

Benefit – Risk Assessment

Introduction

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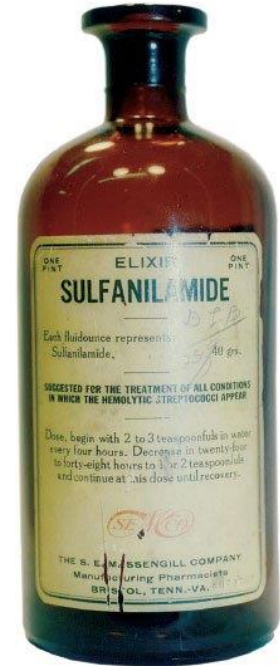
Outline

- History of drug safety regulations
- Benefit – Risk Assessment Definition
- Benefit – Risk Assessment lifecycle

Elixir Sulfanilamide Tragedy (1937)

1937

Elixir sulfanilamide killed 107 persons, many of whom were children, dramatizing the need to establish drug safety before marketing and to enact the pending food and drug law.



Elixir Sulfanilamide Tragedy (1937)

In 1935, sulfanilamide was discovered to treat infections caused by streptococcal.

Before august 1937, sulfanilamide was marketed as capsules and powders. However, liquid forms was demanded for young children.

A chemist worked for Massengill company invented a formula for the liquid form.

Sulfanilamide – 58-½ pounds

Elixir flavor – 1 gallon

Raspberry extract – 1 pint

Saccharine soluble – 1 pound

Amaranth solution 1/16 (red dye) – 1-½ pints

Caramel – 2 fluid ounces

Diethylene glycol (solvent) – 60 gallons

Water – enough to make 80 gallons

Elixir Sulfanilamide Tragedy (1937)

Two months after the liquid form was marketed, an urgent telegram was delivered to the American Medical Association (AMA):

“A group of Tulsa, Oklahoma doctors expressed their great concern over the recent death of six children. All had died from strep throat within the previous ten days exhibiting very similar symptoms: all had lower-than-normal temperatures, respiration had slowed, and then their bodies stopped producing urine before succumbing to whatever had killed them.” October 1937

The FDA did not have power. However, the commissioner ordered all staff (~250) to trace the causes.

**DRUG FATALITY CAUSE
IS TRACED TO ‘ELIXIR’**
**A.M.A. Chemists Say Diethylene
Glycol Added to Sulfanilamide
Killed 13**

**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 nation-wide race with death, to stop recovery of more than 700 bottles, mostly pints, of a new liquid medicine, named Elixir of Sulfanilamide, which has already caused at least 36 deaths, was described today at the headquarters here of the American Medical Association.
The race, sponsored by the United States Food and Drug Administration, and Dr. Morris Fishbein, president of the Medical Association, is meant to save the country from the poison. By some time on Monday, said J. O. Clarke of the Food and Drug Administration, it is hoped that all of the “outstanding” shipments will be recovered.
It is the fact that large drug stores are careless with sulfanilamide preparations.
The medicines stop the kidneys, the Medical Association headquarters its efforts were said to be the first of its kind in history. The medicine is known as “Elixir.” It is made of sulfanilamide and diethylene glycol, a very poisonous substance.
The principal shipments, said Mr. Clarke, went to the South and Midwest. But in addition, shipments have been traced to the Northern Provinces of Michigan, to a distributing house in New York City and to another in New Brunswick, N.J.

****Diethylene glycol****

Thalidomide Scandal (1956-1964)

Quickly discovered to also be an effective anti-emetic and used to treat morning sickness in pregnant women in European countries.

Marketed in ~ 46 countries with following statements:

“...drug of choice to help pregnant women”

“completely safe for pregnant women”

However:

No studies in pregnant women (or animals) had been conducted.

Practically nothing was known about the drug at the time of its marketing

this
child's
life

may depend on the safety of 'Distaval'

Consider the possible outcome in a case such as this—had the bottle contained a conventional barbiturate. Year by year, the barbiturates claim a mounting toll of childhood victims. Yet it is simple enough to prescribe a sedative and hypnotic which is both highly effective... and outstandingly safe. 'Distaval' (thalidomide) has been prescribed for nearly three years in this country, where the accidental poisonings rate is notoriously high; but there is no case on record in which even gross overdosage with 'Distaval' has had harmful results. Put your mind at rest. Depend on the safety of

As a hypnotic at bedtime:
ADULTS: 50 mg.—200 mg.
INFANTS AND CHILDREN: 25 mg.—100 mg.
As a daytime sedative:
ADULTS: 25 mg. two or three times daily.
INFANTS AND CHILDREN: Half to one 25 mg. tablet, according to age, one to three times daily.
'Distaval': 25 mg. tablets.
'Distaval': Forte (100 mg. tablets).
Basic cost to N.H.S. of 12 tablets from dispensing pack of one hundred: 1/- or 2/6d. according to strength.

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Practitioner, 1959, 72, 52.
J. clin. exp. Psychopath., 1959, 26, 249.
J. Child. exp. Pract., 1959, 2, 288.
Brit. med. J., 1959, 2, 635.
Med. 9/5 (Lancet), 1959, 91, 26.
Brit. J. Pharmacol., 1960, 7, 111.

'DISTAVAL'

THE DISTILLERS COMPANY (Biochemicals) LIMITED
Broadway House, The Broadway, Wimbledon, London, S.W.19 Telephone: Liberty 9600
"Beware of the trade mark 'Distaval'"

Thalidomide Scandal (1956-1964)

In the US, there was a hero: Dr. Frances Kelsey

Even though it had already been approved in Canada and more than 20 European and African countries, Dr. Kelsey withheld approval for the drug and requested further studies.

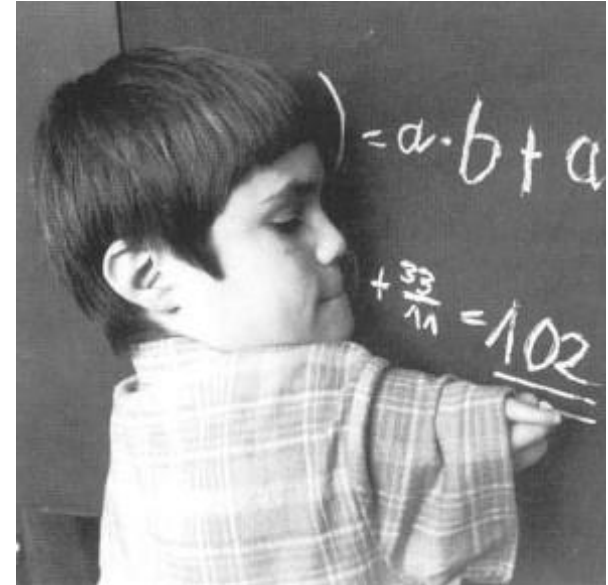
On Aug. 1, 1962, President John F. Kennedy issued a warning during his speech: *“Every woman in this country, I think, must be aware that it’s most important that they check their medicine cabinet and that they do not take this drug.”*



Thalidomide Scandal (1956-1964)

Lessons learned:

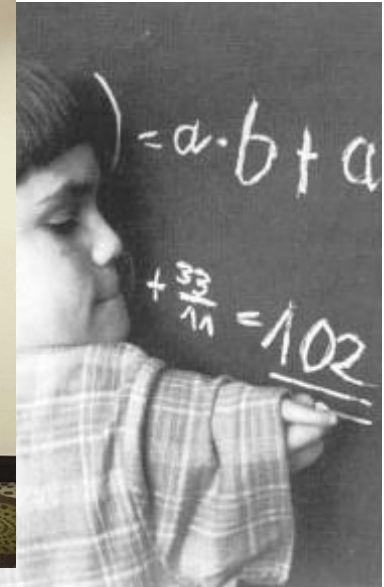
- Recognition of epidemic of rare defects took almost 4 more years
- Around 10,000 infants were born with deformities worldwide; only about 5,000 survived beyond childhood
- The need for post-marketing surveillance programs



Thalidomide Scandal (1956-1964)

Lessons learned:

- Recognition of the problem almost 40 years later
- Around 10,000 children with severe deformities survived because of early detection and treatment
- The need for regulatory programs



Pre-approval information is not enough

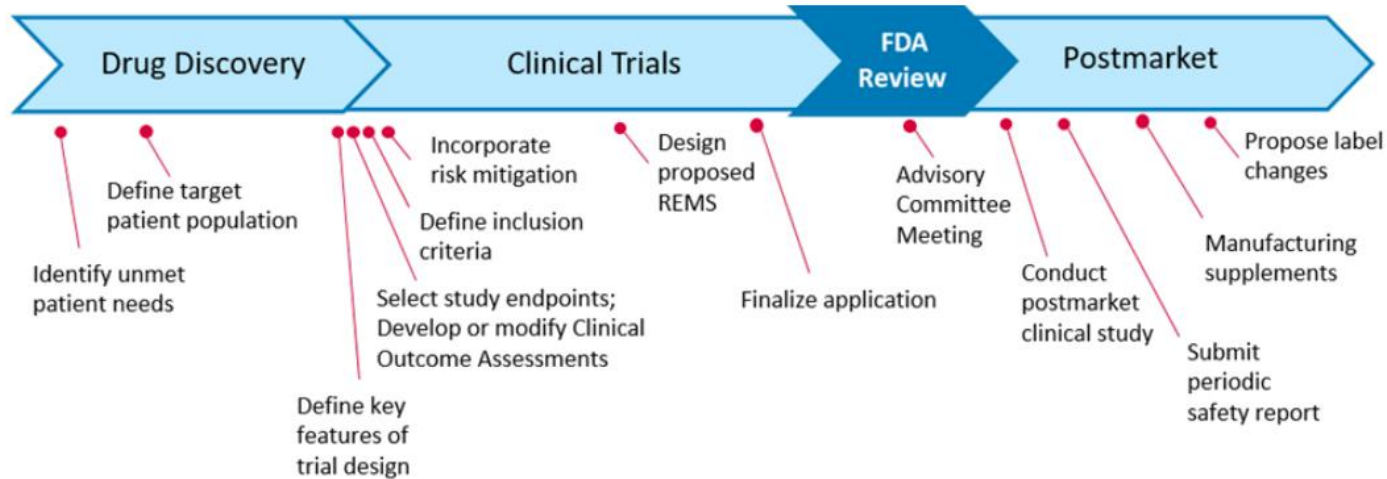
Drug	Unexpected Drug Effect
Isotretinoin (1987)	Birth Defect
Troglitazone (1997)	Hepatotoxicity
Cerivastatin (2001)	Rhabdomyolysis
Rofecoxib (2005)	Heart Attack
?? (2024)	??

BRA definition

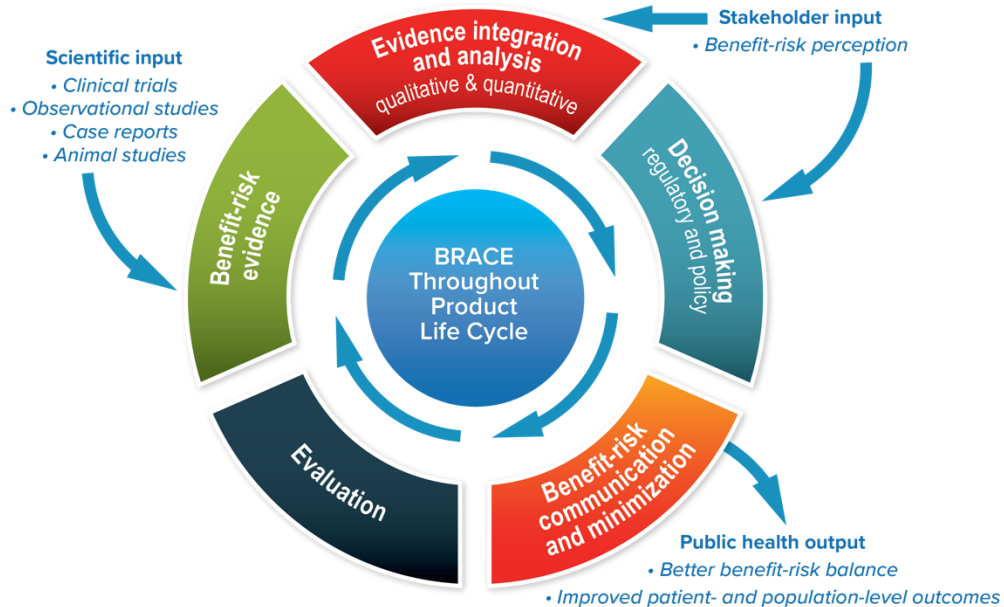
Drug benefit-risk assessment is a process used by regulatory authorities, healthcare professionals, and pharmaceutical companies to evaluate the benefits and risks associated with a particular drug or therapy. This involves analyzing the potential benefits of the drug in terms of its potential therapeutic effects, as well as the potential risks and adverse effects that may occur when using the drug.

Development activities along drug lifecycle

Sample milestones along the drug lifecycle that may have a particular bearing on benefit-risk assessment of a marketing authorization.



Benefit-Risk Assessment, Communication, and Evaluation (BRACE) Throughout the Life Cycle of Medicinal Products and Devices



* Evaluation includes (1) effectiveness of risk communication and risk management; and (2) re-assessment of benefit-risk.

Development activities along drug lifecycle

FDA's Benefit-Risk Framework: Structured approach for human drug review

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Therapeutic context for weighing benefits and risks	
Current Treatment Options		
Benefit	Product-specific assessments based on available evidence	
Risk and Risk Management		
Conclusions Regarding Benefit-Risk		

Thank you

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