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History and Introduction to Clinical Trials

History of Clinical Trials – Part 1

Global Pharmaceutical Market

- Global pharmaceuticals market is worth US$300 billion
- 2.6 billion $ ~ average cost to research and development a new medicine
- 10 years ~ average time it takes to bring a new medicine from research pipeline to patents
- 12% ~ the portion of drug candidates that enter clinical testing and are eventually approved for use by patients
- 2 out of 3 medicines ever recoup the money invested in R&D

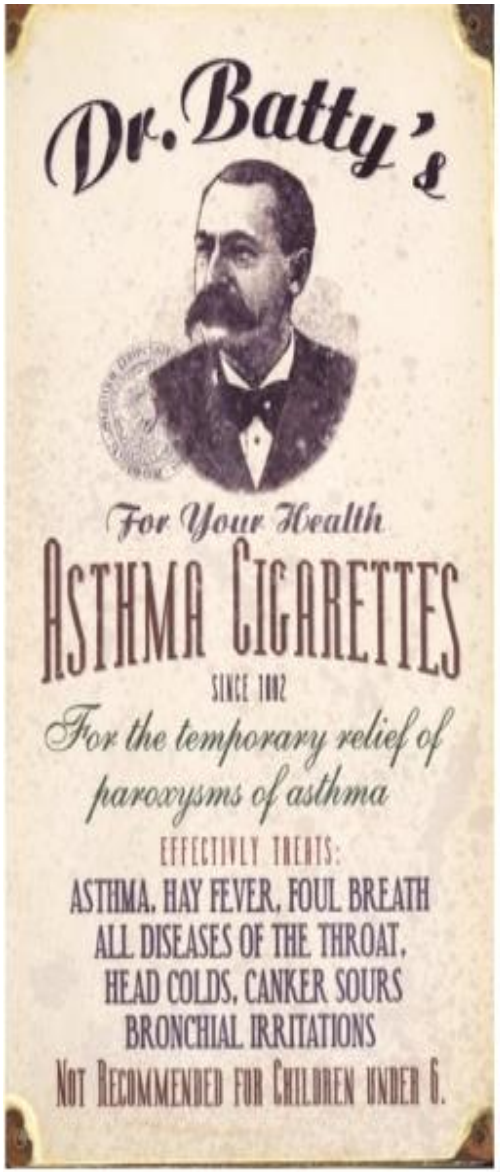
Top 15 Pharma companies by 2014 Revenue

1	Johnson & Johnson	9	Bayer
2	Novartis	10	Gilead Sciences
3	Roche	11	Teva
4	Pfizer	12	Amgen
5	Sanofi	13	AbbVie
6	Merck	14	Eli Lilly
7	GlaxoSmithKline	15	Bristol-Myers Squibb
8	AstraZeneca		

Ref: http://www.who.int/trade/glossary/story073/en/
www.phrma.org
http://www.fiercepharma.com/special-reports/top-15-pharma-companies-2014-revenue

Have asthma? Smoking is the cure!!

- Got Asthma?
- Smoke cigarettes!!
- Your 7 year old nephew got Hay fever:
- Give her cigarettes too!!
- A 19th century flier



http://blog.psprint.com/designing/5-flyers-youre-glad-you-didnt-post/

Opium - Heroin

- Opium poppy was cultivated in lower Mesopotamia as long ago as 3400 BC
- Chemical analysis of opium in the 19th century:
  - Two alkaloids, codeine and morphine.
- The head of Bayer's research department reputedly coined the drug's new name, "heroin," based on the German *heroisch*, which means "heroic, strong.'Bayer scientists were not the first to make heroin, but their scientists discovered ways to make it, and Bayer led commercialization of heroin.
- From 1898 through to 1910, diacetylmorphine was marketed under the trademark name Heroin as a non-addictive morphine substitute and cough suppressant

Ref: http://en.wikipedia.org/wiki/Heroin

2015: Australian Father Treating 2 year Old Daughter Faces 20 Years Jail

Treating cancer, ethics, legal drug

- 2 year old baby girl with stage 4 Neuroblastoma
  - a pediatric cancer that develops from immature nerve cells
  - a very serious abdomen cancer
- In Australia, medical marijuana is illegal
- Medical use of cannabis is legal in many countries

https://www.yahoo.com/parenting/dad-arrested-for-giving-cannabis-oil-to-daughter-108654025667.html

History of Clinical Trials – Part 1

- Outline
  - Nuremberg Code
  - Declaration of Helsinki
  - Thalidomide Disaster

Nuremberg Code

- The Second World War (WW II, 1939-1945)
  - The Allies and the Axis
- The Holocaust (1941-1945)
  - Jews were targeted
  - Methodically murdered in a genocide
  - By the Nazi regime
  - Nazi human experimentation
- The Nuremberg Trial
  - A series of military tribunals
  - Held by the Allied forces after World War II
  - In the city of Nuremberg, Germany
  - Trying 23 of the most important political and military leaders of the Nazi Germany
- The Doctors Trial
- The Nuremberg Code

- Ref: Wikipedia

Nuremberg Code – Contd.

- The Doctors' Trial (United States of America v. Karl Brandt, et al.)
  - Karl Brandt: a German physician
  - Hitler's escort physician: 1934
  - A member of Hitler's inner circle
  - Brandt's medical ethics:
  - Society's weakest, most invalid and incurable members were only parts that should be removed
  - Discussed multiple killing techniques during the initial planning of the euthanasia program with Hitler
  - Trial focused on doctors involved in the human experiments in concentration camps
  - Doctors' argument in the trial:
    - No international law regarding medical experimentation
- The Nuremberg Code

- Ref: Wikipedia

Nuremberg Code – A set of research ethics principles for human experimentation

1. Voluntary Consent
2. For the good of the society
3. Based on the results of animal experimentation and a knowledge of the natural history of the disease
4. Should be so conducted as to avoid all unnecessary physical and mental suffering and injury
5. No experiment should be conducted where there is a prior reason to believe that death or disabling injury will occur
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations and adequate facilities to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. Should be conducted only by scientifically qualified persons.
9. Subject should be at liberty to bring the experiment to an end.
10. The scientist in charge must be prepared to terminate the experiment at any stage.

Ref: Wikipedia

Declaration of Helsinki - 1964

- An idea born in the House of the British Medical Association in 1945
  - An informal conference of doctors
  - From several countries
  - Convened in London
  - To initiate plans for an international medical organization
  - The World Medical Association formed in 1946
- 1946: Declaration of Geneva
  - A modernized wording of the ancient oath of Hippocrates
- Recommendations guiding physicians in biomedical research involving human subjects
- Declaration of Helsinki – 1964
  - A set of ethical principles regarding human experimentation
  - Several revisions later on

Ref: Wikipedia, www.wma.net

Thalidomide Disaster

- First marketed in 1957 in West Germany
  - Primarily prescribed as a sedative or hypnotic
  - Claimed to cure “anxiety, insomnia, gastritis, and tension
  - Later, used against nausea and to alleviate morning sickness in pregnant women
  - Maker’s safety claims:
  - “completely safe” for everyone, including mother and child, “even during pregnancy”
  - By 1960, thalidomide was marketed in 46 countries
  - Australian obstetrician Dr. William McBride discovered that the drug also alleviated morning sickness. He started recommending this off-label use

Image: https://helix.northwestern.edu/article/thalidomide-tragedy-lessons-drug-safety-and-regulation

Thalidomide Disaster: Aftermath of scandal

- In 1961, Dr. McBride began to associate this so-called harmless compound with severe birth defects in the babies he delivered
- In Germany, between 5,000 and 7,000 infants were born with phocomelia (malformation of the limbs)
- Only 40% of these children survived
- In US, Frances Kathleen Oldham Kelsey, physician of US FDA, withheld approval of thalidomide and requested further studies despite pressure from thalidomide's manufacturer
- Received the President's Award for Distinguished Federal Civilian Service from President John F. Kennedy for blocking sale of thalidomide in the United States in 1962
- 2010: FDA established the Dr. Frances O. Kelsey Drug Safety excellence Award.
- Dr. Kelsey received the first Kelsey Award

History of Clinical Trials – Part 2

Outline

- History and timeline of FDA and other regulatory agencies
- Modern day drug approval
- Drug safety in recent times
  - Vioxx
  - Avandia
- Some interesting approvals

History US FDA: Key Milestones (1/3)

- 1820: Eleven physicians meet in Washington, D.C.
  - Establish the U.S. Pharmacopeia, the first compendium of standard drugs for the United States.
- 1848: Drug Importation Act
  - Passed by Congress
  - Requires U.S. Customs Service inspection to stop entry of adulterated drugs from overseas.
- 1862: President Lincoln appoints a chemist, Charles M. Wetherill
  - To serve in the new Department of Agriculture.
  - Beginning of the Bureau of Chemistry, the predecessor of the Food and Drug Administration.
- 1902: The Biologics Control Act
  - To ensure purity and safety of serums, vaccines, and similar products
- 1906: The Meat Inspection Act
  - Insanitary conditions in meat-packing plants
  - Use of poisonous preservatives and dyes in foods
  - Cure-all claims for worthless and dangerous patent medicines
- 1927: Reorganization:
  - Regulatory functions are located in the Food, Drug, and Insecticide Administration

Ref: http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm

History US FDA: Key Milestones (2/3)

- 1930: The name Food and Drug Administration (FDA) under an agricultural appropriations act
- 1937: Elixir of Sulfanilamide containing a poisonous solvent, kills 107 persons, many of whom are children
- The public outcry caused by this Sulfanilamide tragedy led to the passing of
- The Federal Food, Drug, and Cosmetic (FDC) Act of 1938
  - Requiring new drugs to be shown safe before marketing
  - Safe tolerances be set for unavoidable poisonous substances
  - Authorizing factory inspections
  - ….
- 1949: FDA publishes guidance to industry for the first time.
  - Procedures for the Appraisal of the Toxicity of Chemicals in Food
- 1962: Post Thalidomide tragedy
  - Kefauver-Harris Drug Amendments passed
  - To ensure drug efficacy and greater drug safety.
  - For the first time, drug manufacturers are required to prove to FDA the effectiveness of their products before marketing them

Ref: http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm

History US FDA: Key Milestones (3/3)

- 1970: FDA requires first patient package insert

Humira Package Insert 2014

Avandia Package Insert 2008

- 1983: Orphan Drug Act passed
- 1985: AIDS test for blood approved by FDA
- 1991: Regulations published to Accelerate the Review of Drugs for life-threatening diseases
- 1995: FDA declares cigarettes to be "drug delivery devices." Restrictions are proposed
- 1998: Pediatric Rule: conduct studies to assess safety and efficacy in children
- 1999: www.ClinicalTrials.gov is founded

Ref: http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm

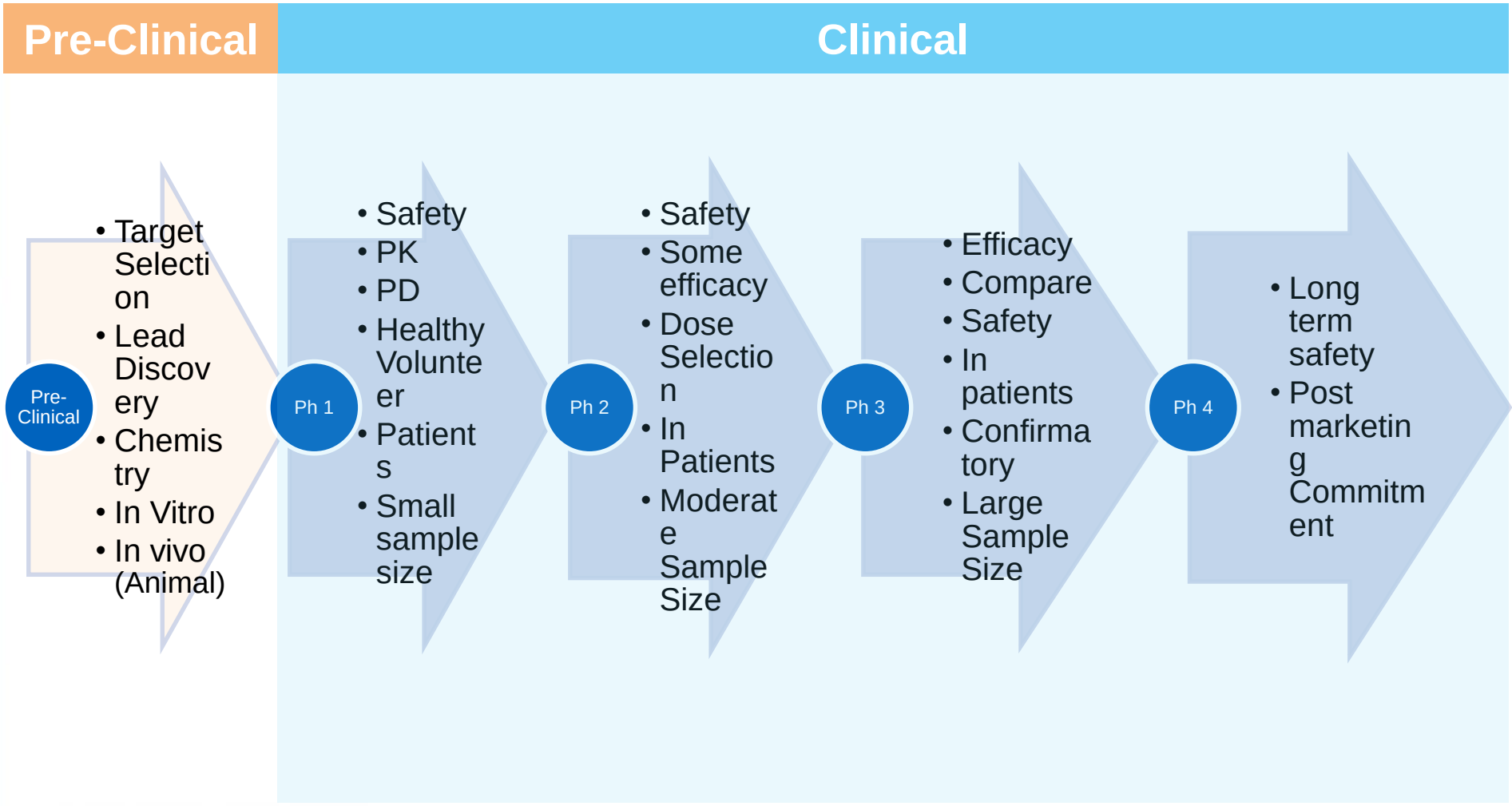
EMA and Some Other Regulatory Agencies

- EU: 1965:Need for Evidence based authorization of medicinal products
- 1995: European Medicines Agency (EMA) starts business
- Japan: Began in 1979
- 2004: Pharmaceutical and Medical Devices Agency (PMDA) established
- China: China Food and Drug Administration (CFDA)

Modern Day Drug Approval

FDA Drug Approval Process

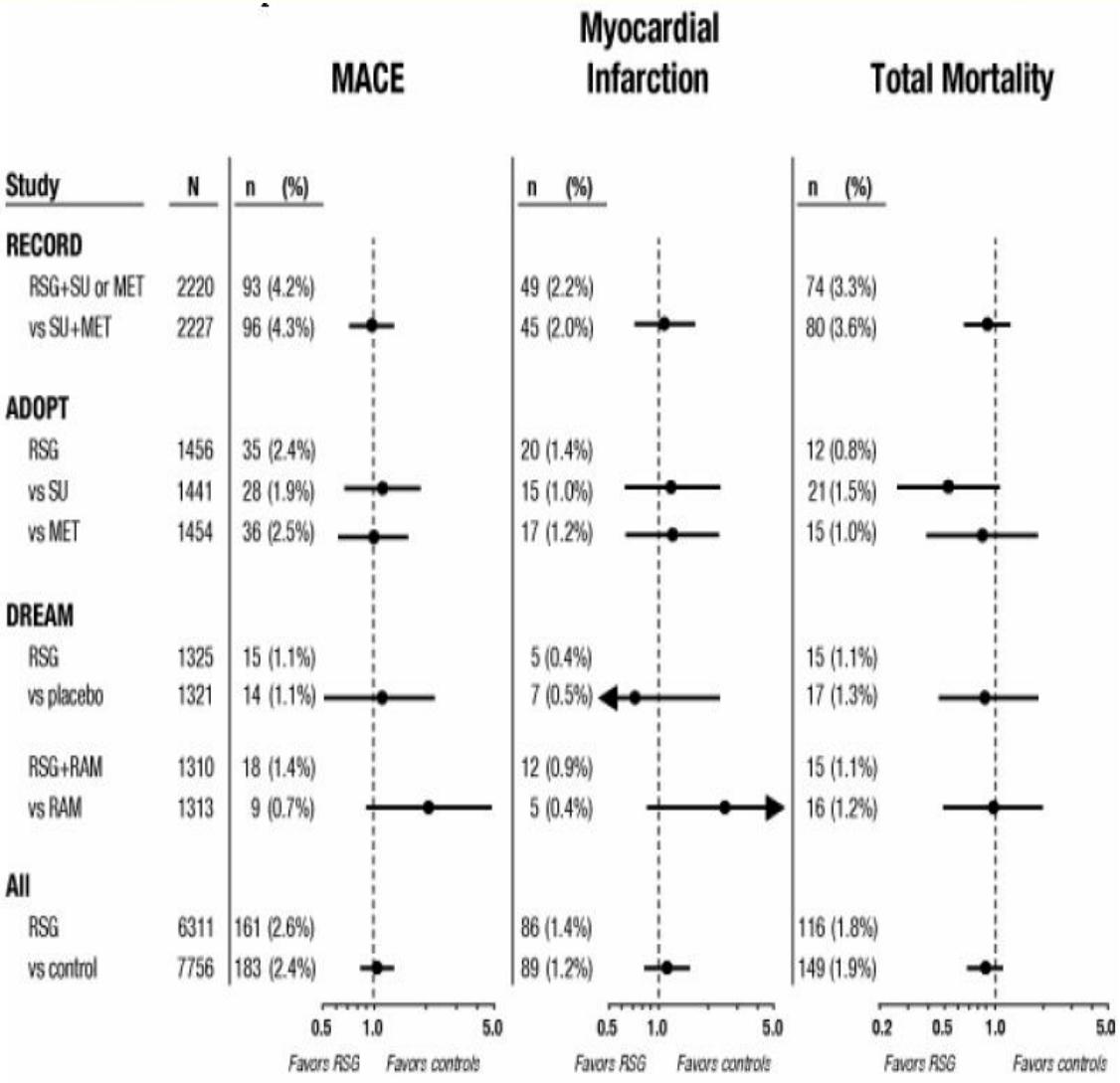
FDA Drug ›val Process Infogr



Requirements Outlined in FDA Guidance

- Independent CV endpoints committee to prospectively adjudicate, in a blinded fashion – All Phase 2 and 3 trials
- Trials are appropriately designed and conducted so that a meta-analysis can be performed
- Obtain sufficient endpoints to allow a meaningful estimate of risk, the phase 2 and phase 3 programs
  - Include patients at higher risk of cardiovascular events
- Sponsors should perform a meta-analysis of the important cardiovascular events across phase 2 and phase 3 controlled clinical trials and explore similarities and/or differences in subgroups (e.g., age, sex, race), if possible
- The report of this meta-analysis should contain sufficient detail for all the analyses; conventional graphical plots for meta-analysis finding by study, subgroup, and overall risk ratio

FDA Avandia AdCom 2010

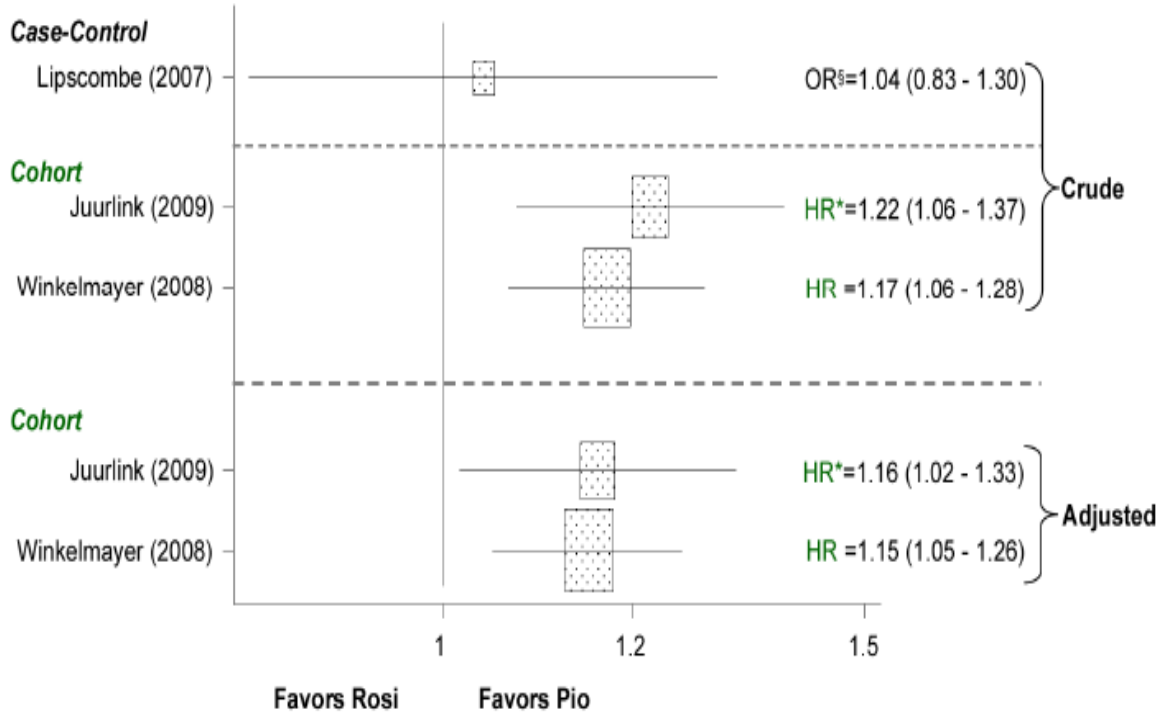


Ref: FDA Webpage

RSG = rosiglitazone; SU = sulfonylurea; MET = metformin; RAM = ramipril

Avandia and Actos: A comparison

9.3.1.3 Outcome: all-cause mortality – rosiglitazone vs. pioglitazone



Boxes indicate individual study point estimates. The box size denotes the size of the study. The width of the horizontal lines represents the 95% CI for each point estimate.

§ Estimated unadjusted OR comparing rosi vs pio calculated from data provided in published article.

HR=reciprocal of point estimate (reciprocal of upper 95%CI – reciprocal of lower 95%CI)

Ref: FDA Webpage

Introduction to Clinical Trials

What are Clinical Trials?

- Clinical trials are research studies that explore whether a medical strategy, treatment, or device is **safe** and **effective** for humans.
- Clinical trials are one of the final stages of a long and careful research process. The process often begins in a laboratory, where scientists first develop and test new ideas.
- If an approach seems promising, the next step may involve animal testing. This shows how the approach affects a living body and whether it's harmful.
- But, an approach that works well in the lab or animals doesn't always work well in people. Thus, research in humans is needed.

What are clinical trials?

- For safety purposes, clinical trials start with small groups of patients to find out whether a new approach causes any harm.
- In later phases of clinical trials, researchers learn more about the new approach's risks and benefits.
- Clinical research is done only if doctors don't know:
  - Whether a new approach works well in people and is safe
  - Which treatments or strategies work best for certain illnesses or groups of people

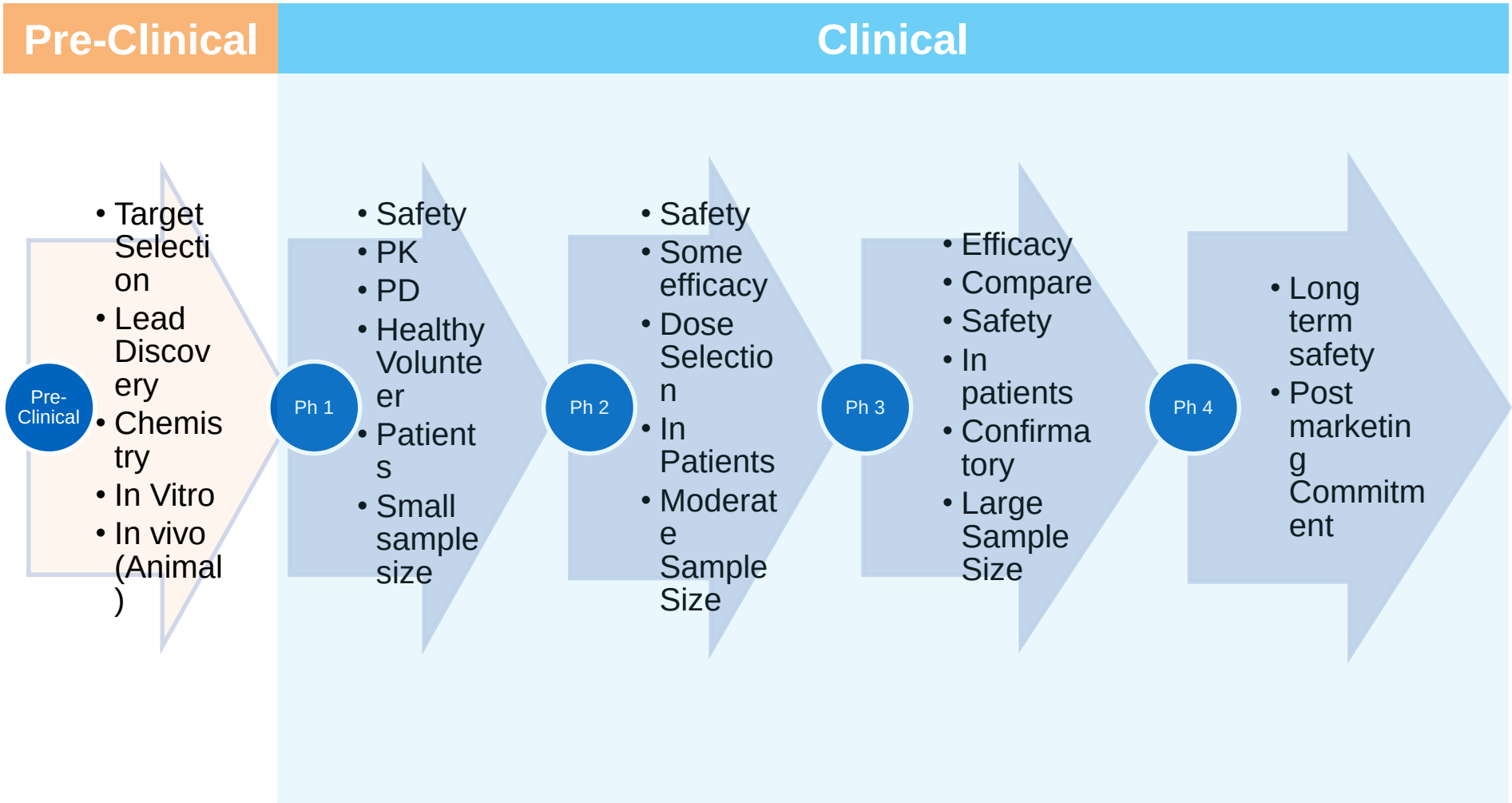
Clinical Trials – Guiding Principles

- Ethics
- Scientific validity and integrity
- Medical relevance
- Regulatory and medicolegal issues
- Costs

Modern Day Drug Approval

FDA Drug Approval Process

FDA Drug ›val Process Infogr



Clinical Trial Phases: Phase I

- **Phase I** [small number of healthy volunteers; in certain cases, i.e., virology/oncology, also patients]
  - Goal: to understand what happens to the investigational compound in the body from the time it is swallowed or injected until it is excreted, when it is excreted and how the human body reacts to the new compound from a safety and tolerability point of view.
  - Study participants are monitored for the occurrence and severity of any side effects that they may experience.

Clinical Trial Phases: Phase II

- **Phase II**
  - Goal: to evaluate the safety and efficacy of an investigational compound in patients with a specific disease or condition.
  - Typically conducted in a group of patients who are at the same stage of a disease.
  - Patients are given various doses of the compound and closely monitored to compare the effects and to determine the safest dosing regimen.
  - In many instances, multiple Phase II studies are conducted to test the compound in a variety of patient populations or indications.

Clinical trial phases: Phase III

- **Phase III**

- Goal: To confirm the safety and efficacy of an investigational compound, and the dosage regimen chosen, in large numbers of patients with a specific disease or condition.
- The safety and efficacy of the investigational compound is compared to that of the currently accepted standard treatment or Placebo.
- Information obtained from Phase III studies is used to determine how the compound is best prescribed to patients in the future.
- The complete information available on the new compound is submitted to Health Authorities.

Clinical Trial Phases: Phase IV

- **Phase IV**
  - Phase IV studies take place after the drug has been approved for marketing
  - These studies are designed:
    - to provide broader experience in evaluating the safety and effectiveness of the new drug in larger numbers of patients, subpopulations of patients, and to compare and/or combine it with other available treatments.
    - to evaluate the long-term effects of the drug. Under these circumstances, less common adverse events may be detected.

Clinical Trial Phases: Summary

Phase	Objective	Efficacy/Endpoint
Phase I	Safety evaluation Patient tolerance	None
Phase II	Identify efficacy endpoints and doses for Phase III	"Exploratory" Primary Secondary
Phase III	Efficacy & Safety Evaluate for general use	Primary- Indication Secondary- may be described in label
Phase IV	Expand efficacy & safety	Expand patient reported outcomes

Phase I Clinical Trial: Investigational New Drug Application (IND)

- Pre-clinical testing on Animals
  - No safety signals
  - Some therapeutic areas / indications identified
- May seek advise from FDA even before filing IND
  - Early communications between sponsors and new drug review divisions
  - Provide guidance on the data necessary to warrant IND submission
  - Issues related to data needed to support the rationale for testing a drug in humans;
  - Design of nonclinical pharmacology, toxicology, and drug activity studies
  - PK issues, known / unknown metabolites
- FDA IND Regulations: 21 Code of Federal Regulations (CFR) 312 (Drugs and Biologics)

IND Requirements (Not all are listed here)

- Chemistry
  - Strength of drug, impurities, stability, product consistency
- Pharmacology an Toxicology data
  - Life threatening toxicity in rodents
  - Non-rodent (may be in dogs) to confirm tolerability
  - Proposed clinical trial with same schedule, duration, formulation and route as in PK and TOX studies
- Choice of starting dose for first-in-human trial
- Non-Onco
  - Healthy volunteers
  - Doses: for further studies; not Maximum Tolerated Dose (MTD)
- Oncology
  - Usually cancer patients
  - Doses: for further studies; Maximum Tolerated Dose (MTD)

FDA Guidance
MRSD 2005

Beginning Studies in Human

- FDA's review of IND is complete
- Also reviewed by a local Institutional Review Board (IRB)
  - What is an IRB?