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JOHNS HOPKINS
BLOOMBERG
SCHOOL *of* PUBLIC HEALTH

Biostatistics in Medical Product Regulation: Introduction

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Course Objectives

- To understand the relevance and application of statistics in the regulatory process
- To learn about clinical research in the development and evaluation of new medical products
- To be aware of sources for regulatory requirements and regulatory review and evaluation information

Course Outline

- Regulation
- Study design, hypotheses
- Eligible populations
- Treatment allocation
- Comparisons/controls
- Outcomes, responses
- Data analysis issues
- Missing data, multiplicity
- Equivalence, superiority, and non-inferiority trials
- Bridging studies
- Interim monitoring

Purpose of Regulation

- Establish the authority . . .
 - To regulate medical products
 - To protect the public health by assuring their safety and efficacy
 - To apply standards to quality, purity, and potency

Regulations in the U.S.

- 1902: Biologics Control Act
- 1906: Food and Drugs Act
- 1938: Food, Drug, and Cosmetic Act
- 1951: Durham-Humphrey Amendments
- 1962: Kefauver-Harris Amendments
- 1992: “Accelerated Approval”
- 2002: “Animal Rule”

Kefauver-Harris Amendments

“Evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”

— *FD & C Act Section 505(d)*

Impact of 1962 Amendment

- The effectiveness standard was generally interpreted to mean two adequate and well-controlled studies with statistical significance at the $p < .05$ level

Hierarchy of Strength of Evidence

Anecdotal case reports
Case series without controls
Series with literature controls
Analyses using computer databases
"Case-control" observational studies
Series based on historical control groups
Single randomized controlled clinical trials
Confirmed randomized controlled clinical trials

Regulations in Europe

- Historically, much has followed behind (sometimes closely behind) the U.S. (FDA)
- More recently, non-U.S. and U.S. regulators and regulations have moved roughly in parallel
- They are not always identical (and that can cause a problem); but the FDA is not typically more, or less, stringent than other well-developed regulators

The Thalidomide Disaster

- In the early 1960s
- Epidemic of children born with phocomelia (extreme shortening of the long bones)
- This ultimately led (in the UK) to the 1968 Medicines Act
- Similar legislation developed in other European Union countries

The European Medicines Agency (EMA)

- A cooperative group of the 27 member states of the European Union
- Each of the member states provides scientific assessors to consider
 - Quality
 - Pre-clinical safety
 - Clinical safety and efficacy
- Member states share and pool their scientific expertise

- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
 - Regions: European Union, Japan, U.S.
 - Observers: WHO, others
 - Co-sponsors: EC, the European Federation of Pharmaceutical Industries and Associations (EFPIA), MHW, Japanese Products Manufacturers Association (JPMA), Food and Drug Administration (FDA), Pharmaceutical Research and Manufacturers of America (PhRMA)

ICH and Sharing Data

- ICH has been a successful forum to agree on standards, requirements, etc., and to produce guidelines
- National and international laws sometimes prohibit one agency sharing data, results, etc., with other agencies
- Collaboration is ever increasing but still not universal

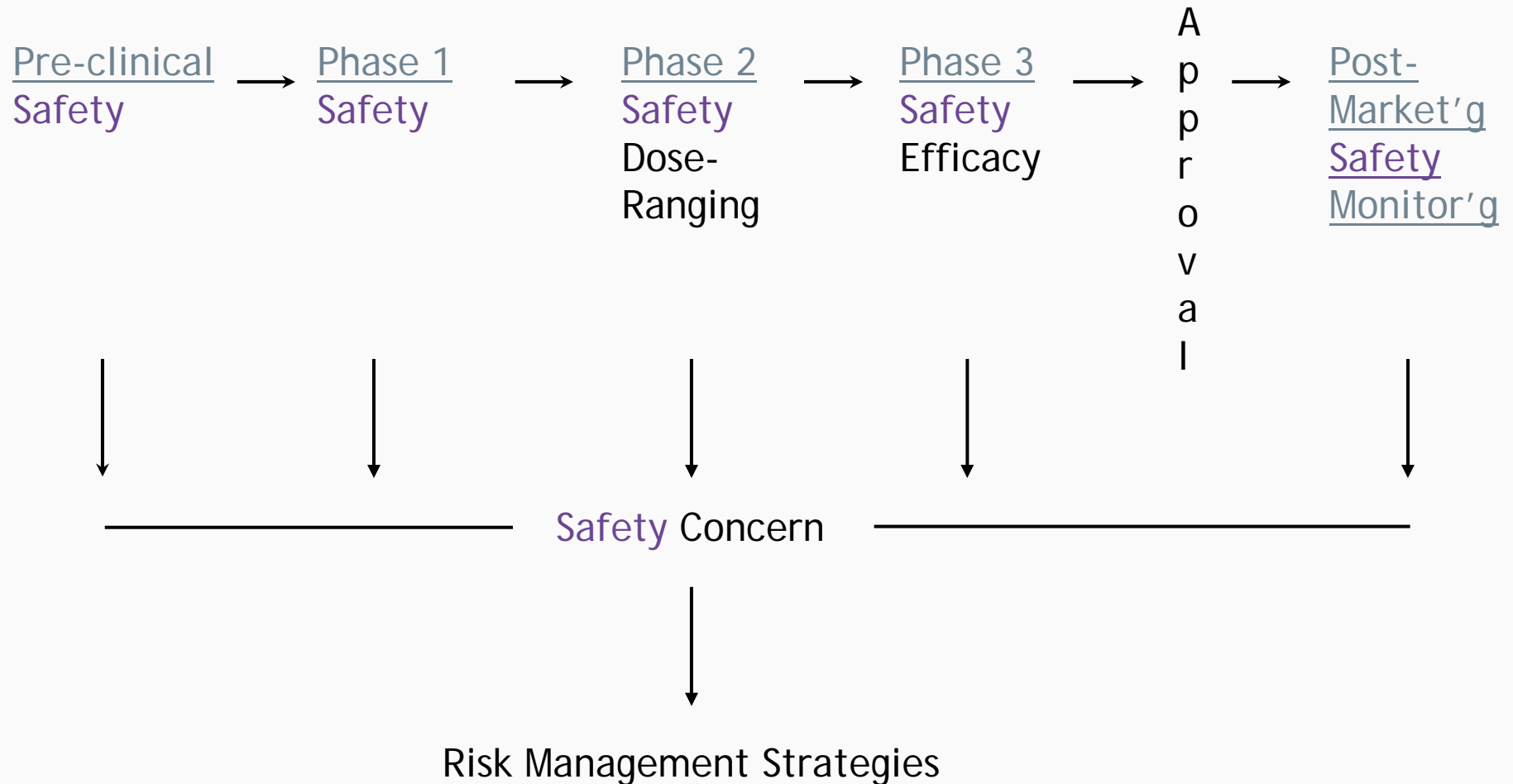
Developing a New Product

- Historically, this has been a very “step-by-step” approach
- Give the drug to a few healthy volunteers and see how they tolerate it
- Try it in patients; explore different doses and dose-regimens
- Confirm what we think we have discovered (“learn and confirm” principal)
- Expand knowledge of drug once it is on the market

Objectives by Phase

- Phase I
 - Determine optimal or tolerable dose
 - Describe adverse event or PK profile
 - Establish feasibility of treatment approach
- Phase II
 - Estimation of activity
 - Comparison of doses or schedules
 - Estimation of factors for Phase III
- Phase III
 - Demonstrate superiority or non-inferiority
 - Estimate rates of adverse events
- Phase IV
 - Address remaining outstanding issues

Lifecycle of a Product



Knowledge Is always “Provisional”

- It is important to realise that we can never know the “true” effect of a drug, nor all of it’s effects
- We do our best to estimate the effect as reliably as possible (from imperfect data)
- There might always be hidden problems (and opportunities) as yet unknown

In the Next Lecture We'll Look At . . .

- Study designs
 - Phases of trials
 - Parallel groups
 - Factorial designs
 - Crossover designs
 - (Cluster designs)