Benefit – Risk Assessment

Introduction

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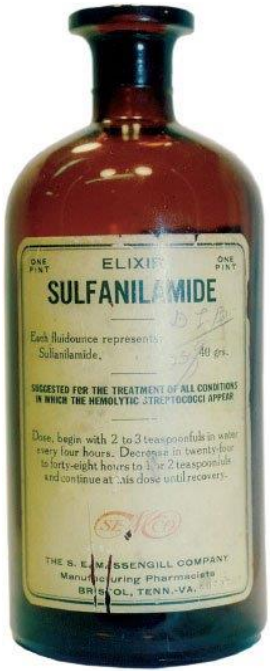
Outline

- 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.

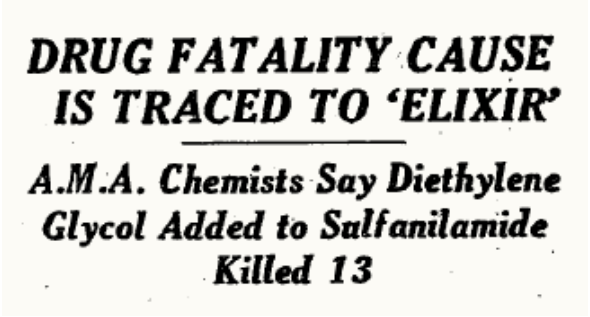
Sulfanilamide – 58-½ pounds
Elixir flavor – 1 gallon
Raspberry extract – 1 pint
Saccharine soluble – 1 pound
Amaranth solution 1/16 (red dye) – 1-½ pints
Caramel – 2 fluid ounces
Diethylene glycol (solvent) – 60 gallons
Water – enough to make 80 gallons

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***

<u>The FDA did not have power</u>. 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

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:

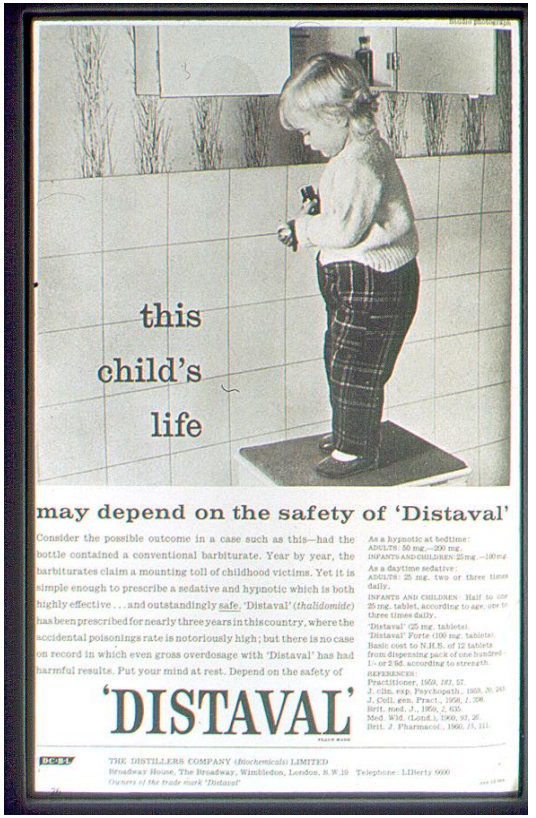
“…drug of choice to help pregnant women”

“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



Thalidomide Scandal (1956-1964)

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

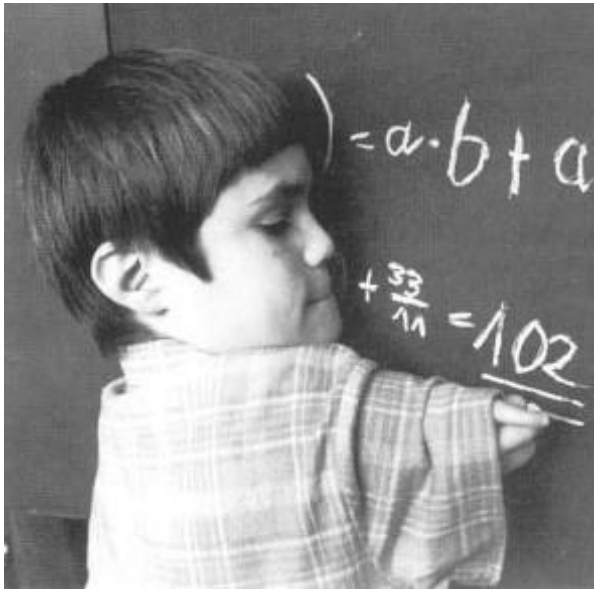
Even though it had already been approved in Canada and more than 20 European and African countries, Dr. Kelsey withheld approval for the drug and requested further studies.

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:

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- The need
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Pre-approval information is not enough

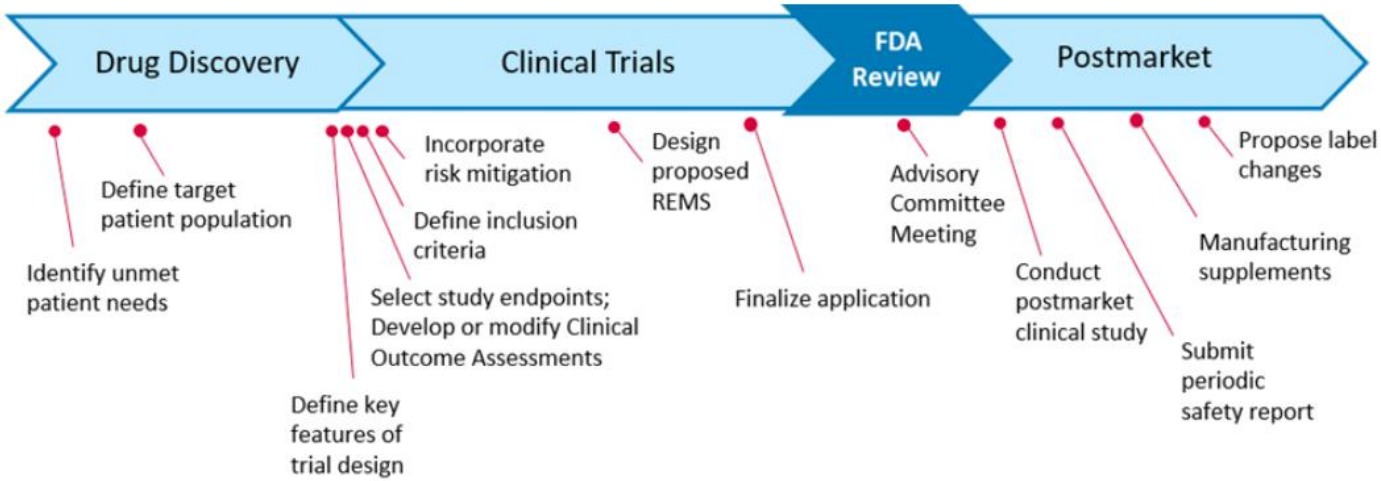
Drug	Unexpected Drug Effect
Isotretinoin (1987)	Birth Defect
Troglitazone (1997)	Hepatotoxicity
Cerivastin (2001)	Rhabdomyolysis
Rofecoxib (2005)	Heart Attack
?? (2024)	??

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

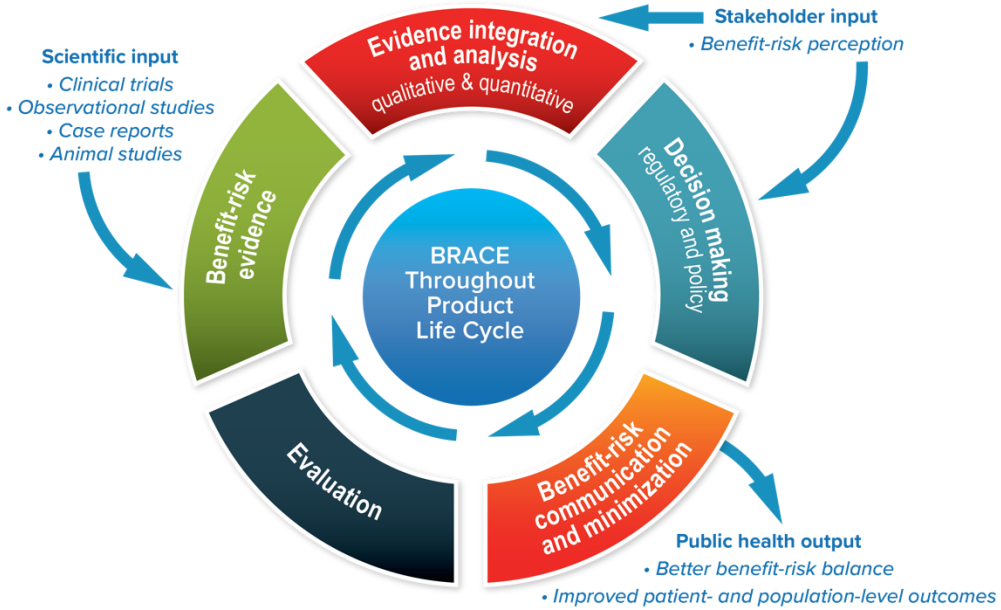
Sample milestones along the drug lifecycle that may have a particular bearing on benefit-risk assessment of a marketing authorization.



2019 FDA Discussion Document: https://healthpolicy.duke.edu/sites/default/files/atoms/files/discussion_guide_b-r_assessment_may16.pdf

BRA lifecycle

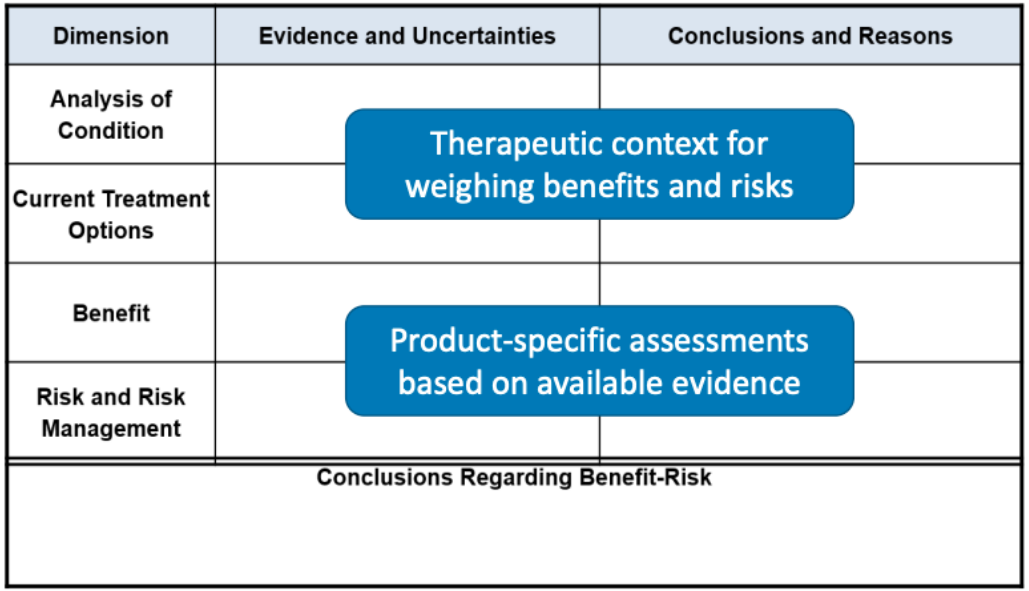
Benefit-Risk Assessment, Communication, and Evaluation (BRACE) Throughout the Life Cycle of Medicinal Products and Devices



* 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



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Thank you

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