K, Cl, Mg, Ca reabsorption in the loop of Henle

Metabolism and toxicology:
- Oxidized in liver by cytochrome P-450 monooxygenase CYP2C9
- Two metabolites can covalently bind to liver enzymes leading to hepatotoxicity

The Practice of Medicinal Chemistry (4th ed.) 2015

Infamous Drugs Recalled from the Market

Mechanism of action:
- Cholesterol-lowering drug
- Bayer's response to Pfizer's highly successful Lipitor®
- Withdrawn due to high risk of rhabdomyolysis and kidney failure (10-50 times higher than for other statins)
- 52 death, 385 non-fatal cases of rhabdomyolysis
- >2,800 court cases, resulting in total $1.1 billion in out-of-court deals
- Further investigation showed that Bayer did not disclose relevant information about dose-dependent toxicity to FDA

MedChem Route:
- 1) EtOH/benzene, reflux
- 2) Separation of diast.
- 3) NaOH, EtOH, reflux
- 4) HCl, water

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**Mechanism of action:**
- Interferes with bacterial DNA gyrase and topoisomerase IV (required for transcription and replication of bacterial DNA) which leads to strand breakage of bacterial chromosome
- Effective against both gram-positive and gram-negative bacteria
- In gram-positive bacteria topoisomerase IV is the main target
- In gram-negative bacteria DNA gyrase is the main target

**Fluoroquinolone Toxicology:**
- Phototoxicity and hepatotoxicity:
  - Me > H > NH₂
  - Excitotoxic effect due to GABA receptors binding
- Chelating group: adverse interactions with antacids, Fe, Mg, Ca
- Responsible for phototoxicity: F > Cl > H > OMe

**Other fluoroquinolones recalled by FDA:**
- **Grepafloxacin** (Raxar®, Glaxo Wellcome)
  - FDA approved 1997; withdrawn 1999
  - Cause: serious CV events and sudden death
- **Gatifloxacin** (Tequin®, Kyorin Pharmaceuticals)
  - FDA approved 1999; withdrawn 2006
  - Cause: increased risk of dysglycemia
- **Sparfloxacin** (Zagam®, Sumitomo Dainippon)
  - FDA approved 1993; withdrawn 2001
  - Cause: serious CV events and phototoxicity

**Trovafloxacin MedChem route:**

*Image: Clin. Sci. 2016, 130, 1165*
**Infamous Drugs Recalled from the Market**

**Mechanism of action:**
- Selective serotonin agonist in the 5-HT₄ receptor subtype
- Stimulation of 5-HT₄ receptor increases acetylcholine release in enteric nervous system; as a result gastric emptying and intestinal transit is accelerated

**Toxicology:**
- Was found to be potent inhibitor of K voltage-gated channels (HERG) in the human heart (IC₅₀ = 44.5 nM)
- Inhibition of HERG leads to long QT syndrome - condition affecting relaxing of the heart after a heartbeat
- Result is increased risk of irregular heartbeat, seizures or sudden death

**Drug Metab. Pharmacokinet. 2006, 21, 347**

![Cisapride](image1)

**Cisapride**
- Propulsid®, Janssen
- FDA approved 1993; withdrawn 2000

**Process route:**
- ![Chemical structure](image2)
  - **Process route:**
  - 1) Br₂, CHCl₃ >99%
  - 2) NaOMe, MeOH, 82%
  - 1) BuNH₂, EtOH 74%
  - 2) Pd/C, H₂ 96%

**Metabolic pathways:**
- ![Chemical structure](image3)
  - ![Chemical structure](image4)

**Non-toxic metabolites**
- R = SO₄²⁻ or glucuronate


**Toxicology:**
- Hepatotoxicity of troglitazone results from the combination of metabolic and nonmetabolic factors
- Metabolic factors: major metabolic pathways produce highly reactive metabolites which may form conjugates with glutathione or numerous enzymes (see on the right)
- Nonmetabolic factors: troglitazone inhibits functions of canalicular bile salt export pump (BSEP/ABC11), which may result in accumulation of toxic bile salts in liver cells


**Troglitazone**
- Rezulin®, Daiichi Sankyo
- FDA approved 1997; withdrawn 2000

**Mechanism of action:**
- Marketed as treatment for diabetes type 2
- Withdrawn due to high hepatotoxicity
- Between 1997 and 1999 caused 90 liver failures and 63 deaths
- In US distributed by Parke-Davis
- In 1996 John Gueriguan - FDA medical officer rejected Rezulin® application based on "potential harm to the liver and the heart"
- Parke-Davis filled a complaint to FDA after which the drug was approved

**Pfizer who acquired Parke-Davis in 2000 spent $750 million to resolve >35,000 trials over Rezulin® toxicity**

**Baran Group Meeting**
- 10/15/22
Troglitazone MedChem Route:

1) Br₂, DMF
2) MeOH

MeO

O

MeOh, 80°C

K₂CO₃, NaI
acetone, reflux

70%

OHC

O

HO

+ MeS

- Na

+ MeOH

MeS

- Na

+ MeOH

80%

Michal Ociepa

Baran Group Meeting

10/15/22

Troglitazone

Process Route (yields not reported):

Lysergic acid

H₂, Pd/C

MeOH

nPrO

O

O

Me

Me

MsCl

EtOAc/pyridine,

0°C

TMS

1) pyrrolidine, 4 Å MS, DCM
2) MeO₂C

75%

9,10-DHLA

De Novo Synthesis of 9,10-DHLA:

OH

Br

NH₂

1) ACO₂O, then K₂CO₃/MeOH
2) MeO₂C, THF
3) Ph₃P

KOTBu, THF

59%

OMe

OH

Br

In, THF, reflux

82%

9,10-DHLA

Single diastereoisomer

OH

1) Mel, 80°C
2) NaBH₄(CN), MeOH, then AcOH

82%

9,10-DHLA


Tetrahedron 2015, 71, 5897


Inflamous Drugs Recalled from the Market

Marketed as treatment for Parkinson’s disease
Several studies linked pergolide with life-threatening CV events
Withdrawn due to increased risk of serious heart valve damage

Mechanism of action:
Parkinsons’s disease is associated with reduced dopamine activity in the brain
Pergolide acts as agonist of dopamine D₁ (Kᵢ = 339 nM) and D₂ receptors (Kᵢ = 26 nM), and serotonin 5-HT receptors
Hallucinogenic due to activation of 5-HT₂A receptors

Neuropsychopharmacology 2010, 35, 1356

Toxicity:
Activate cardiac 5-HT₂B receptors causing proliferation of cardiac myocytes
Uncontrolled proliferation of cardiac cells leads to cardiac fibrosis and heart valve damage

Appendix: Other notable FDA recalled drugs

**Lorcaserin**
Belviq®, Arena Pharmaceuticals
(appetite suppressant)
FDA approved 2012; withdrawn 2020
Cause: potentially cancerogenic

**Pemoline**
Cylet®, Abbott Laboratories
(stimulant; ADHD treatment)
FDA approved 1975; withdrawn 2010
Cause: hepatotoxicity

**Dextropropoxyphene**
Darvon®/Darvocet®, Eli Lilly
(antihistamine)
FDA approved 1955; withdrawn 2010
Cause: risk of serious CV events, hepatotoxicity
>2000 deaths reported

**Phenformin**
DBI, Ciba-Geigy
(antidiabetic)
FDA approved 1959; withdrawn 1978
Cause: severe lactic acidosis

**Diethylstilbestrol**
DES, Grant Chemical Co.; BMS; Eli Lilly
(nonsteroidal estrogen substitute)
FDA approved 1940; withdrawn 1971
Cause: cancerogenic, teratogenic

**Bromfenac**
Duract®, Wyeth-Ayerst
(NSAID)
FDA approved 1997; withdrawn 1998
Cause: hepatotoxicity
From 2005 approved as eye drops to reduce inflammation after cataract surgery

**Levamisole**
Ergamisol®, Janssen
(antiparasitic)
FDA approved 1989; withdrawn 2000
Cause: agranulocytosis

**Alosetron**
Lotronex®, GSK
(gastrointestinal drug)
FDA approved Feb 2000; withdrawn Nov 2000
Cause: potential life-threatening gastrointestinal effects
From 2002 approved with restricted indication

**Sibutramine**
Meridia®, Boots
(appetite suppressant)
FDA approved 1997; withdrawn 2010
Cause: increased risk of serious CV events

**Terodiline**
Micturin®, Forest Laboratories
(antispasmodic)
FDA approved 1969; withdrawn 1991
Cause: potential cardiotoxicity

**Mibebradil**
Posicor®, Roche
(calcium channel blocker)
FDA approved 1997, withdrawn 1998
Cause: deadly interactions with >25 other drugs

**Methaqualone**
Quaalude®, William H. Rorer Inc.
(sedative)
FDA approved 1962; withdrawn 1985
Cause: highly addictive

**Zimelidine**
Zelmid®, Astra AB
(antidepressant)
FDA approved 1982; withdrawn 1982
Cause: Guillain-Barré syndrome;
increased risk of suicide

**Astemizole**
Hismanal®, Janssen
(antihistamine)
FDA approved 1988; withdrawn 1999
Cause: potential severe CV events