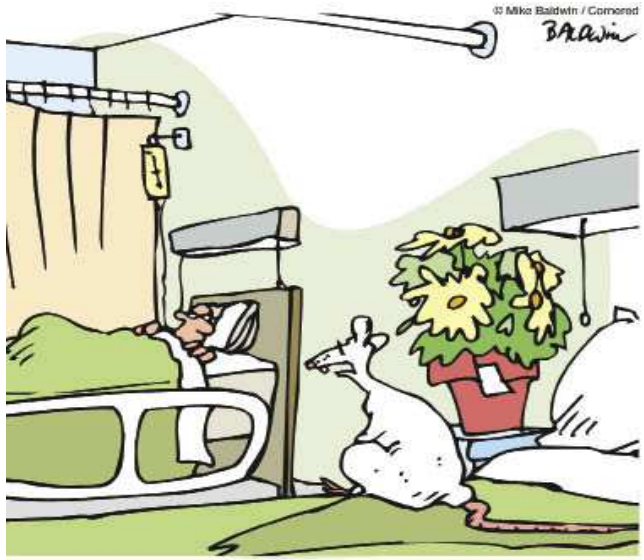
Safety in Drug Development: The Link Between Historical Medical Cases and Current Regulations.



"I go home today. They cured me using this new miracle drug. I'm afraid it'll be years before it's approved for humans."

First clue that the latest medical breakthrough isn't quite there yet.

Ref: www.cartoonstock.com

Zindy Raida
Research Scientist, DVM, Phd.
Safety Pharmacology & Exploratory Toxicology.

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Safety in Drug Development: The Link Between Historical Medical Cases and Current Regulations.

- Medical scandals through history
- The regulatory impact
- Safety Pharmacology as a discipline
  - a regulatory consequence

Drugs for disease

Drugs for allergy

Drugs for pain

Drugs for mental health

Drugs for pleasure

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No regulations to protect the public from dangerous drugs until early 1900

- Food and d
- Marked full
- Medicine ma
- Medicines co
  - -arse
  - -quick
  - -alcoh
  - -deterg
  - -morphi
  - -heroine
  - -cocaine
- No labelling or w

nce

- Active ingredient was Acetanilide
- Impairs release of oxygen from blood to tissue
- Primary active metabolic product is paracetamol

Drugs for pain

Www.BibliOdyssey.blogspot.dk

Washington Post from February the 3rd, 1881.

The Tetanus Scandal– United states 1901

- Diphtheria caused many deaths pr. Year
  -Germany 50.000 deaths pr. year
- 1890: Antitoxin was discovered in blood serum
  in animals injected with diphteria toxin
- Now possible to control infectious disease

- Jim the milk wagon horse produced >30 L of antitoxin filled serum in 3 years
- Jim died of Tetanus in 1901
- 13 children died after receiving serum from Jim containing Diphtheria toxin

the cancer after the first treatment."

LOCKJAW IN DIPHTHERIA CURE.

Eight Deaths in St. Louis Supposedly from the Antitoxin.

Special to The New York Times.

ST. LOUIS, Mo., Nov. 1.—Eight deaths have now been reported to the city Health Department as the result of lockjaw, caused, it is said, by the physicians who attended the various cases, by the administration of the city bacteriologist's specially prepared antitoxin for diphtheria. Eleven other children are sick with lockjaw and death is expected to ensue in each case.

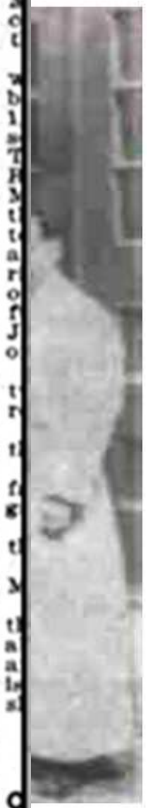
Alarm is spreading. The physicians who administered the remedy are earnest in demanding the investigation of the cause of death in each case, to discover positively if the serum used for the manufacture of the antitoxin was infected with tetanus toxin from the city's serum horse, which was found to be suffering with lockjaw on Oct. 1 and was killed.

Dr. Amand Ravold, city bacteriologist, who prepared the antitoxin and distributed it, said to-day: "The horse from which the city has been drawing its supply of serum for the making of diphtheria antitoxin for the last few years showed no symptoms of tetanus on Aug. 24, when the last serum was withdrawn from him.

He developed symptoms of lockjaw on Oct. 1. If the tetanus toxin was in the horse's blood prior to Aug. 24 it was beyond the range of human knowledge to detect it by an inspection of the animal.

Numerous applications have been received by the Health Department for tetanus antitoxin, which the city announced it would distribute free.

MINISTERS RIVALS IN POLITICS.



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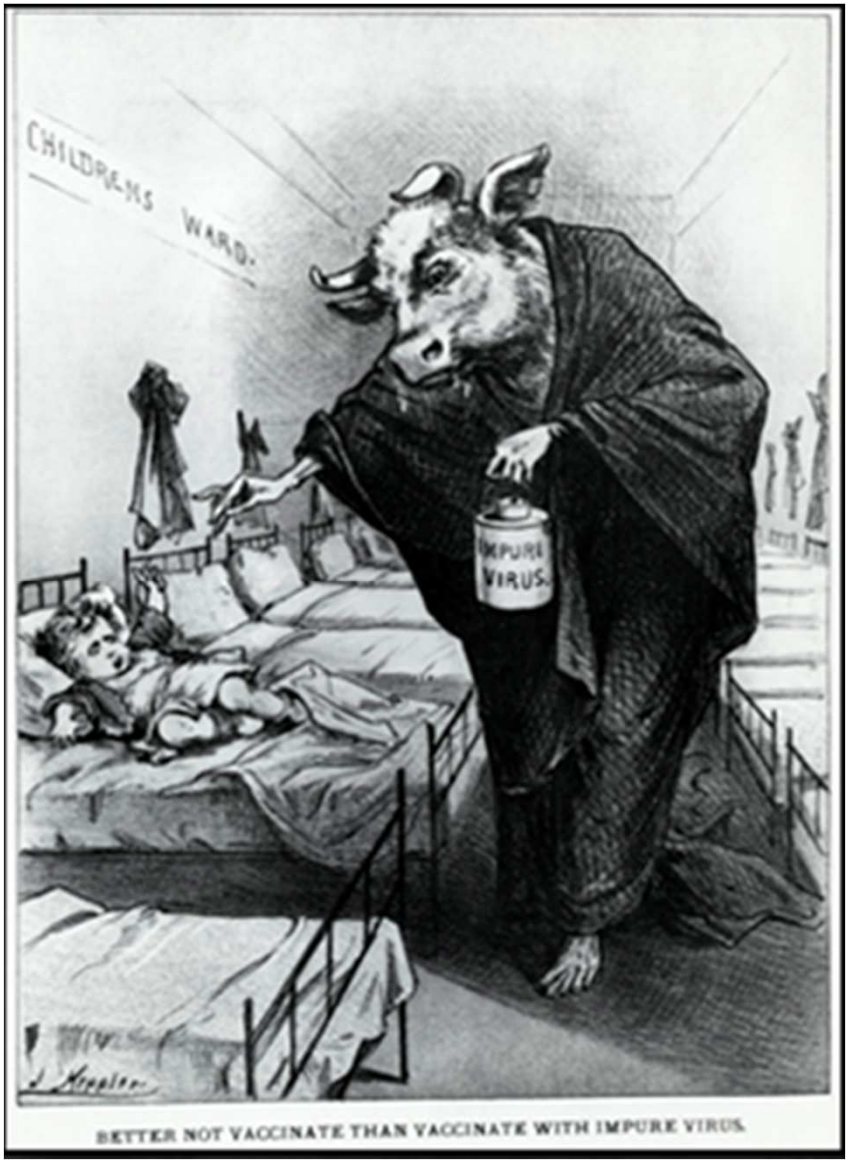
Biologics Control Act of 1902 – "Virus-Toxin Law"

- Name, date, expiration date and license number of manufacturer should be on label
- Specialist should supervise the production
- Regular inspections by authorities
- Annual licensing
- Products tested for purity and potency



Mrs Winslows Soothing Syrup (1844-1930) – The baby killer

US National Library of Medicine, 1875. Advertising image

Ingredients:

- Powdered Morphine
- Opium
- Sodium Carbonate (water softener)
- Aqua Ammonia (a cleaning agent)

- *"This Preparation contains no Poisonous Ingredient and may be used with Perfect Safety"*
- Cure for teething pain and diarrhea
- Quieting infants, small children
- Used as ingredient in recipes, advertised in recipe books, calendars, news papers
- Unknown number of deaths

1849: Put on the Marked
1868: More than 1.5 million bottles were sold annually
1911: The public was made aware in an article
1930: Sale was discontinued in the UK.

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Drug Safety – still not accomplished

www.FDA.gov

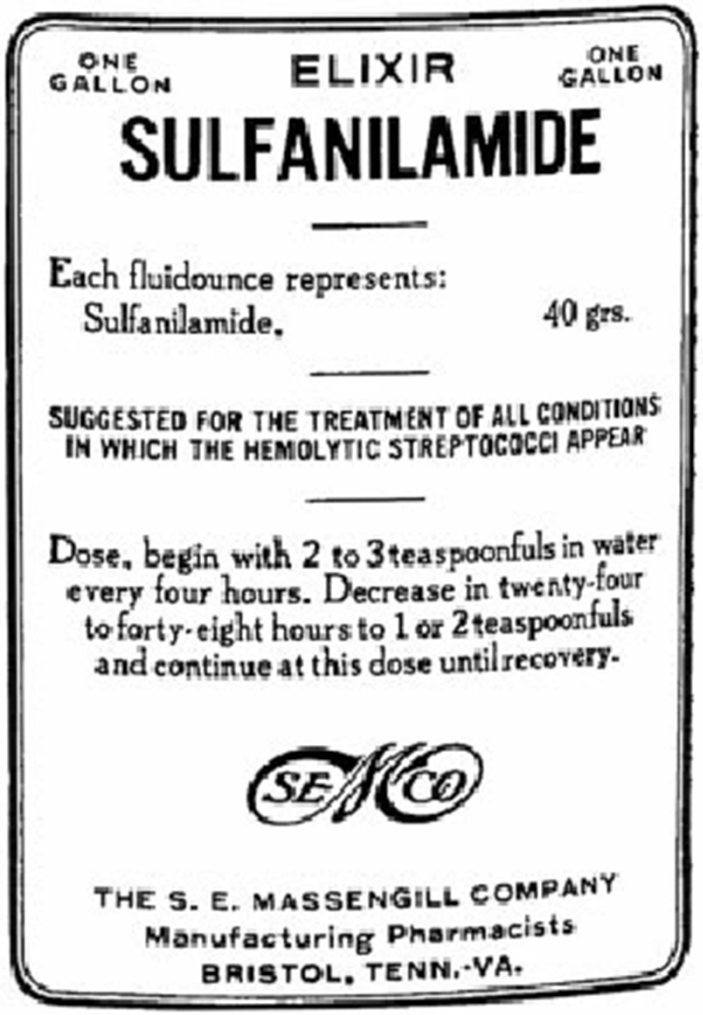
- ***Shortcomings of the 1906 Act***
  - ***No formal government approval was required to marked new drugs***
  - **Lack of inspections**
  - **Inability to control false claims**

"There had to be some truth to what drug companies were selling but in terms of safety let alone efficacy that wasn´t part of the equation"

Ref: The Scientist, June 1, 2013

Elixir Sulfanilamide tragedy - 1937

- Harold Watkins, chief chemist at S.E Masenngill in Bristol
- German bacteriologist
- Used Diethylene Glycol as a solvent, not put on label.
- Discovered Prontosil (Sulfanila
- First commercial antibiotic
- Lab. tested for appearance, fragrance and taste
- Diethylene Glycol belongs to the antifreeze family and was known to be toxic
- 1300 bottles was distributed across the U.S



Elixir Sulfanilamide tragedy - 1937

- Ini
  - >300 people hospitalized. >100 people died many of them children
  - S.E Massengill was charged with misbranding under the Food and Drug Act of 1906
  - The company was fined to pay 16.800 $ for it´s false label
- As ys)
- Lat
  - Public was angry and forced lawmakers to respond

U. S. Races Death to Save 700 From Elixir

Recovery of Pint Bottles Sold to Patients Goal as Deaths From Poison Reach 36

By Associated Press.

CHICAGO, Ill., October 24.—A search with race with death, to effect recovery of more than 700 bottles, mostly pints, of a new liquid medicine, named Elixir of Sulfanilamide, which has already caused 36 verified deaths, was described today at the headquarters here of the American Medical Association.

Every agent of the United States Food and Drug Administration, and Dr. Morris Fishbein, spokesman of the Medical Association, is working like mercury to recover the bottles. By some time on Monday, said J. G. Clarke of the Food and Drug Administration, it is hoped that all of the "astounding" shipments will be recovered.

Due to the fact that large dosages are customary with sulfanilamide preparations.

The medicine stops the kidneys, Medical Association headquarters in Chicago says and is the cause of incalculable misery. No antidote is known yet. The "Elixir" is made of sulfanilamide and diethylene glycol, a near relative of auto antifreeze fluid. The deliberate intent to disguise the poisonous effect, although not itself absent as a poison.

The principal shipments, said Mr. Clarke, went to the South and Midwest. But in addition consignments have been traced to the Northern Peninsula of Michigan, to a distributing house in New York City and to another in San Francisco. All

Federal Food, Drug and Cosmetics Act of 1938 – "Drug Safety law"

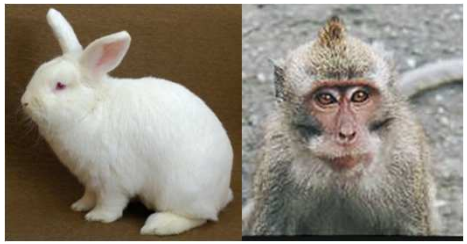
- Required proof of safety
- Authorized inspections
- Required truth in marketing and outlawed false claims of bogus therapeutic effects
- Safe tolerances should be set for some unavoidable poisonous drugs
- FDA could withdraw approvals if safety was questioned post marketing

Label revolution II

- Complete list of ingredients
- Adequate directions for safe use
- Warnings when necessary
- Drugs for **prescription use only**

Before the Thalidomide episode

- Placenta is an effective barrier
- Not standard to test on pregnant animals
  - pregnant rat/mice → no malformations
  - malformations in New Zealand rabbits dose 25-300 x human dose
  - malformations in monkeys dose 10x human dose
- No regulated systematic tests performed in humans before approval
- Test drugs were handed out to doctors who passed them on to their patients
  - no requirement for physicians to keep log of drugs prescribed
  - no requirement to follow-up on patients
- If FDA did not approve a drug within 6 months it was automatically approved !!!



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Thalidomide – regulatory consequences

- Systematic testing for developmental toxicity
  - Fertility, teratogenicity, fetal development, perinatal development
  - Should include a rodent and a non-rodent species carefully selected
- Sponsor must provide a detailed study plan to FDA before human trials
- Progress of human studies must be monitored and findings reported to the FDA

Increased safety for human patients

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Once the best-selling antihistamine in the world

Seldane

VistaGen

FDA Wants

Toxicology studies were found to be insufficient in predicting rare adverse events

Washington Post January 1997

Million

US Prescriptions in 1996

FDA Says *Seldane* Should Be Withdrawn

Los Angeles Times January 1997

Treatment for allergy – no drowsiness or fatigue

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Toxicology versus safety pharmacology

Toxicology

- Repeat dose studies
  - Organ weights, morphology, histopathology
- AUC

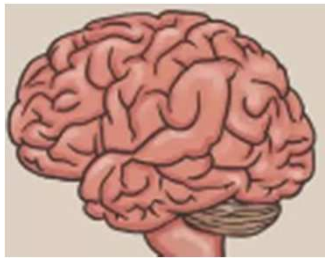
Safety Pharmacology

- Single dose studies
  - reversible, functional effects recorded from conscious animals
    - Onset, duration and magnitude of effects
- Cmax

Investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above

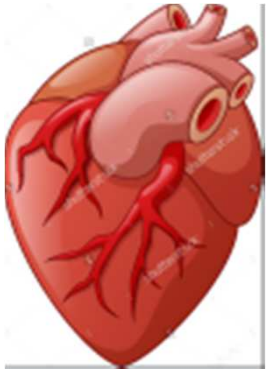
What is Safety Pharmacology

Core battery

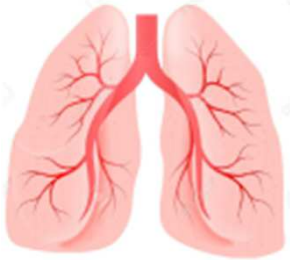


- *In vivo* studies should be conducted in:
  - *conscious* animals
  - unrestrined using telemetri is preferred
- Route of adm.
  - *Clinical route* or multiple routes if neccesary
  - Exposure achieved must be similar to human exposure or above
- Should be conducted in accordance to GLP

- Central nervous system



- Cardiovascular system



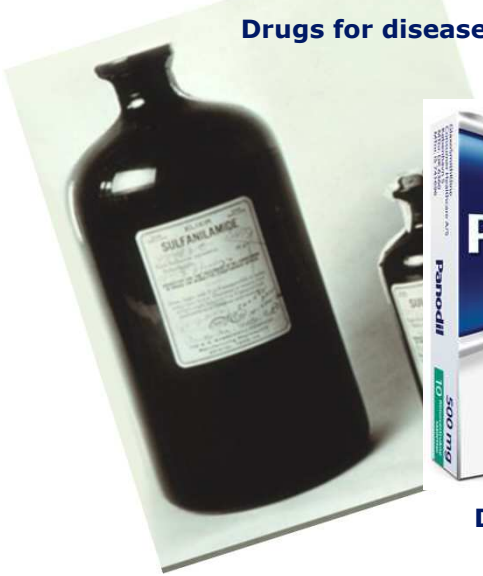
- Respiratory system

3R accomplishments in Safety Pharmacology

- Group housing of primates in telemetry studies
- Focus in training of primates and dogs
- Re-use of animals
- Implement safety pharmacology in toxicology studies
- No positive reference drugs in each respiration and CNS study

Why are we using animal experimentation in drug development ?

Drugs for disease



Drugs for pain

Drugs for mental health

Drugs for allergy

Drugs for pleasure

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Thank you !

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